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FULL PAPER

Tumor stiffness measured by quantitative and qualitative shear wave elastography of breast cancer

EUN JEE SONG, MD, PhD, YU-MEE SOHN, MD, PhD and MIRINAE SEO, MD, PhD

Department of Radiology, Kyung Hee University Hospital, College of Medicine, Kyung Hee University, Seoul, South Korea

Address correspondence to: MD Yu-Mee Sohn
E-mail: *sonyumee@naver.com*

Objective: To correlate clinicoradiologic and pathological features of breast cancer with quantitative and qualitative shear wave elastographic parameters.
Methods: 82 breast cancers in 75 patients examined by B-mode ultrasound and shear wave elastography (SWE) were included. SWE parameters including quantitative factors [maximum elasticity (E_{max}), mean elasticity (E_{mean}), elasticity ratio (E_{ratio}) and standard deviation (SD)] and qualitative factor (color pattern) were correlated with clinicoradiologic and pathological features using univariate and multivariate linear regression analyses.
Results: Presence of symptoms and larger tumor size on ultrasound were significantly associated with higher E_{max}, E_{mean}, E_{ratio}, and SD (all $p < 0.05$) on univariate analysis. Older age was significantly correlated with higher E_{max} and E_{mean} (p = 0.026, 0.018). Lymphovascular invasion and larger pathologic size were significantly associated with higher E_{max} (p = 0.036, 0.043) and SD ($p < 0.001$, 0.019). No immunohistochemical biomarkers were significantly correlated with SWE parameters. There was no significant correlation between color pattern and any variable. Multivariate logistic regression analysis showed that the symptom, tumor size on ultrasound and lymphovascular invasion were independent factors that influenced the SWE values.
Conclusion: Tumor stiffness as measured by SWE and B-mode ultrasound could help predict cancer prognosis.
Advances in knowledge: Clinicoradiologic factors had correlation with quantitative and qualitative SWE parameters. Using SWE parameters and B-mode ultrasound, we can predict breast cancer prognosis.

INTRODUCTION

Breast cancer is considered as a heterogeneous disease entity with various histological types, clinical courses, and prognoses. Pre-operative prediction of prognosis is important not only to know the natural course of the disease, but also to decide the proper treatment. Prognostic factors of breast cancer are related to tumor size, histological type, histological grade, lymphovascular invasion (LVI), and lymph node status.[1,2] More recently, gene expression analyses using DNA microarrays have classified different molecular subtypes that are significantly associated with different disease prognoses.[3] Immunohistochemical study is based on the following cancer biomarkers: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Instead of molecular classification, immunohistochemical profiles of breast cancer for evaluating the expression of hormonal receptors (ER, PR), HER2, and Ki-67 have been used.[4] Several studies report that breast cancer subtypes classified by immunohistochemical expression of ER, PR, HER2, and Ki-67 show different clinical, radiologic and pathological features.[5,6]

Breast ultrasound elastography is a method used to measure the stiffness of breast lesions. Many studies have shown that US elastography improves differentiation between benign and malignant lesions in breast tissue.[7–9] There are two main methods for assessment of stiffness: strain elastography and shear wave elastography (SWE).[10] Strain elastography assesses stiffness from the degree of strain caused by manual compression. The efficacy of strain elastography to assess stiffness is limited by the operator's ability to provide adequate repetitive compression, and SWE was introduced to overcome this limitation.[9] The SWE system uses acoustic radiation to induce mechanical vibrations and quantifies the stiffness of a lesion by capturing propagating shear waves.[11] This technique results in quantitative measurement of tissue elasticity in kilopascals (kPa) or meters per second (m s^{-1}).[9,11] Moreover, the color overlay image obtained using B-mode imaging can provide information about stiffness of the breast lesion from the color pattern or from quantitative parameters.[8,10,12–15]

Relationships between prognostic factors including immunohistochemical features of breast cancer and their SWE

values have been the subject of ongoing research. Evans et al[16] demonstrated a significant correlation between cancer size and mean elasticity (E_{mean}) value. Youk et al[17] reported that palpable abnormality, histologic grade, and LVI were significantly associated with E_{mean}, but immunohistochemical factors were not. Ganau et al[18] concluded that there were no significant differences among the subtypes of invasive tumors in maximal elasticity (E_{max}) and E_{mean}. Several groups have reported that breast cancers with poorer prognosis based on histologic prognostic features, immunohistochemical profiles, and subtypes have a higher E_{mean}[19,20] and E_{ratio}.[21] However, there have been different conclusions about the relationship between prognostic clinicopathologic factors of breast cancer and SWE parameters [E_{max}, E_{mean}, elasticity ratio (E_{ratio}), and standard deviation (SD)]. Moreover, to our knowledge, few published studies have compared all SWE parameters, including both quantitative and qualitative factors, with the prognostic features of breast cancer.[16,17,20]

Therefore, the purpose of this study was to correlate quantitative and qualitative SWE parameters with clinical, radiologic and pathologic factors, including immunohistochemical biomarker profiles, in breast cancer.

