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Original Article

# The role of shear wave elastography in determining molecular subtypes in breast cancer

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***ABSTRACT***

**Objectives:** This study aimed to measure with shear wave elastography (SWE) the stiffness degree, which is a phenotypic reflection of the tumor in patients with breast cancer, and to manifest how the measured value relates to prognostic factors and molecular subtypes.

**Materials and methods:** This study included 99 female patients (mean age 48 years; range 29 to 78 years) diagnosed with breast cancer, underwent SWE, and received treatment at the Breast Health Center of Istanbul Florence Nightingale Hospital between January 2014 and March 2016. Those excluded were the patients who previously had an operation on the same breast or axillary fossa, who had noninvasive breast cancer, and who received neoadjuvant chemotherapy.

**Results:** A positively significant correlation was determined between the tumor diameter and the elastography value (p=0.001, r=0.32). There was no significant difference between elastography values of the tumors and histological type, intraductal component presence, histological grade, lymphovascular invasion, lymph node metastasis, Ki67 value, hormone receptor status, and molecular subtype.

**Conclusion:** In our study, it was shown that there was a positive correlation between elastography values and tumor size. No significant relationship was found between elastography values and other parameters. However, further studies with larger series may provide additional significant links.

***Keywords:*** Breast cancer, elastography, molecular subtype, shear wave, ultrasonography.

Breast cancer is a heterogeneous disease having many different histological types. Determining prognostic and predictive factors plays a key role in the development of a suitable treatment approach. Prognostic factors of breast cancer are tumor stage, lymph node metastasis, tumor size, and molecular subtype of the tumor.[1] In many studies, it was shown that the survival

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rate in breast cancer incidents is connected with tumor stage and molecular subtype as well.[2-4]

Gene expression studies show that different tumor molecular subtypes provide different clinical and radiological findings.[1] In terms of etiology, prognosis, and response to treatment, breast cancers are divided into four molecular subtypes by using immunohistochemical staining findings. These are luminal A and B, human epidermal growth factor receptor 2 (HER-2), and basal-like/triple-negative groups.[5] In this respect, estrogen receptor (ER), progesterone receptor (PgR), and HER-2 positivity are taken as a basis. Luminal subtypes are divided into two groups as luminal A and luminal B according to PgR positivity rate and Ki67 proliferation rate.[6,7] In breast cancer cases, subtype classification determines how general treatment approach will be, and it is essential to form an effective strategy for the treatment of the disease.

Shear wave elastography (SWE) is a method used to measure the elasticity difference with the tissue around a lesion.[8] Shear wave elastography ensures to measurement of the stiffness of the lesion quantitatively. When compared to the compression technique, it was found that SWE did not have any significant difference among different operators.[8] It was stated that elasticity measurements besides grey scale ultrasonography (USG) are useful in the diagnosis of malign breast tumors, and it was demonstrated that these masses are of stiffer structure than normal parenchymal structures and tumors.[9,10] Therefore, SWE is used to determine the stiffness degree of the tumor and distinguish the tumors as benign or malign.[9,10] In some studies, it was reported that the quantitative stiffness degrees of invasive ductal carcinoma is higher than ductal carcinoma *in situ*.[11,12] There are also some studies suggesting that having a higher level of stiffness with SWE indicates a poor prognosis in invasive breast cancer.[12] In the study by Evans *et* al.,[13] it was stated that high tumor stiffness is associated with tumor size, lymph node metastasis, and high histologic grade.

In this study, it is aimed to measure with SWE the stiffness degree, which is a phenotypic reflection of the tumor in patients with breast cancer, and to manifest how the measured value relates to prognostic factors and molecular subtypes.

