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Accuracy of tumor size measurement on shear wave elastography (SWE)
Correlation with histopathologic factors of invasive breast cancer

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Abstract

The aim of this study is to investigate the accuracy of tumor size assessment by shear wave elastography (SWE) in invasive breast cancer and also evaluated histopathologic factors influencing the accuracy.

A total of 102 lesions of 102 women with breast cancers of which the size was 3 cm or smaller were included and retrospectively analyzed. Tumor size on B-mode ultrasound (US) and SWE were recorded and compared with the pathologic tumor size. If tumor size measurements compared to pathological size were within ±3 mm, they were considered as accurate. The relationship between the accuracy and histopathologic characteristics were evaluated.

The mean pathologic tumor size was 16.60 ± 6.12 mm. Tumor sizes on SWE were significantly different from pathologic sizes (18.00 ± 6.71 mm, $P < 0.001$). The accuracy of SWE (69.6%) was lower than that by B-mode US (74.5%). There was more size overestimation than underestimation (23.5% vs 6.9%) using SWE. Conversely, there was more size underestimation than overestimation (18.6% vs 6.9%) using B-mode US. The accuracy of SWE was associated with ER positivity ($P = .004$), PR positivity ($P = .02$), molecular subtype ($P = .02$), and histologic grade ($P = .03$). In the multivariate analysis, ER positivity ($P = .002$) and molecular subtype ($P = .027$) significantly influenced the accuracy of tumor size measurement by SWE.

In conclusion, the accuracy of the tumor size measured with SWE was lower than that measured with B-mode US and SWE tends to overestimate the size. ER positivity and molecular subtype are significantly associated with the accuracy of SWE in tumor size assessment.

Abbreviations: ACR = American College of Radiology, BI-RADS = Breast Imaging Reporting and Data System, DCIS = ductal carcinoma in situ, ER = estrogen receptor, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, IRB = Institutional Review Board, MRI = magnetic resonance imaging, PR = progesterone receptor, PTS = peritumoral stiffness, SWE = shear wave elastography, US = ultrasound.

Keywords: breast cancer, tumor size, shear-wave elastography, ultrasound

1. Introduction

Accurately measuring the size of breast cancer before surgery is not only an essential factor in determining the surgical method

but also plays an important role in determining the patients prognosis. Most patients with small breast cancer undergo breast-conserving surgery, which requires accurate knowledge of the size of the mass, so surgeons can completely remove the breast cancer and minimize the loss of normal breast tissue to enhance the patient's cosmetic satisfaction.

Tumor size in breast cancer patients can be measured by clinical examination and imaging studies such as mammography, ultrasound (US), and magnetic resonance imaging (MRI).[1–3] Although MRI is the most accurate imaging modality for determining tumor extent in breast cancer, routine use of preoperative breast MRI is controversial because increased mastectomy rate is associated with MRI without improving patient outcomes.[4,5] Therefore, breast US remains the mainstay for tumor size estimation in many institutions and guiding method in the medical procedures.[6,7] However, it has already known that the US tends to underestimate tumor size and increases the likelihood of incomplete excision of the tumor and a positive resection margin with a subsequent increase in the chance of tumor recurrence.[8–10]

Shear wave elastography (SWE) increases the sensitivity and specificity of breast cancer diagnosis and can be performed at the time of preoperative US before surgery, which has the advantage of obtaining highly reproducible and quantitative information.[11–15] Breast cancers often show a "stiff rim" sign, which refers to areas of increased stiffness at the tumor margin. The

presence of the stiff rim sign in malignant lesions might have several explanations. The first explanation is a desmoplastic reaction or the infiltration of cancer cells into the interstitial tissues.[12,16] The second one is the low shear wave amplitude or noise within the malignant lesion, which might be caused by attenuation of the energy of the shear wave in the peritumoral region of the lesion.[17,18] However, what the stiff rim of SWE is not certainly pathologically proven.[19]