METHODS AND MATERIALS

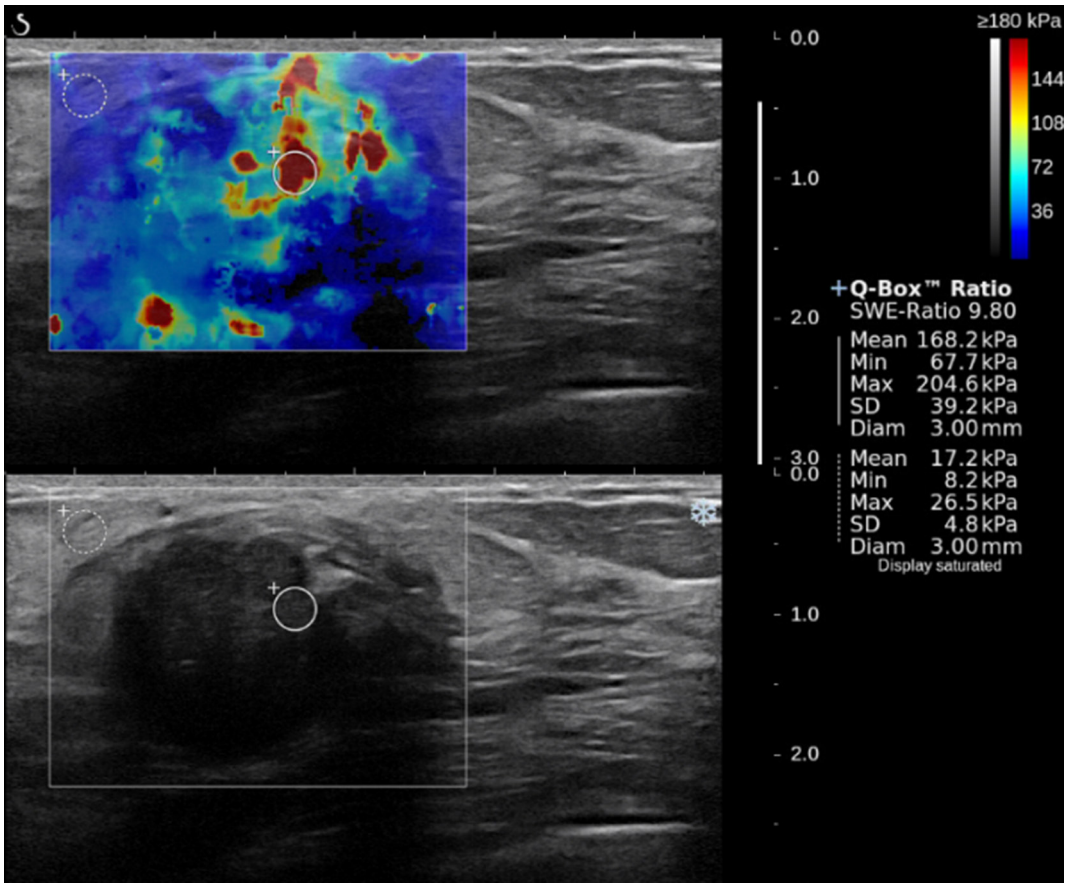
Patients

The Institutional Review Board of our hospital approved this retrospective study, and neither patient approval nor informed consent was required for the review of medical records or radiological images. Signed informed consent was obtained from all patients before ultrasound-guided biopsy procedures or surgery. From August 2013 to May 2015, 129 patients were diagnosed with breast cancer. Among them, patients who had no SWE images (n = 31), patients who underwent neoadjuvant chemotherapy before surgery (n = 16) or had lack of data on immunohistochemical factors such as ER, PR, HER2, and Ki-67 (n = 7) were excluded from the study. Ultimately, 82 breast cancers in 75 females (age range: 32–80 years, mean age: 57.4 years) were included in the final study.

Ultrasound examinations

Conventional ultrasound and SWE images were obtained using the Aixplorer system (Supersonic Imagine, Aix-en Provence, France) equipped with a 4–15 MHz linear array transducer by one radiologist (Y-MS) with 10 years of experience and other radiologist (MS) with 6 years of experience in breast imaging.

Figure 1. A 75-year-old female with a 26.5 mm, Grade 3, intraductal carcinoma in the left breast. SWE color map (top) shows that the colored area was heterogeneously present in the interior of the mass (Pattern 4), and the lesion had high stiffness (E_{max}, 204.6 kPa; E_{mean}, 168.2 kPa; E_{ratio}, 9.8; SD, 39.2 kPa). On pathology, the cancer showed lymphovascular invasion, positive ER and PR, negative HER2, and positive Ki-67. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SD, standard deviation; SWE, shear wave elastography.



Final assessments based on B-mode ultrasound findings were made and recorded by the American College of Radiology Breast Imaging Reporting and Data System.[22] After B-mode ultrasound, SWE imaging before biopsy was performed by the same radiologist with no pressure induced by the transducer. The region of interest (3 × 3 mm) was set to include the lesion and surrounding normal breast parenchyma. The B-mode semitransparent color map revealed stiffness with a range from dark blue to red (0–180 kPa). After a few seconds of immobilization to let the image stabilize, the SWE image was obtained.

Image analysis

The following data from B-mode images were retrospectively measured and recorded by one radiologist (EJS) with 2 years of experience in breast imaging: lesion size (maximum diameter on ultrasound images), breast thickness (maximum vertical distance from the skin to the pectoralis muscle on the ultrasound image including the breast mass targeted for biopsy), and lesion depth (vertical diameter from the skin to the center of the breast mass).

For quantitative SWE analysis, we recorded the following parameters: maximum elasticity (E_{max}), mean elasticity (E_{mean}), elasticity ratio (E_{ratio}), and SD. E_{max} and E_{mean} represent the general stiffness of the lesion. E_{ratio} is the ratio between elasticity values of the tumor and the reference tissue. SD refers to the internal heterogeneity of the lesion. For qualitative analysis from SWE, we (EJS and Y-MS) independently recorded color patterns according to the classifications proposed by Tozaki and Fukuma using a four-color overlay.[12] Disagreements were resolved by consensus. Images were classified as follows: "Pattern 1," the color around the lesion was not different from the margin of the lesion or its interior, showing a homogeneously blue pattern; "Pattern 2," the color extending beyond the lesion was different from the color around the lesion, showing continuous vertical stripes on the cutaneous or thoracic wall side; "Pattern 3," the localized colored area was at the margin of the lesion; and "Pattern 4," the colored areas were heterogeneously present in the interior of the lesion.[12] Of the qualitative SWE pattern classifications, patterns 1 and 2 were considered benign, while patterns 3 and 4 were considered malignant.[12]

Clinical and pathologic analysis

Each patient's medical records were reviewed and data on age and presence of clinical symptoms such as palpability and breast pain were collected. Pathologic reports of surgical specimens were also reviewed to determine tumor type, tumor size, histological grade, lymphovascular invasion (LVI), and lymph node status. Tumor size was defined as the largest diameter in

Figure 2. A 51-year-old female with a 4 mm, Grade 1, ductal carcinoma *in situ* in the left breast. B-mode ultrasound (bottom) shows that mass has irregular shape and non-circumscribed margin. SWE color map (top) shows that blue color around the lesion continues vertically on the cutaneous side (Pattern 2) and low SWE values (E_{max}, 33.5 kPa; E_{mean}, 27.0 kPa; E_{ratio}, 1.4; SD, 3.7 kPa). On pathology, the cancer showed no lymphovascular invasion, negative ER, negative PR, negative HER2, and negative Ki-67.