## MATERIALS AND METHODS

Among 112 patients, 99 female patients (mean age 48 years; range 29 to 78 years), who underwent SWE with the diagnosis of breast cancer at the Breast Health Center of Istanbul Florence Nightingale Hospital between January 2014 and March 2016, who were diagnosed with invasive breast cancer and did not receive neoadjuvant treatment, and who previously did not have an operation on the same breast or axillary fossa, were included in this study. A written consent was obtained from each patient. The study protocol was approved by the Istanbul Bilgi University Ethics Committee (Date: 25/07/2019-No: 2019-40016-125). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Radiologic evaluation of the patients was made by two radiologists, who have at least 10 years of experience in breast radiology and five years of experience in elastography, by conventional USG and subsequent SWE (Siemens Acuson S3000 US®; Siemens Healthcare, Erlangen, Germany). After adjusting the elastography window in such a way that the tumor was wholly covered with 9L4 transducer in the range of 4-9 MHz during the examination, first qualitative (colored elastography) and then quantitative measurements (at 10 parts of the tumor at least) were carried out, and the values obtained were recorded. Shear wave velocities were quantitatively measured by using Virtual Touch Tissue Quantification (VTTQ). Average tumor elastography value was recorded.

Histopathological categorization was made based on the World Health Organization's classification.[10] In microscopic evaluation of ER, PgR, and HER-2, criteria suggested by the American Society of Clinical Oncology (ASCO)/College of American Pathologists were taken as a basis.[14] For ER and PgR tumor cells, the existence of ≥1% of stained cells was accepted as positive. For HER-2 positivity, standard criteria were applied, and a score of 0 and 1 were accepted as negative, a score of 2 as suspicious positive, and a score of 3 as positive.[14] In the tumors with a score of 2 (suspicious), gene amplification existence was examined by *in situ* hybridization method, and the tumors, in which amplification was determined, were accepted as HER-2 positive. Tumors were divided into four molecular subtypes

according to *"St. Gallen International Expert Panel"* consensus: luminal A (ER +, PgR ≥2%0, HER-2 -, and Ki-67 <14%), luminal B (ER + and PgR <20%, HER-2 +, or Ki- 67 ≥14%), HER-2 positive (HER-2+ and ER-, PgR -), basal-like/triple-negative (ER-/HER-2- and PgR -).[6,7]

### Statistical analysis

Statistical analysis was performed by using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Compatibility of variables with normal distribution was examined with visual

**Table 1.** Histologic features of the tumors and the relationship between molecular subtypes and median elastography values

| | n | Median elasto value (m/s) | *p* |
|---|---|---|---|
| Age (year) | | | 0.28* |
| <50 | 54 | 5.78 (3.84-6.46) | |
| ≥50 | 45 | 5.70 (4.02-6.50) | |
| Histologic type | | | |
| Invasive ductal carcinoma | 77 | 5.76 (3.84-6.50) | 0.615** |
| Invasive lobular carcinoma | 10 | 5.70 (4.30-6.15) | |
| Other types | 12 | 5.92 (4.42-6.20) | |
| Tumor size (mm) | | | 0.016* |
| ≤20 | 54 | 5.63 (3.84-6.46) | |
| >20 | 45 | 5.87 (4.57-6.50) | |
| Histologic grade | | | 0.27** |
| I | 8 | 5.25 (4.42-6.43) | |
| II | 53 | 5.80 (3.84-6.50) | |
| III | 38 | 5.80 (4.33-6.39) | |
| Lympho-vascular invasion | | | 0.54* |
| Yes | 40 | 5.80 (4.21-6.39) | |
| No | 59 | 5.72 (3.84-6.50) | |
| Intraductal component | | | 0.80* |
| Yes | 72 | 5.78 (4.21-6.46) | |
| No | 27 | 5.70 (3.84-6.50) | |
| Lymph node metastasis | | | 0.41* |
| Yes | 43 | 5.80 (4.36-6.39) | |
| No | 56 | 5.73 (3.84-6.50) | |
| ER | | | 0.53* |
| Positive | 84 | 5.75 (3.84-6.50) | |
| Negative | 15 | 5.82 (4.87-6.20) | |
| PgR | | | 0.63* |
| Positive | 73 | 5.76 (3.84-6.50) | |
| Negative | 26 | 5.75 (4.33-6.20) | |
| Ki 67 (%) | | | 0.75* |
| <14 | 33 | 5.75 (4.02-6.43) | |
| ≥14 | 66 | 5.80 (3.84-6.50) | |
| Molecular subtype | | | 0.70** |
| Luminal A | 30 | 5.60 (4.02-6.43) | |
| Luminal B | 53 | 5.80 (3.84-6.50) | |
| HER 2 (+) | 5 | 5.76 (4.87-6.32) | |
| Basal like/triple negative | 11 | 5.82 (5.17-6.20) | |