In the clinical field, when we measure the size of breast cancer using US and SWE, for certain cancers, we have experienced that tumor size including the stiff region of SWE correlates well with the pathological tumor size than the size measuring the hypoechoic area of B-mode US. Although several studies have been published on the accuracy of mass size measurement on SWE and US, to our knowledge, the association of the accuracy of breast cancer size measurement on SWE and histopathologic characteristics of breast cancer has never been evaluated.[14,20]

Therefore, we aimed to investigate the accuracy of tumor size assessment by SWE in invasive breast cancers and also evaluated histopathologic factors influencing the accuracy.

2. Methods

2.1. Study population

The Institutional Review Board of our institution approved this retrospective study. The requirement of informed consent was waived due to its retrospective nature. Between January 2015 and December 2017, a total of 206 consecutive patients with surgical and histological diagnosis of invasive breast cancer underwent mammography, US, and SWE at our institution. Among these 206 patients, those who had a prior history of breast radiation or mastectomy (n=15) or interstitial mammoplasty (n=2), those who were lost to follow-up (n=26), and those who underwent neoadjuvant chemotherapy (n=19) were excluded from this study. Also, we only included tumors measured 3 cm or smaller because the full diameter of the SWE region-of-interest (ROI) box was 3 cm. When patients had multifocal or multicentric breast cancers, we only evaluated index cancer. Finally, a total of 102 lesions from 102 patients were evaluated in this study.

2.2. Breast US and SWE examination

Conventional B-mode US and SWE were performed with knowledge of clinical and mammographic findings using a 4 to 15 MHz transducer with Aixplorer System (Supersonic Imagine, Aix en Provence, France) by 1 of 3 board-certified radiologists (each with 5–10 years of experience in breast ultrasound and SWE). All radiologists were well informed of clinical and mammographic findings of the patient before US examinations. The size of the tumor was measured in transverse and longitudinal planes and the largest diameter recorded in the US image was used in this study.

After the conventional US, SWE was conducted by the same radiologist. The built-in ROI (Q-box; Supersonic Imagine) of the system was set to include the mass and the surrounding breast parenchyma tissue which demonstrated a semi-transparent color map of tissue stiffness overlaid on the B-mode image. The color map ranged from dark blue indicating the lowest stiffness to red indicating the highest stiffness (0-180 kPa). The size of each ROI box was 2.5×1.5 cm by default, with a maximal size of 3×2.5 cm.

Quantitative elasticity values were measured in all cases via two 3 mm-diameter circular quantification ROIs. One was placed by the investigator on the hardest portion of the lesion while the other ROI was placed on the soft normal fatty tissue. The system automatically calculated and visualized the maximum elasticity (E_{max}), mean elasticity (E_{mean}), standard deviation (E_{SD}), and elasticity ratio (E_{ratio}, the ratio of E_{mean} value in the stiffest portion of the mass to the E_{mean} value of normal fatty tissue).

2.3. Image analysis

The maximum diameter of the main tumor measured in the same plane by B-mode US and SWE was compared to the lesion size described in the pathologic report. Soft breast lesions were homogeneously blue on SWE, as was surrounding normal fat tissue. The SWE size was comparable to conventional B-mode US size because the transparency setting revealed B-mode US images throughout the blue map. The SWE size of heterogeneously stiff breast lesions was measured on the color map, including the entire heterogeneous component (Fig. 1).

Tumor size measurements were carried out in consensus by 2 radiologists with 8 to 15 years of experience in breast imaging on a dedicated workstation without any knowledge of the final pathological results. For each breast mass, tumor size measurement was performed 3 times. If tumor size measurements compared with pathological size were within ±3 mm, they were considered as accurate. The tumor was considered overestimated or underestimated if the size of the tumor was >3 mm larger or smaller than the pathologic tumor size. Most of the previous studies used the standard of concordance defined a difference of <5 mm as concordant.[21] However, as we only included the small (≤3 cm) breast cancers, some strict standard with a difference of <3 mm was used for evaluation of accuracy.