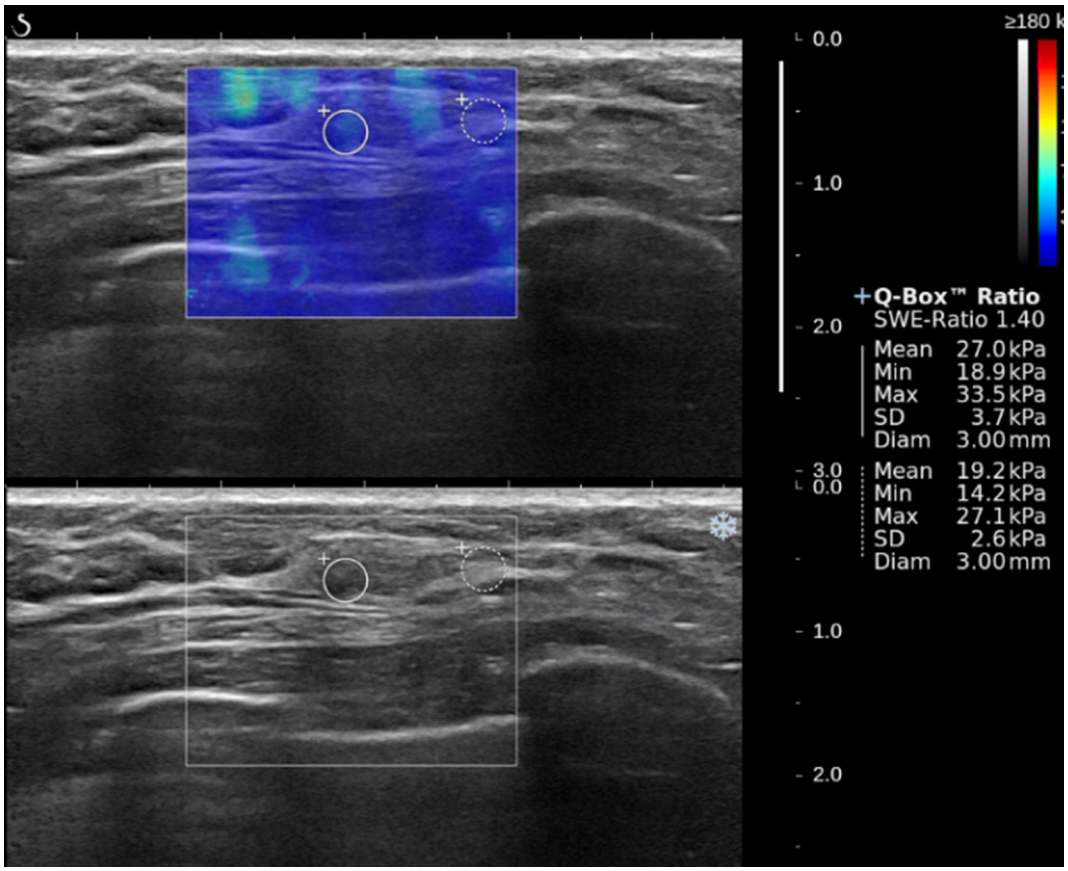


Table 1. Correlation of clinicoradiologic factors with quantitative SWE parameters on univariate analysis

			Emax			Emean			Eratio			SD	
Variable	n	Mean ± SD	β coefficient	*p*	Mean ± SD	β coefficient	*p*	Mean ± SD	β coefficient	*p*	Mean ± SD	β coefficient	*p*
Age	82	169.16 ± 70.30	1.49 ± 0.66	0.026	131.17 ± 52.76	1.19 ± 0.49	0.018	8.00 ± 8.16	0.09 ± 0.08	0.237	23.60 ± 19.45	0.24 ± 0.19	0.200
Symptom													
Absent	40	135.20 ± 59.32	0		108.89 ± 47.62	0		6.11 ± 4.10	0		16.66 ± 12.55	0	
Present	41	199.59 ± 64.56	64.39 ± 13.79	<0.001	151.48 ± 49.20	42.59 ± 10.76	<0.001	9.93 ± 10.53	3.82 ± 1.78	0.035	30.24 ± 22.76	13.58 ± 4.10	0.001
Ultrasound size	82	169.16 ± 70.30	4.18 ± 0.88	<0.001	131.17 ± 52.76	2.79 ± 0.68	<0.001	8.00 ± 8.16	0.36 ± 0.11	0.001	23.60 ± 19.45	1.06 ± 0.25	<0.001
Ultrasound size													
<10 mm	15	129.85 ± 60.22	0		103.82 ± 47.59	0		5.76 ± 4.04	0		13.85 ± 6.51	0	
10–20 mm	45	152.02 ± 61.67	22.17 ± 17.74	0.215	119.18 ± 47.24	15.36 ± 13.70	0.266	5.79 ± 3.49	0.03 ± 2.20	0.989	20.90 ± 16.36	7.05 ± 5.37	0.193
>20 mm	22	231.04 ± 54.16	101.19 ± 19.92	<0.001	174.34 ± 41.91	70.52 ± 15.39	<0.001	14.05 ± 12.96	8.30 ± 2.47	0.001	35.77 ± 25.12	21.91 ± 6.03	<0.001
Thickness													
10–20 mm	45	166.46 ± 66.07	0		129.35 ± 46.81	0		6.62 ± 5.91	0		22.88 ± 19.13	0	
>20 mm	37	172.44 ± 75.93	5.98 ± 15.68	0.704	133.39 ± 59.80	4.04 ± 11.77	0.733	9.67 ± 10.09	3.05 ± 1.79	0.092	24.48 ± 20.05	1.60 ± 4.34	0.714
Lesion depth													
<10 mm	21	155.89 ± 69.91	0		123.54 ± 51.98	0		8.91 ± 8.00	0		20.41 ± 16.74	0	
≥10 mm	61	173.73 ± 70.43	17.85 ± 17.79	0.319	133.80 ± 53.20	10.26 ± 13.38	0.446	7.68 ± 8.26	−1.23 ± 2.07	0.555	24.70 ± 20.31	4.28 ± 4.93	0.387

E_{max}, max elasticity; E_{mean}, mean elasticity; E_{ratio}, elasticity ratio; SD, standard deviation; SWE, shear wave elastography.
p-values < 0.05 were considered statistically significant.