ER: Estrogen receptor; PgR: Progesterone receptor; HER: Human epidermal growth factor receptor; * Mann-Whitney U test; ** Kruskal-Wallis.

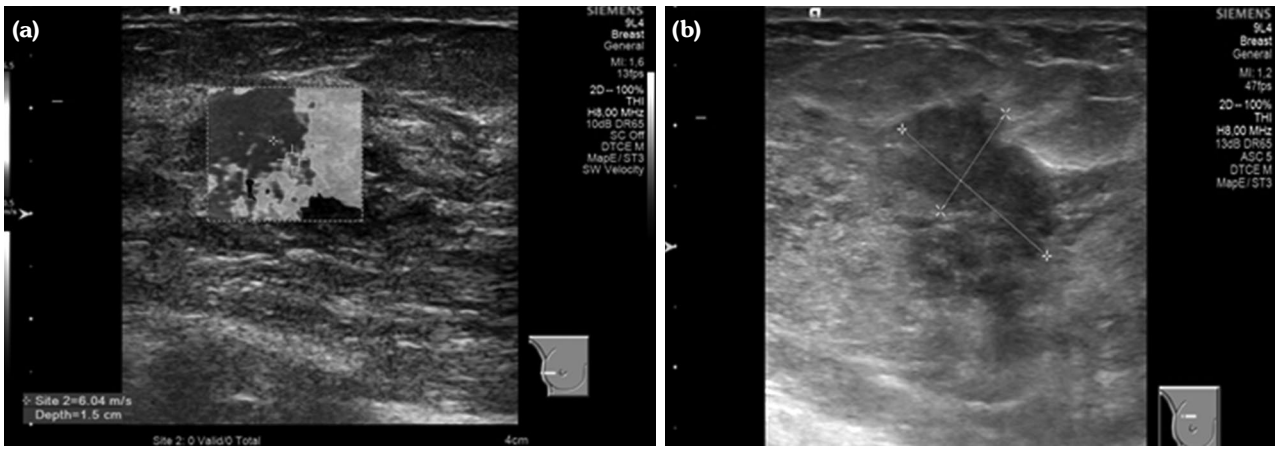


**Figure 1. (a)** The elastography value of the tumor with luminal A subtype is seen to be 6.04 m/s and **(b)** the grey scale ultrasonography image is presented. The tumor has a radius of 40 mm.

(histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive data were displayed for the non-normally distributed variables by using median and frequency tables.

The differences between variables were compared by using Kruskal-Wallis and Mann-Whitney U test. A *p* value of <0.05 was considered statistically significant.

## RESULTS

Ninety nine patients diagnosed with invasive breast carcinoma were included in this study. The median elastography value was 5.76 m/s (3.84-6.5). Sixty of the patients were premenopausal and 39 of them were postmenopausal.

Although the relationship between the age of the patient and tumor elastography value was not statistically significant, it was found that tumors occurred at an early age have higher elastography values (Table 1). No significant difference was determined between elastography values and histological types of the tumors.