2.4. Histopathological analysis

A core biopsy was performed after imaging studies were completed. All patients in this study underwent and mastectomy (n=10), or breast-conserving surgery (n=92). The tumor size on the final pathologic report was considered as a standard reference. Histologic diagnoses were made by 1 of 3 pathologists with 16 to 20 years of experience in breast histological evaluation. Tumor diameter, histological type, histological or nuclear grade, and levels of estrogen receptor (ER), progesterone receptor (PR), and HER2 were evaluated based on surgical and histopathological findings. ER and PR positivity were defined using a cut-off value of 10%. HER2 expression was considered negative when the immunohistochemical result was negative or had a staining score of 1+. Otherwise, it was considered positive when the staining score was 3+. HER2 results based on fluorescence in situ hybridization were preferred over immunohistochemical results. The Ki 67 index was dichotomized into tumors expressing low and high Ki-67 indices using a 20% cutoff. A molecular subtype of the tumor was classified into 4 subtypes: luminal A (ER–positive and/or PR-positive, HER2-negative, and low Ki-67); luminal B (ER–positive and/or PR-positive and HER2-positive or HER2-negative with high Ki-67); HER2-enriched (ER-negative, PR-negative, and HER2-positive); and triple-negative (ER-negative, PR-negative, and HER2-negative) subtypes.
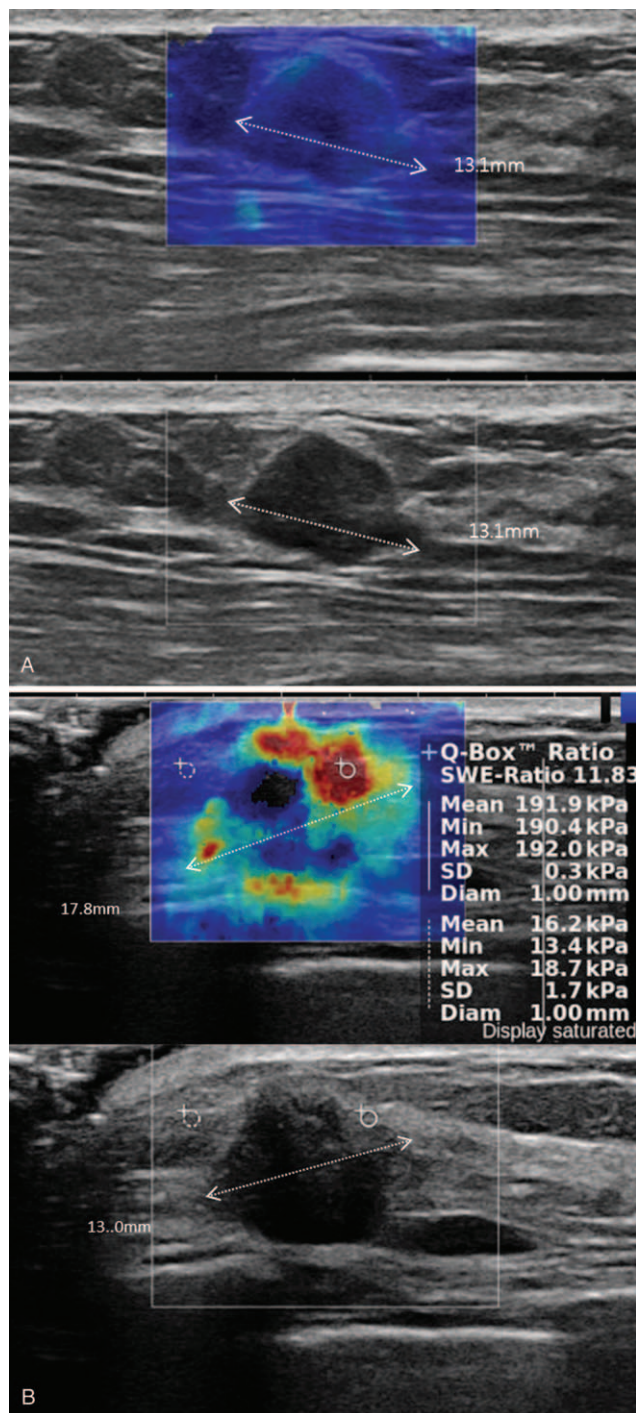
Figure 1. (a) Examples of tumor size measurements by B-mode US and SWE. (a) SWE size on the color map is the same as B-mode US size (13.1 mm) in the soft lesion. (b) Examples of tumor size measurements by B-mode US and SWE. (b) SWE size corresponding to the maximum diameter of the heterogeneous component on color map (17.8 mm, superior part) is larger than B-mode US size (13.0 mm, inferior part).