Table 2. Correlation of pathologic factors with quantitative shear wave elastographic parameters on univariate analysis

			Emax		Emean			Eratio			SD	
Variable	n	Mean ± SD	β coefficient	*p*	Mean ± SD	β coefficient	*p*	Mean ± SD	β coefficient	*p*	Mean ± SD	β coefficient	*p*
Pathologic size	82	169.16 ± 70.30	0.92 ± 0.45	0.043	131.17 ± 52.76	0.44 ± 0.34	0.206	8.00 ± 8.16	0.03 ± 0.05	0.578	23.60 ± 19.45	0.29 ± 0.12	0.019
Pathologic size													
<10 mm	17	137.56 ± 74.87	0		108.69 ± 57.83	0		6.53 ± 8.53	0		18.13 ± 17.26	0	
10–20 mm	31	155.66 ± 54.81	18.10 ± 20.11	0.371	124.62 ± 45.32	15.93 ± 15.39	0.304	6.84 ± 5.04	0.31 ± 2.45	0.899	18.71 ± 9.15	0.58 ± 5.64	0.918
>20 mm	34	197.27 ± 72.00	59.70 ± 19.80	0.003	148.38 ± 52.33	39.69 ± 15.15	0.011	9.79 ± 9.97	3.27 ± 2.41	0.179	30.80 ± 24.83	12.67 ± 5.55	0.025
Histologic grade													
1	17	170.06 ± 64.85	0		133.30 ± 45.99	0		6.91 ± 4.79	0		20.55 ± 11.04	0	
2	41	160.55 ± 72.59	−5.84 ± 19.49	0.765	124.90 ± 54.59	−5.77 ± 14.67	0.695	6.24 ± 4.26	−0.46 ± 2.17	0.832	23.88 ± 22.80	3.89 ± 5.43	0.476
3	22	187.60 ± 71.84	21.21 ± 22.00	0.338	143.30 ± 56.15	12.63 ± 16.55	0.448	12.40 ± 13.29	5.70 ± 2.44	0.022	26.20 ± 18.78	6.22 ± 6.13	0.314
Lymph node status													
Negative	66	170.51 ± 67.30	0		134.14 ± 51.00	0		7.36 ± 5.98	0		21.54 ± 14.69	0	
Positive	16	163.59 ± 83.80	−6.93 ± 19.70	0.726	118.93 ± 59.68	−15.21 ± 14.70	0.304	10.62 ± 13.97	3.26 ± 2.26	0.153	32.11 ± 31.80	10.57 ± 5.32	0.05
LVI													
Negative	75	164.21 ± 70.53	0		129.12 ± 54.55	0		7.54 ± 6.11	0		21.21 ± 15.84	0	
Positive	7	222.20 ± 42.31	57.99 ± 27.20	0.036	153.10 ± 16.31	23.98 ± 20.81	0.253	12.96 ± 20.19	5.43 ± 3.19	0.092	49.20 ± 34.28	27.99 ± 7.07	<0.001
Pathologic type													
IDC	59	180.83 ± 65.61	12.75 ± 27.22	0.641	140.50 ± 50.02	0.69 ± 19.91	0.973	9.34 ± 9.30	3.13 ± 3.21	0.333	24.95 ± 18.98	5.88 ± 7.88	0.458
ILC	5	167.18 ± 53.52	−0.89 ± 39.80	0.982	131.56 ± 44.08	−8.25 ± 29.11	0.778	6.19 ± 2.64	−0.02 ± 4.70	0.996	24.64 ± 12.41	5.57 ± 11.52	0.63
DCIS	13	119.37 ± 90.85	−48.70 ± 31.86	0.131	85.45 ± 56.54	−54.36 ± 23.31	0.022	3.78 ± 2.49	−2.43 ± 3.76	0.521	19.73 ± 27.50	0.66 ± 9.22	0.943
Etc	5	168.07 ± 38.18	0		139.81 ± 33.02	0		6.21 ± 3.65	0		19.07 ± 7.18	0	
ER													
Negative	22	160.57 ± 74.42	0		120.20 ± 54.32	0		5.87 ± 3.58	0		21.73 ± 18.78	0	
Positive	60	172.31 ± 69.11	11.75 ± 17.58	0.506	135.19 ± 52.06	14.99 ± 13.13	0.257	8.78 ± 9.20	2.91 ± 2.02	0.154	24.29 ± 19.80	2.55 ± 4.87	0.601
PR													
Negative	25	159.42 ± 65.29	0		126.89 ± 55.54	0		6.36 ± 3.68	0		18.58 ± 10.96	0	
Positive	57	173.43 ± 72.53	14.01 ± 16.90	0.41	133.05 ± 51.89	6.16 ± 12.72	0.629	8.72 ± 9.42	2.36 ± 1.95	0.23	25.81 ± 21.89	7.23 ± 4.62	0.122
HER2													
Negative	61	169.96 ± 65.05	0		132.09 ± 48.09	0		7.40 ± 7.93	0		23.09 ± 17.21	0	

(Continued)

Table 2. (Continued)