A significant correlation was determined between tumor diameter and elastography value (p=0.001, r=0.32). When tumors were divided into two groups as tumors larger than 2 cm and equal to or smaller than 2 cm, it was determined that the elastography values of the tumors larger

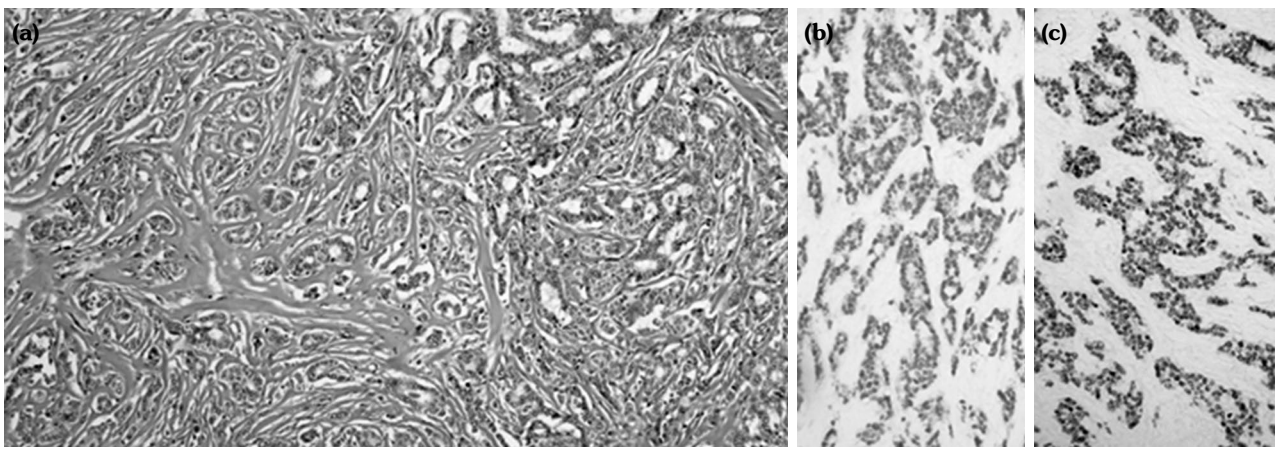


**Figure 2. (a)** The tumor's histologic image (H-E, 10), **(b)** immunohistochemical estrogen receptor positivity, and **(c)** immunohistochemical positivity with progesterone receptor.

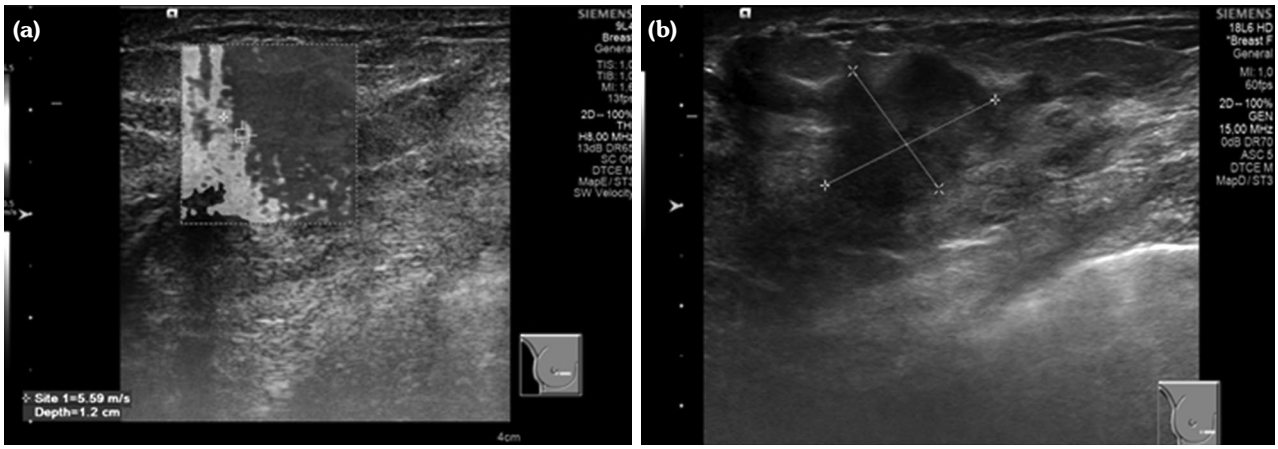


**Figure 3. (a)** The elastography value of HER-2 positive subtype tumor is seen to be 5.59 m/s, and **(b)** the grey scale ultrasonography image is presented. The tumor has a radius of 25 mm.
HER-2: Human epidermal growth factor receptor 2.