2.5. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) while categorical variables are presented as frequencies and percentages. The maximum lesion sizes estimated with B-mode US and SWE were compared with pathologic sizes using paired t test. We compared pathological characteristics (hormone receptor status, lymphovascular invasion, histological grade, and molecular subtype) and quantitative elasticity values (E_{max}, standard deviation, and elasticity ratio) between accurate and inaccurate groups using the Chi-squared test and Wilcoxon rank sum test. Univariate and multivariate logistic regression analyses were performed to identify independent variables associated with the accuracy of tumor size measurements on SWE. All statistical analyses were performed using SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was considered if the P value was less than .05.

3. Results

This study included 102 invasive breast cancers in 102 patients. Their age ranged from 36 to 80 years (mean age: 54.0 years). There were 37 premenopausal (36%) and 65 postmenopausal women (64%). Histopathological diagnosis revealed invasive ductal carcinoma (IDC, n=81, 79.4%), invasive lobular carcinoma (ILC, n=6, 5.9%), mucinous carcinoma (n=4, 3.9%), papillary carcinoma (n=3, 2.9%), tubular carcinoma (n=3, 2.9%), and other histological types (n=5, 4.9%).

The mean pathologic tumor size was 16.60 ± 6.12 mm. Among 102 breast tumors, 82(80.4%) were ≤2 cm and 20 (19.6%) were >2 cm. Tumor size varied from 7 to 30 mm in the B-mode US (mean: 16.08 ± 6.27 mm) and from 5 to 35 mm in SWE (mean: 18.00 ± 6.71 mm). Tumor sizes on SWE were significantly different from pathologic sizes (18.00 ± 6.71 mm, $P < .001$). However, tumor sizes on the B-mode US were not significantly different from pathologic sizes (16.08 ± 6.27 mm, $P = .61$). The mean differences in tumor size between SWE and B-mode US compared with pathology were 1.39 ± 3.40 mm and −0.52 ± 2.66 mm.

Based on our standard (within ± 3 mm), the overall accuracy of tumor size by the B-mode US was 74.5% (76/102) and that by SWE was 69.6% (71/102). There was more size underestimation (18.6%, 19/102) than overestimation (6.9%, 7/102) based on the B-mode US. Conversely, there was more size overestimation (23.5%, 24/102) than underestimation (6.9%, 7/102) using SWE.

A comparison of histopathologic characteristics affecting the accuracy of tumor size assessment by SWE is shown in Table 1. The accuracy of SWE was associated with ER positivity ($P = .004$), PR positivity ($P = .02$), molecular subtype ($P = .02$), and histologic grade ($P = .03$) (Fig. 2). Of a total of 53 luminal A tumors, 43 (81%) were accurately measured. Meanwhile, 40% (4 of 10) HER2-enriched tumors and 55% triple-negative tumors (11 of 20) were accurately measured. All quantitative elasticity values between tumors measured accurately and inaccurately by SWE showed no statistically significant differences (Table 2). For patients with ILCs (n=6), B-mode US and SWE accurately measured tumor sizes in 3 patients but underestimated sizes in the remaining 3 patients. The mean difference was −5.83 mm ± 2.32 for the B-mode US and −3.59 mm ± 1.52 for the SWE.