Variable	n	Mean ± SD	Emax			Emean			Eratio			SD		
			β coefficient	*p*	Mean ± SD	β coefficient	*p*	Mean ± SD	β coefficient	*p*	Mean ± SD	β coefficient		*p*
Positive	21	166.86 ± 85.53	−3.10 ± 17.89	0.863	128.49 ± 65.78	−3.60 ± 13.43	0.789	9.74 ± 8.77	2.33 ± 2.06	0.261	25.08 ± 25.30	1.98 ± 4.95		0.690
Ki67														
<14%	38	166.59 ± 78.51	0		127.91 ± 57.01	0		6.74 ± 4.88	0		22.91 ± 20.54	0		
≥14%	32	176.00 ± 63.84	9.41 ± 17.32	0.589	140.19 ± 53.13	12.29 ± 13.26	0.357	10.68 ± 11.43	3.94 ± 2.04	0.058	24.37 ± 18.20	1.46 ± 4.68		0.756

DCIS, ductal carcinoma *in situ;* E_{max}, max elasticity; E_{mean}, mean elasticity; E_{ratio}, elasticity ratio; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasiveductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; PR, progesterone receptor; SD, standard deviation.
p-values < 0.05 were considered statistically significant.

the formalin-fixed pathologic specimen. Histological grade was determined by the Elston modification of the Scarff–Bloom–Richardson criteria.[23,24] Immunohistochemical staining was performed to determine ER (Novocastra, Newcastle upon Tyne, UK), PR (Novocastra), HER2 (Ventana Medical Systems, Tucson, AZ), and Ki-67 (MIB-1; Dako, Glostrup, Denmark) status. ER and PR status were assessed by nuclear staining, which was graded from 0 to 8 using the Allred score.[25] The results were categorized as positive when the total score, expressed as the sum of the proportion score and immunointensity score, was 3 or more. For HER2 evaluation, membranous staining was graded as follows: score 0, 1, 2, and 3 +.[26] HER2 status was regarded as positive with a score of 3 + and negative with a score of 0 or 1 +. Tumors with a score of 2 + were evaluated using the Zytolight Spec Her2/Cen17 dual color probe kit (ZytoVision, Bremerhaven, Germany) for fluorescence *in situ* hybridization testing, which determines HER2 amplification in the event that the ratio of the HER2 gene signal to chromosome 17 signal is more than 2, which is considered positive. Ki-67 ≥ 14% was considered positive.

Statistical analyses

Quantitative SWE parameter values (E_{max}, E_{mean}, E_{ratio}, and SD) were correlated with clinical, radiologic and pathologic factors using simple linear regression models. For qualitative analysis of color patterns, we used logistic regression. Multiple linear regression analysis with statistically significant variables from the univariate analysis was used to determine variables independently correlated with SWE parameters. All statistical analyses were performed with statistical software SAS (v. 9.2, SAS Institute Inc., Cary, NC). Differences were considered statistically significant at p-value < 0.05.

RESULTS

Demographic and clinical characteristics

The mean age of the 75 females was 57.4 years (range, 32–80 years). The mean pathologic size of tumors was 20.88 ± 17.10 mm and radiologic cancer size was 16.2 ± 7.89 mm. The histologic cancer types were as follows: invasive ductal carcinoma (IDC, n = 59), ductal carcinoma *in situ* (DCIS, n = 10), invasive lobular carcinoma (ILC, n = 5), invasive mucinous carcinoma (IMC, n = 1), mixed invasive ductal and lobular carcinoma (n = 1), invasive apocrine carcinoma (n = 1), histiocytoid variant metaplastic carcinoma (n = 1), and papillary carcinoma (n = 1).

The quantitative SWE parameters of the 82 cancers were as follows: E_{max} 169 ± 70.3 kPa, E_{mean} 131.17 ± 52.76 kPa, E_{ratio} 8.00 ± 8.16, and SD 23.60 ± 19.45 kPa. For qualitative analysis, color patterns 1 and 2 were present in 3 breast cancers and color patterns 3 and 4 were present in 79 masses (Figures 1 and 2).

Correlation of clinicoradiologic factors with quantitative SWE parameters on univariate analysis

Tumor size measured on ultrasound was significantly correlated with higher E_{max} (p < 0.001), E_{mean} (p < 0.001), E_{ratio} (p = 0.001), and SD (p < 0.001). The presence of symptoms such as breast pain and palpability was also significantly associated with E_{max} (p = 0.003), E_{mean} (p = 0.018), E_{ratio} (p = 0.035), and SD (p = 0.050).

Table 3. Correlation of clinicoradiologic factors with color pattern on univariate analysis

Variable	Color pattern		OR (95% CI)	*p*-value
	Negative	Positive		
Age	3 (100.0)	79	1.041 (0.932, 1.163)	0.475
Symptom				
Absent	2 (66.7)	38 (48.7)	0	
Present	1 (33.3)	40 (51.3)	1.753 (0.215, 14.276)	0.600
Ultrasound size				
<10 mm	1 (33.3)	14 (17.7)	0	
10–20 mm	2 (66.7)	43 (54.4)	1.800 (0.207, 15.643)	0.594
>20 mm	0 (0.0)	22 (27.9)	4.655 (0.163, 132.726)	0.368
Thickness				
10–20 mm	2 (66.7)	43 (54.4)	0	
>20 mm	1 (33.3)	36 (45.6)	1.398 (0.172, 11.391)	0.754
Lesion depth				
<10 mm	2 (66.7)	19 (24.1)	0	
≥10 mm	1 (33.3)	60 (75.9)	5.171 (0.622, 42.972)	0.128

CI, confidence interval; OR, odd ratio.
p-values < 0.05 were considered statistically significant.

Older age showed a significant association with higher E_{max} (p = 0.026) and E_{mean} (p = 0.018). There was no significant correlation with lesion depth or breast thickness and SWE parameter values (Table 1).

Correlation of pathologic factors with quantitative SWE parameters on univariate analysis

Table 2 provides a detailed summary of the results. Larger surgical specimen size had a significantly higher E_{max} (p = 0.043) and SD (p = 0.019). Lymphovasular invasion (LVI) was also associated with Emax (p = 0.036) and SD (p < 0.001). There were no significant differences related to lymph nodal status or histologic grade. Although no statistically significant differences were found, histological Grade 3 had higher values of quantitative SWE parameters than the rest. There was no significant difference in SWE parameters between different pathologic types. However, DCIS tended to have lower quantitative values (E_{max} 119.37 kPa, E_{mean} 85.45 kPa, E_{ratio} 3.78, and SD 19.73 kPa) than IDC or ILC. In terms of immunohistochemical biomarkers, there was no significant correlation with SWE parameters and hormonal receptors such as ER and PR. Although there was no significant difference in SWE parameters between Ki-67 positive and negative cancers, Ki-67 positive cancers tended to have higher values for all SWE parameters compared to Ki-67 negative cancers.