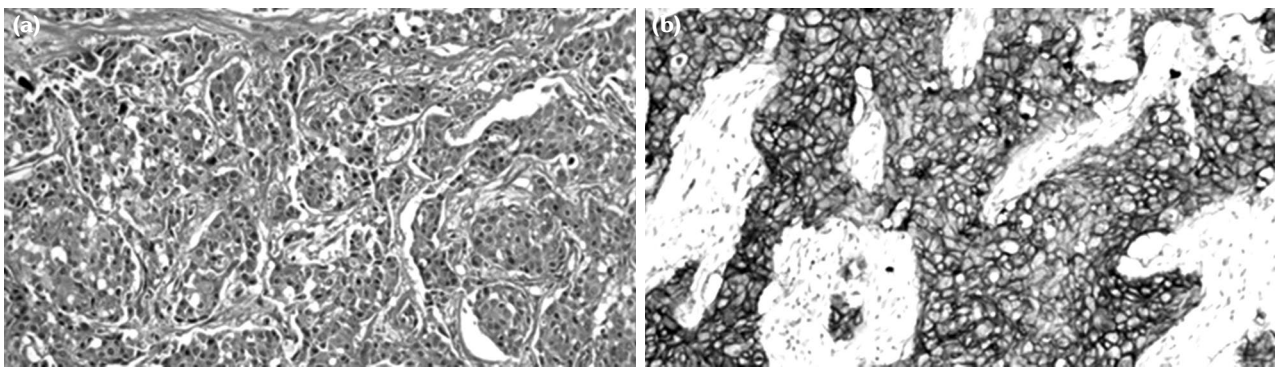


**Figure 4. (a)** The tumor's microscopic image (H-E, ×10) and **(b)** immunohistochemically positive staining (Score 3) with HER-2.
HER-2: Human epidermal growth factor receptor 2.

than 2 cm were significantly higher than others (5.63 *vs.* 5.87, p=0.016).

Thirty (30.3%) of the patients were evaluated as luminal A, 53 (53.5%) of them as luminal B, 5 (5.1%) of them as HER-2 positive, and 11 (11.1%) of them as basal-type/triple-negative (Figure 1-4). No significant difference was determined between elastography values of the HER-2 positive and negative tumors. Although there was a difference between maximum median elastography values (5.82; 5.17-6.20) found in triple-negative tumors and minimum elastography values (5.60; 4.02-6.43) found in luminal A molecular subtype, the difference between elastography median values and molecular subtypes was not statistically significant (Table 1). Moreover, there was no statistically significant difference between elastography values of the tumors and histologic type, intraductal component existence, histologic grade, presence of lympho-vascular invasion and lymph node metastasis, Ki67 value, and hormone receptor status (Table 1).

No relationship was identified between menopause status, birth, oral contraceptive use, or estrogen exposure time (menarche age-menopause age) and elastography values of tumors.

## DISCUSSION

It is known that elastography values are higher in the surrounding breast tissues of malign breast tumors than benign ones.[8,11,12,15,16] However, elastography values may imitate

benign masses in soft malign types like mucinous carcinoma.[17] As stated by Yoon et al.,[18] if focal necrosis areas are found in the tumor, then it is another situation where elastography is limited. Moreover, the use of elastography in malign tumors with a diameter larger than 20 mm, which let up due to tumor heterogeneity, and masses with a diameter less than 10 mm is limited in the differential diagnosis.[18]

Several studies investigating the relationship of elastography value with molecular subtypes and prognosis in breast cancer incidences found contradictory results. In many studies, the relationship of tumor size, axillary lymph node involvement, high histologic grade, increased proliferative index, and lymphovascular invasion with high elasticity values were displayed.[19-22] Chang et al.[23] demonstrated that HER-2 positive and triple-negative tumors are of stiffer structure. Ganau et al.[24] found a relationship between elasticity parameters of tumors and molecular subtypes. However, in the study of Ganau et al.,[24] contrary to the result found by Chang et al.,[23] it was demonstrated that the average elasticity value and maximum elasticity value in all tumors showing excessive HER-2 expression and in triple-negative tumors are less than luminal tumors regardless of hormone receptor status. However, in some studies in the literature, no significant relationship was found between tumor elastography values and molecular subtypes.[21,23] In our study, the highest elastography value was seen in triple-negative cases. Elastography value in patients with HER-2 positive, triple-negative, and Luminal B was higher than the patients with Luminal A. The minimum value was found in the patients with Luminal A. However, this difference between the groups was not statistically significant.