In the multivariate analysis, ER positivity ($P = .002$) and molecular subtype ($P = .027$) significantly influenced the accuracy of tumor size measurement by SWE (Table 3). For the luminal A subtype breast cancers, when the sizes on the B-mode US were converted to the sizes measured on SWE, the overall accuracy of the B-mode US for luminal A cancers increased from 71.7% (38 of 53) to 81.1% (43 of 53) ($P = .03$).

Table 1

Histopathologic factors influencing accuracy of tumor size measurements by SWE.

Characteristics	Accurate (n=71)	Inaccurate (n=31)	Total 102	P value
Estrogen receptor				.004
Negative	15 (21.1)	16 (51.6)	31	
Positive	56 (78.9)	15 (48.4)	71	
Progesterone receptor				.016
Negative	28 (39.4)	21 (67.7)	49	
Positive	43 (60.6)	10 (32.3)	53	
HER-2				.200
Negative	54 (76.1)	19 (61.3)	73	
Positive	17 (23.9)	12 (38.7)	29	
Molecular subtype				.021
Luminal A	43 (60.6)	10 (32.2)	53	
Luminal B	13 (18.3)	6 (19.4)	19	
HER-2 positive	4 (5.6)	6 (19.4)	10	
Triple negative	11 (15.5)	9 (29.0)	19	
Lymphovascular invasion				.189
Negative	60 (84.5)	22 (71.0)	82	
Positive	11 (15.5)	9 (29.0)	20	
Histologic grade				.027
1	11 (15.5)	2 (6.5)	13	
2	37 (52.1)	10 (32.2)	47	
3	23 (32.4)	19 (61.3)	42	

4. Discussion

In this study, we found that tumor size measurements on SWE were significantly different from the histopathologic measurements. The overall accuracy of SWE for tumor size estimation was lower (69.6%) than that of B-mode US (74.5%). There was a more size overestimation of 23.5% (24/102) than an underestimation of 6.9% (7/102) using SWE. Conversely, tumor sizes based on the B-mode US were underestimated in 18.6% (19/102) and overestimated in 6.9% (7/102). Although several studies have compared accuracies of preoperative tumor size assessment on US and elastography, there are inconsistencies in results.[22–24] Such discrepancy in results might be due to differences in study design, like as study group (including patients with benign masses and only patients with malignant masses) and type of elastography (static and shear wave). Similar to our result, Zippel et al,[25] have reported that breast elastography, but not B-mode US, would overestimate the size of breast tumors compared with final pathologic measurement. Even though we only included tumors measured 3 cm or smaller because it is difficult to accurately measure the size when the mass is larger than the full size of SWE ROI, the tumor sizes on SWE were significantly different from pathologic sizes. From these results, it is limited to use SWE as a primary method for tumor sizing.