Correlation of clinicoradiologic and pathologic factors and color pattern on univariate analysis

There was no significant correlation between color pattern and any variable (Tables 3 and 4). Although there was no significant correlation between pathologic cancer size and color pattern, larger tumors (greater than 20 mm) tended to have a positive color pattern [odd ratio = 11.13, 95% confidence interval (0.478–259.383)] compared to lesions of other sizes. Moreover, IDC with higher histologic grade tended to have a positive color pattern.

Multivariate analysis

For the variables significantly associated with SWE parameters on univariate analysis, multiple linear regression analysis demonstrated that the presence of symptoms was an independent factor for E_{max} (p = 0.003) and E_{mean} (p = 0.018). The β regression coefficient for the presence of symptoms was higher at E_{max} and E_{mean} (46.05, 28.91, respectively) than that without symptoms (Table 5). Mass size on US independently influenced E_{mean} (β coefficient = 1.85, p = 0.035) and E_{ratio} (β coefficient = 0.30, p = 0.035). LVI independently influenced SD (p = 0.009) on multivariate regression analysis. Table 5 provides detailed results.

Comparison of small (≤20 mm) and large tumors (>20 mm)

Mass size on ultrasound was an independent factor for E_{mean} (p = 0.035) and E_{ratio} (p = 0.035) in the multivariate analysis. When tumors were classified by sizes of <10, 10–20 mm, and >20, >20 mm larger tumors had the most significant association with higher stiffness (Table 2). Accordingly, tumors were regrouped into small tumors (≤20 mm) and large tumors (>20 mm) for analysis of pathologic factors, since no pathologic factor other than LVI showed a significant association with SWE parameters. In large tumors (>20 mm), positive lymph node status was significantly correlated with higher SD (p = 0.039). Positive LVI was also significantly associated with higher SD (p = 0.001). No significant difference was found among other factors with quantitative SWE parameters (Table 6).

Table 4. Correlation of pathologic factors with color pattern on univariate analysis

Variable	Color pattern		OR (95% CI)	*p*-value
	Negative	Positive		
Pathologic size	3 (100.0)	79 (100.0)	1.262 (0.981, 1.624)	0.070
Pathologic size				
<10 mm	2 (66.7)	15 (19.0)	0	
10–20 mm	1 (33.3)	30 (38.0)	3.280 (0.379, 28.423)	0.281
>20 mm	0 (0.0)	34 (43.0)	11.131 (0.478, 259.383)	0.134
Histologic grade				
1	0 (0.0)	17 (22.1)	0	
2	3 (100.0)	38 (49.3)	0.314 (0.014, 6.958)	0.464
3	0 (0.0)	22 (28.6)	1.286 (0.022, 75.402)	0.904
Lymph node status				
Negative	3 (100.0)	63 (79.8)	0	
Positive	0 (0.0)	16 (20.2)	1.819 (0.082, 40.209)	0.705
LVI				
Negative	3 (100.0)	72 (91.1)	0	
Positive	0 (0.0)	7 (8.9)	0.724 (0.028, 18.595)	0.846
Pathologic type				
IDC	0 (0.0)	59 (71.9)	7.667 (0.120, 488.030)	0.337
ILC	0 (0.0)	5 (6.3)	0.733 (0.009, 60.153)	0.890
DCIS	3 (100.0)	10 (12.7)	0.200 (0.007, 5.465)	0.340
Etc	0 (0.0)	5 (6.1)	0	
ER				
Negative	1 (33.3)	21 (26.6)	0	
Positive	2 (66.7)	58 (73.4)	1.633 (0.196, 13.597)	0.650
PR				
Negative	1 (33.3)	24 (30.4)	0	
Positive	2 (66.7)	55 (69.6)	1.359 (0.164, 11.233)	0.776
HER2				
Negative	2 (66.7)	59 (74.7)	0	
Positive	1 (33.3)	20 (25.3)	0.574 (0.069, 4.798)	0.609
Ki67				
<14%	2 (100.0)	36 (52.9)	0	
≥14%	0 (0.0)	32 (47.1)	4.452 (0.197, 100.748)	0.348

CI, confidence interval; DCIS, ductal carcinoma *in situ;* ER,estrogen receptor; HER2, humanepidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasivelobular carcinoma; LVI, lymphovascularinvasion; OR, odd ratio; PR, progesterone receptor.
p-values < 0.05 were considered statistically significant.

DISCUSSION

This study investigated correlations between various clinicoradiologic and pathologic features and SWE parameters. For the evaluation of clinical factors, older age was significantly correlated with higher E_{max} and E_{mean} (p = 0.026, 0.018, respectively). The presence of symptoms such as breast pain and palpability was significantly associated with E_{max} (p = 0.003), E_{mean} (p = 0.018), E_{ratio} (p = 0.035), and SD (p = 0.050) on univariate analysis. Multivariate logistic regression analysis showed that the presence of symptoms was significantly associated with higher E_{max} (p = 0.003) and E_{mean} (p = 0.018). These findings are consistent with previous studies. Youk et al[17] demonstrated that palpable abnormalities were significantly associated with E_{mean}. Berg et al reported that E_{ratio} was significantly greater in palpable masses than in nonpalpable masses.[27]

Table 5. Results of multivariate logistic regression analysis for clinicoradiologic and pathologic factors