In a study conducted on experimental animals by Chamming et al.,[21] a positive correlation between tumor fibrosis and stiffness was found, whereas a negative correlation was found between tumor necrosis and stiffness. Based on this result, since more necrosis is seen in HER-2 positive tumors and triple-negative tumors, a lower elasticity value can be expected. Similarly, because more fibrosis exists in luminal tumors, a higher elasticity value can be expected. There are a lot of studies emphasizing that there is a close relationship between tumor stiffness and the tumor's stromal structure.[25-28] In those studies, it was demonstrated that tumor stiffness is also connected with carcinogenesis and tumor progression. Some changes occur in the extracellular matrix (ECM) secondary to the interaction between the tumor and stroma during carcinoma invasion. Reconstruction of the ECM and the stiffness resulting from this reconstruction are closely related to cellular and intercellular micro-signals.[28] It is thought that the storage of increased collagen in tumor stroma and the increased abnormal collagen cruciate ligaments play a role in tumor stiffness.[29] The stiff structure of reconstructed ESM increases interstitial pressure, deforms vein organization, and causes an increased physical resistance.[30] It is thought that this resistance may affect the chemotherapy response in a negative way.[21] These studies demonstrate that many factors, including a complex combination of cellularity, microvascular density, necrosis, and fibrosis, as well as histologic composition of the tumor, may play a role in tumor stiffness.

Evans et al.[13] revealed that high histologic grade is associated with high tissue stiffness. In this study, tumor stiffness difference in the tumors with histologic grades 1 and 2 compared to tumors with histologic grades 2 and 3 was more significant.[13] Since triple-negative tumors seen in young women with a genetic mutation can be monitored in USG generally as rounded and benign masses such as fibroadenomas, determination of stiffness in elastography is important.[31-33] Similarly, in our study, histologic grades 1 and 2 were compared, and although not statistically significant, the average tumor elasticity value in tumors with histologic grade 2 was higher.

In many studies, the relationship between tumor size and high elasticity value was demonstrated.[8,11,15,16] Choi et al.[34] found a significant positive relationship between tumor size and maximum elastography value. Evans et al.[13] also stated that big tumors have higher elastography values. In our study, in parallel with these researchers, we determined that the average elastography value increases with tumor size (stiffness of tumor tissue) and that this result is statistically significant. An increase in elastography values with tumor size can be

secondary to increscent ESM amount and changes in the ESM structure.

Lymphovascular invasion is significant because it is determinative of axillary lymph node metastasis in breast cancer. In the literature, there are some studies stating that high elastography values of tumors can be a determinant factor in terms of axillary lymph node metastasis.[13,21] There was no result supporting this finding in our study.

This study shows that elastography method is inadequate to determine molecular subtypes in breast cancer. Although the median elastography value of Luminal A tumors was lower than Luminal B, HER-2 positive, and triple-negative tumors, this result was not statistically significant. Shortage in the number of patients in our study is the reason for this result. It was found that elastography value is positively related to tumor size. Moreover, further studies examining the tumor-stroma relationship molecularly in terms of how the reconstruction of the ESM causes tumor stiffness shall provide an opportunity to improve the radiological interpretation of the elastography values.

In conclusion, it was demonstrated that there is a positive correlation between elastography values and tumor size, and no significant relationship was found between elastography values and histologic subtypes. Studies with larger series, in which microscopic findings take place in detail, may provide additional significant links between elastography values and other parameters.

**Declaration of conflicting interests**

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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