We evaluated histopathologic factors influencing the accuracy of tumor size measurement on SWE. Surprisingly, ER positivity (P=.002) and molecular subtype (P=.027) significantly influenced the accuracy of tumor size measurement by SWE. To the best of our knowledge, this is the first study correlating accuracy in tumor size assessment by SWE with a molecular subtype of breast cancer. During the last 15 years, many studies have reported imaging features according to molecular subtypes of breast cancer. Triple-negative breast cancer is more likely to be seen as a mass with relatively circumscribed margins but less likely to show posterior shadowing on B-mode US.[26] Unlike
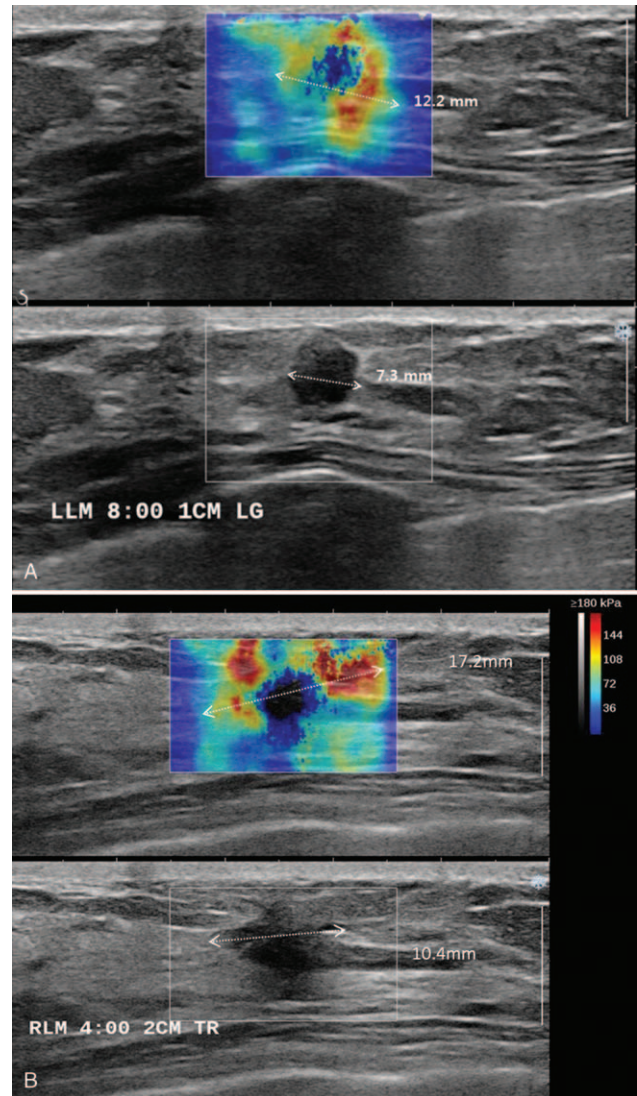

Figure 2. (a). A 57-year-old woman diagnosed with left breast cancer (invasive ductal cancer, triple-negative subtype). The tumor size on SWE was 12.2 mm (superior part). However, B-mode US size was 7.3 mm which showed agreement with pathologic tumor size (inferior part). (b). A 43-year-old woman diagnosed with right breast cancer (invasive ductal cancer, Luminal A type). The tumor size on SWE was 17.2 mm (superior part). However, the B-mode US size was 10.4 mm (inferior part). Pathologic tumor size (16.0 mm) showed agreement with tumor size by SWE.

triple-negative breast cancer, ER-positive cancers often present as an irregular mass with an indistinct margin on breast US.[27,28] During the measurement of the size of breast cancer using B-mode US, a few radiologists have only assessed the hypoechoic portion

Table 2

Quantitative elasticity values influencing accuracy of tumor size measurements by SWE.

Elasticity values	Accurate	Inaccurate	P value
E_max (kPa)	113 (range, 63.5–167.5)	121 (range, 79.3–165.4)	.063
E_ratio	9.1 (range, 5.4–16.3)	9.0 (range, 5.5–11.5)	.419
E_sd (kPa)	5.5 (range, 3.1–9.9)	6.2 (range, 3.2–10.6)	.741

E_{max} = maximum elasticity, E_{ratio} = elasticity ratio, E_{sd} = standard deviation.

Table 3

Multivariate logistic regression analysis of possible factors influencing the accuracy of tumor size measurement by SWE.