Variable		Emax			Emean			Eratio			SD		
	Mean ± SD	β coefficient	p	Mean ± SD	β coefficient	p	Mean ± SD	β coefficient	p	Mean ± SD	β coefficient	p
Age	169.16 ± 70.30	0.97 ± 0.58	0.097	131.17 ± 52.76	0.89 ± 0.46	0.055	8.00 ± 8.16	0.08 ± 0.08	0.318	23.60 ± 19.45	0.12 ± 0.17	0.489
Symptom												
Absent	135.20 ± 59.32	0		108.89 ± 47.62	0		6.11 ± 4.10	0		16.66 ± 12.55	0	
Ppresent	199.59 ± 64.56	46.05 ± 15.06	0.003	151.48 ± 49.20	28.91 ± 11.94	0.018	9.93 ± 10.53	0.37 ± 1.97	0.851	30.24 ± 22.76	8.68 ± 4.36	0.050
Ultrasound size	169.16 ± 70.30	2.12 ± 1.08	0.055	131.17 ± 52.76	1.85 ± 0.86	0.035	8.00 ± 8.16	0.30 ± 0.14	0.035	23.60 ± 19.45	0.49 ± 0.31	0.123
Pathologic size	169.16 ± 70.30	0.07 ± 0.44	0.878	131.17 ± 52.76	−0.18 ± 0.35	0.612	8.00 ± 8.16	−0.09 ± 0.06	0.121	23.60 ± 19.45	0.11 ± 0.13	0.388
LVI												
Negative	164.21 ± 70.53	0		129.12 ± 54.55	0		7.54 ± 6.11	0		21.21 ± 15.84	0	
Positive	222.20 ± 42.31	19.16 ± 24.73	0.441	153.10 ± 16.31	−4.54 ± 19.62	0.818	12.96 ± 20.19	2.15 ± 3.23	0.507	49.20 ± 34.28	19.13 ± 7.17	0.009

E_{max}, max elasticity; E_{mean}, mean elasticity; E_{ratio}, elasticity ratio; LVI, lymphovascular invasion; SD, standard deviation.
p-values < 0.05 were considered statistically significant

We found a significant correlation between ultrasound cancer size and SWE parameters, with larger tumors demonstrating significantly higher values of E_{max}, E_{mean}, E_{ratio} and SD. Larger pathologic size of surgical specimens was also correlated with higher E_{max} ($p = 0.043$) and SD ($p = 0.019$). LVI was significantly associated with higher E_{max} ($p = 0.036$) and SD ($p < 0.001$). These findings are similar to other studies. Youk et al[17] reported that larger cancer size ($p = 0.013$) and LVI ($p < 0.0001$) were significantly associated with higher E_{mean}. Choi et al[21] found that larger cancer size ($p = 0.009$) was significantly correlated with higher E_{ratio}. We analyzed cancer size (maximal diameter) separately as measured by either ultrasound images or pathologic reports, whereas previous studies only used one method for size measurement. Au et al[11] determined mean cancer size from ultrasound images by averaging length x height x width and mean cancer size was significantly correlated with higher E_{max}, E_{mean} and E_{ratio} (all $p < 0.001$). Chang et al[20] also determined the maximal tumor diameter from ultrasound, while several groups determined cancer size from pathologic reports.[16,17,21] The results of our study showed the difference between tumor size measured on ultrasound and pathologically confirmed tumor size. Most differences were found in DCIS, a complex pathologic entity, and could be explained by the lack of morphologic changes detected on ultrasound.[28] Previous studies have reported that the presence of DCIS has a significant impact on the accuracy of tumor size measurement.[28,29]

In the multiple linear regression analysis, mass size on US was an independent factor for E_{mean} (β coefficient = 1.85, $p = 0.035$) and E_{ratio} (β coefficient = 0.30, $p = 0.035$). However, pathologic cancer size was not independently associated with SWE parameters. LVI was significantly positively correlated with higher SD ($p = 0.009$). LVI, which means invasion of the tumor into lymphatic spaces or vessels in the peritumoral area, has been associated with poor prognosis in patients with breast cancer.[30] In this study, SD was an independent factor in SWE parameters. Evans et al[15] suggested that SD was useful measurement of heterogeneity, differentiating benign from malignant lesions, because the value was significantly higher in patients with malignant histopathology.

Although there was no significant difference among histologic cancer grades in this study, we found that Grade 3 breast cancers tended to have higher SWE values compared to Grade 1 and 2 cancers, but there was no significant difference between the three histologic grades. Youk et al[17] and Chang et al[20] demonstrated that a higher cancer grade was significantly correlated with higher E_{mean}. Choi et al[21] reported that a higher grade was associated with higher E ratio ($p = 0.015$). However, Ganau et al[18] found no significant correlation between stiffness and histologic grade. In this study, the relatively smaller number of Grade 3 cancers could explain the lack of a significant association of histologic grade with SWE parameters. We demonstrated that DCIS appeared to be softer than IDC or ILC with lower quantitative SWE values. There was only one case of IMC, which was relatively soft (E_{max}: 109.9 kPa, E_{mean}: 89.3 kPa). This observation is expected because IMC has been described as a soft cancer.[11] However, Evans et al[31] reported there were no significant differences in E_{mean} or E_{max}

Table 6. Correlation of pathologic factors withquantitative shear wave elastographic parameters in large tumor (>20 mm)