Factors	Estimate (95% CI)	P value
Estrogen receptor		.002
Negative	0.285 (0.099-0.823)	
Positive	Reference	
Molecular subtype		.027
Others	0.479 (0.249-0.922)	
Luminal A	Reference	

of the lesion while others have measured the largest tumor diameter including the echogenic halo around the hypoechoic lesion. A possible explanation for US-pathology discordance in size for ER-positive cancer is that it is difficult to determine the extent of a tumor by the B-mode US due to vague tumor margin. It was reported that the measurement including hyperechoic halo is superior to measurements limited to the tumors hypoechoic nucleus.[23] In this study, for the luminal A subtype breast cancers, when the sizes on B-mode US were converted to the sizes measured on SWE, the overall accuracy of the B-mode US for luminal A cancers increased from 71.7% to 81.1%. Similar to this study, Mullen R. reported that including the peritumoral stiffness (PTS) size on SWE with grey-scale breast US led to a significantly accurate estimation of final histological size.[29] The results of these studies suggest that when breast cancer appears to be significantly smaller in B-mode US than SWE, following the size seen in SWE can improve the accuracy of tumor sizing for luminal A cancers.

If so, an important, but unanswered question is why the SWE was more accurate in the assessment of tumor size for luminal A subtype breast cancers? Then, can we make the following hypothesis that the meaning of "stiff" boundary on SWE may vary for molecular subtypes? Careful evaluation of peritumoral stiffness on elastography for pathological significance has not been performed yet. Peritumoral stiffness might be secondary to desmoplastic reaction or peritumoral infiltration of cancer cells.[12,16] A number of studies have shown that ER-positive cancers more frequently present as irregular masses or non-mass-like lesions associated with ductal carcinoma in situ than triple-negative breast cancers.[26,30] Tiny invasive tumor infiltration or accompanying DCIS might not present as a subtle echogenic halo which can be easily excluded from tumor size measurement on conventional breast US. However, based on tissue elasticity imaging, elastography might facilitate the differentiation of areas with malignant infiltration that are usually harder than surrounding soft tissues. Based on our results, it can be suggested that the stiff boundary on SWE for luminal A subtype breast cancers represented the "true" tumor margin including microscopic tumor infiltration or accompanying DCIS. Meanwhile, the stiff boundary on SWE might suggest a different meaning in triple-negative breast cancers. Barr et al,[17] have explained that the presence of stiff rim in hard cancers from the low shear wave amplitude and/or noise might be caused by attenuation of the energy of the shear wave in the peritumoral region of the lesion. Triple-negative breast cancer manifests as a marked hypoechoic distinct mass on the US. The low incidence of the peripheral echogenic halo can be explained by rapid tumor growth.[31] These findings represent high cellularity and high histological grade of triple-negative breast cancer.[32] In other words, the stiff

boundary of triple-negative breast cancers on SWE might indicate a noise or "pseudo" margin from low shear wave amplitude due to attenuation of shear wave energy by histologic characteristics.

Although the number of patients with ILC was small, B-mode US and SWE were equally inaccurate. They underestimated the size. ILC tends to spread diffusely or produce a minimal desmoplastic reaction, resulting in underestimation of tumor size on imaging.[33] Therefore, B-mode US and SWE should not be used as standard imaging methods for tumor size estimation in patients with ILC.

Our study has several limitations. First, it was a retrospective study based on a single institution. Second, the sample size was relatively small while malignant tumors were mostly invasive ductal cancers. Third, we did not evaluate intra- or inter-observer variability to determine SWE parameters. However, SWE is known to be a highly reproducible and an operator-independent modality. Furthermore, all radiologists in this study had >5 years of experience with breast US and SWE. Therefore, we believe that these limitations have little effect on our results. Finally, although pathologic tumor size is the gold standard, tumors might be distorted or shrunk during their removal and fixation of the surgical specimen.

In conclusion, the accuracy of SWE in measuring the tumor size is less than that of B-mode US and SWE tends to overestimate the size. However, ER positivity and molecular subtype are significantly associated with the accuracy of SWE in tumor size assessment. Also, converting the size on B-mode US of luminal A breast cancer to the size measured on SWE led to a more accurate estimation of the true pathologic size. It would be a potential additive role of SWE in the size measurement of breast cancer.

Author contributions

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