Variable	n	Emax			Emean			E_{ratio}			SD		
		Mean ± SD	β coefficient	*p*	Mean ± SD	β coefficient	*p*	Mean ± SD	β coefficient	*p*	Mean ± SD	β coefficient	*p*
Histologic grade													
1	5	235.44 ± 44.18			171.36 ± 36.73			10.78 ± 6.73			34.24 ± 8.36		
2	9	201.8 ± 88.92	−33.64 ± 36.05	0.361	150.72 ± 59.23	−20.64 ± 26.7	0.448	8.39 ± 6.54	−2.39 ± 6.85	0.730	38.64 ± 38.97	4.4 ± 14.38	0.762
3	10	233.42 ± 43.06	−2.02 ± 35.41	0.955	185.13 ± 40.34	13.77 ± 26.22	0.605	18.78 ± 17.15	8 ± 6.73	0.248	29.08 ± 13.07	−5.16 ± 14.12	0.719
Lymph node status													
Negative	17	221.94 ± 63.67			173.15 ± 48.83			11.23 ± 9.01			27.09 ± 13.02		
Positive	7	222.09 ± 69.25	0.14 ± 29.3	0.996	160.14 ± 49.59	-13.01 ± 22.02	0.561	18.05 ± 19.1	6.82 ± 5.65	0.241	49.9 ± 38.96	22.81 ± 10.41	0.039
LVI													
Negative	20	217.53 ± 67.03			173.33 ± 51.78			12.26 ± 8.67			26.74 ± 16.96		
Positive	4	244.25 ± 44.29	26.72 ± 35.27	0.457	149.5 ± 17.42	-23.83 ± 26.59	0.380	18.04 ± 26.95	5.78 ± 7.01	0.419	68.78 ± 31.85	42.04 ± 10.77	0.001
Pathologic type													
IDC	21	230.07 ± 55	40.87 ± 56.29	0.476	174.43 ± 42.02	23.93 ± 43.01	0.584	14.2 ± 13.28	7.1 ± 13.59	0.607	34.66 ± 25.97	3.26 ± 26.58 13.1 ± 36.73 -25.4 ± 36.73	0.904
ILC	1	256.70	67.5 ± 77.78	0.396	208.20	57.7 ± 59.43	0.343	9.79	2.69 ± 18.78	0.888	44.50	13.1 ± 36.73	0.725
DCIS	1	50.30	−138.9 ± 77.78	0.089	42.80	−107.7 ± 59.43	0.085	2.13	−4.97 ± 18.78	0.794	6.00	−25.4 ± 36.73	0.497
Etc	1	189.20			150.50			31.0			31.40		
ER													
Negative	6	210.25 ± 22.01			166.35 ± 21.43			8.26 ± 4.74			24.55 ± 14.11		
Positive	18	225.89 ± 72.8	15.64 ± 30.57	0.614	170.36 ± 54.97	4.01 ± 23.28	0.865	14.87 ± 14.16	6.61 ± 5.96	0.280	36.81 ± 27.36	12.26 ± 11.77	0.309
PR													
Negative	6	219.08 ± 41.61			180.03 ± 41.42			8.94 ± 4.46			22.92 ± 10.97		
Positive	18	222.95 ± 70.67	3.87 ± 30.74	0.901	165.8 ± 51.02	−14.23 ± 23.1	0.544	14.64 ± 14.29	5.7 ± 6.01	0.353	37.35 ± 27.5	14.43 ± 11.66	0.229
HER2													
Negative	16	224.49 ± 64.9			165.4 ± 47.11			11.89 ± 13.55			34.01 ± 23.99		
Positive	8	216.96 ± 65.62	−7.53 ± 28.2	0.792	177.28 ± 53.04	11.88 ± 21.25	0.582	15.88 ± 11.2	4 ± 5.56	0.480	33.2 ± 28.69	−0.81 ± 11.08	0.942
Ki67													
<14 %	8	244.1 ± 70.81			168.74 ± 46.63			11.64 ± 7.1			42.29 ± 30.23		
≥14 %	14	222.93 ± 43.66	−21.17 ± 24.25	0.393	179.27 ± 40.26	10.53 ± 18.88	0.583	15.38 ± 15.48	3.74 ± 5.84	0.529	31.63 ± 22.3	−10.66 ± 11.24	0.354

among tumor types such as lobular, mucinous, papillary and metaplastic cancers.

In this study, no immunohistochemical profile of breast cancers was associated with SWE parameters. There was no significant correlation with SWE parameters and hormonal receptors such as ER and PR. In this study, positive Ki-67 expression tended to be associated with higher quantitative SWE values (E_{max}, E_{mean}, E_{ratio} and SD), although this trend did not reach statistical significance. We postulated that Ki-67 expression could be explained by high stiffness on SWE, as it is considered a marker of cellularity.[32]

Since none of the pathologic factors except LVI were significantly associated with SWE parameters, tumors were regrouped into small tumors (≤20 mm) and large tumors (>20 mm) for analysis of pathologic factors. In large tumors (>20 mm), positive lymph node status was significantly correlated with higher SD (p = 0.039). Positive LVI was also significantly associated with higher SD (p = 0.001). No significant difference was found among other factors with quantitative SWE parameters. A recent study by Denis et al[33] found that tumor size was an independent factor for E_{mean}, but the other pathologic factors, including histologic grade and immunohistochemical profiles, were not significantly associated with E_{mean}.

There was no significant correlation between color pattern and any variable. To date, recent studies have focused on correlation of quantitative SWE factors and clinicopathologic factors in breast cancer. However, there have been a few previous studies concerning color map patterns in breast cancer.[34] Lee et al[34] demonstrated an association between color map patterns and clinicopathologic factors in breast cancer. They divided color map patterns into three main categories: Type 1 (diffuse pattern), Type 2 (lateral pattern), and Type 3 (rim-off pattern). In our study, the color map pattern was classified into two main categories: color patterns "1" and "2" *vs* color patterns "3" and "4". Although we observed no significant differences among color patterns, this research has significance in its efforts to investigate correlations between qualitative SWE features and clinicopathologic factors. Further studies on the prognostic value of color map patterns are necessary with a larger study population.

There were several limitations of this study. First, the retrospective design might unavoidably have selection bias, because only excised breast lesions with preoperative SWE and available immunohistochemical profiles were included. Second, only one radiologist measured SWE parameters of each breast cancer. However, SWE parameters have been proven to be highly reproducible with high intra-and interobserver agreement.[35,36] Third, the number of cancers was relatively small. In particular, the qualitative analysis of color patterns was limited because there were only three cases with a color pattern of "1" or "2", precluding definite conclusions about the correlation of SWE parameters and color patterns. However, the strength of this study is that it was a comprehensive assessment of both quantitative and qualitative SWE parameters. Further study with a larger number of patients may enlarge the clinical significance of our findings.

CONCLUSION

The presence of symptoms, older age, larger tumor size on US, larger pathologic cancer size, and LVI were significantly correlated with higher quantitative SWE factors on univariate analysis. Among these variables, the presence of symptoms was an independent factor for E_{max} and E_{mean} on multivariate analysis. Mass size on US was independently correlated with E_{mean} and E_{ratio}. LVI was independently correlated with SD. Accordingly, tumor stiffness measured by SWE and B-mode US could help predict cancer prognosis.

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