

Molecular Subtyping of Breast Cancer: Do We Define Them with B-mode US or ARFI Elastography?

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ABSTRACT

Imaging properties of breast cancer molecular subtypes differ and can be recognized by radiological methods. Acoustic radiation force (ARFI) can be associated with molecular subtypes and grade of breast cancer. The aim of this study was to determine the ultrasound and ARFI elastography correlates of different molecular subtypes of breast cancer.

Seventy-two patients were included in the study. The lesions evaluated by B-mod ultrasound (US) and ARFI elastography methods, and US guided tru-cut biopsies were performed. Molecular subtypes were categorized as triple-negative breast cancer (TNBC), luminal A and B, or human epidermal growth factor receptor 2-enriched cancer at based on the immunohistochemical profiles. Clinicopathological features, B-mod US and elastographic features was analyzed with statistically.

Luminal cancers displayed more frequently an irregular shape, posterior shadowing, echogenic rim, and a hypoechoic or complex echo pattern than TNBC ($p < 0.05$). While the mean shear wave velocity (SWV) value increased as the lesion size increased, there was no significant difference between the molecular subtypes. In the evaluation of Virtual Touch(TM) Tissue Imaging (VTI); small lesions showed more frequently pattern 4b, whereas large lesions showed pattern 3.

Breast radiologist should be careful, to know that a mass that has a well-defined, posterior enhancement may also be malignant. According to accepted literature data; High SWV values and imaging patterns in VTI are helpful in this regard to us.

Key Words: Breast cancer molecular subtype, Sonoelastomics, ARFI elastography

Introduction

Breast cancer is a heterogeneous and complex disease with different morphological, biological and molecular characteristics (1). With the genomic revolution in the early 1990s and the realization that cancer is a genetic disease, medical research turned the design of targeted therapies specific to the genetic structure of the tumor (2).

Radiological imaging plays can help predict molecular subtypes (3). Ultrasound (US) can be used in daily practice to assess the possibility of malignancy by characterizing breast tumors and also to guide biopsies (4) US elastography that is used in addition to US is a new approach to the assessment of the hardness of breast lesions, and is based on qualitative and quantitative tissue strain analyses using acoustic radiation force impulse (ARFI) technology. (4-6). The present study evaluates immunohistochemical (IHC) parameters (i.e. estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER2)) while carrying out a molecular classification of breast lesions. IHC eases considerably the selection of a treatment

approach according to the subtype of breast cancer, being cheaper than gene expression profile (GEP) and also available in underdeveloped regions such as ours.

This study compares the differences in B-mode US and ARFI elastography findings among the molecular subtypes of breast cancer, and seeks to identify any relationship between imaging characteristics and molecular subtypes, lymphovascular invasion (LVI), histological grade.

Materials and Methods

Patients: This study involved a group of patients diagnosed histopathologically with a malignant breast mass in the Department of Radiology of the Van YYÜ. Faculty of Medicine between January 2017 and September 2018. The study protocol was reviewed and approved by the university ethics committee (decision no: 08 date: 09.11.2018). Consent form was obtained from all patients in accordance with Helsinki Declaration. The B-mode and ARFI elastography records of all the patients were accessed through the picture archiving and communication system (PACS).

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B-mode US and Shear Wave US examination: A B-mode Breast US was carried out using an machine (Acuson-S2000, Siemens Medical Solutions, Mountain View, CA, USA) that 14 MHz bandwidth and a wide-format 50 mm linear array transducer. The Shear Wave Elastography (SWE) images of patients that underwent a tru-cut biopsy obtained using a B-mode US and ARFI technologies were saved in the image archive. The B-mode US and SWE images on the PACS were evaluated by two radiologist who was experienced in imaging breasts. The ultrasonographic features were classified in line with the criteria established by American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) for US (7).

At the elastography results obtained with ARFI technologies were used the Virtual Touch Tissue Quantification (VTTQ) and Virtual Touch Tissue Imaging (VTTI) methods. The VTTI application combines an independent plurality of axial tissue displacement information lines to form an image. Conventional US signal definition of the lesions is achieve at the baseline. Next, a push pulse is applied along the same line to achieve the displaced tissue signal. The cross-correlation algorithm allows comparison of basal and postpush signals. This allows computation of differences in tissue position, at each point along the axial line, between relaxed and compressed states. The maximum displacement experienced in a given spatial tissue location is the calculated differences at that location due to the elastic properties of the tissue. The amount of displacement is directly proportional to tissue elasticity. As with conventional B-mode scanning, this process is repeated for each axial line within the ROI. Finally, the elastographic image showing tissue stiffness is generated with all displacements calculated across the entire ROI (8). In SWV measurement, equal number of ROIs placed on the hardest and softest parts of the breast lesion in VTIQ with dimensions of 1×1 mm that provided the related SWV values were placed and then mean SWV values were obtained. The SWV values within the ROIs were automatically quantified in meters per second (m/s) (9). On VTTI, the lesion was classified as pattern 1 if it appeared similar to that noted in B-mode US, as pattern 2 if there was brightness in the lesion, as pattern 3 if the lesion contained both bright and black areas, and as pattern 4 if the lesion appeared to be uniformly black. Pattern 4 lesions were further classified as 4a if the lesion size was equal to that in VTTI and as 4b if the lesion was smaller than in

VTTI [5]. ARFI technology (VTTQ and VTTI) was obtained using a linear-array transducer (9L4; Siemens Medical Solutions) with a bandwidth of 9 MHz.

Histological analysis: Breast cancer types were recorded as invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC) and other. Histological grading was performed according to the Scarff-Bloom-Richardson system in which grade 1 and 2 were regarded as low grade and grade 3 was regarded as high grade (10).

Immunohistochemistry: The cut-off value for the Ki-67 index was set at 14% in line with St. Gallen International Expert Consensus guidelines (11).

-Luminal A; ER-positive, PR-positive-negative, HER2-negative, Ki-67<14%,

Luminal B; ER-positive, PR-positive-negative and HER2-negative, Ki-67≥14% or ER-positive, PR-positive, HER2-positive, Ki 67 insignificant,

-HER2-enrich type (HER2+); ER- and PR-negative, HER2-positive,

-TNBC; ER-negative, PR-negative, and HER2-negative (11).

HER 2: three positives was regarded as positive and less than three positives was regarded as negative. The presence of LVI was also recorded.

Statistical analysis: Descriptive statistics were presented as mean, standard deviation, minimum and maximum values for continuous variables, and number and percentage for categorical variables. Independent t test and One-way analysis of variance (ANOVA) were used for the comparison of group means for continuous variables. A Chi-square test was used to determine the relationship between categorical variables. The level of statistical significance in calculations was set at an alpha of 5% and the SPSS statistical software package was used for the calculations.

Results

We evaluated 77 patients with malignant breast masses with US and SWE data in PACS. Of 77 patients, 5 patients with treatment of neoadjuvant chemotherapy, prior cancer history, and recurrent breast cancer were excluded. A total of 72 breast lesions (71 female, 1 male) with histopathological data were included in the study. The mean age was 52±12.9 years. The distribution of the molecular subtypes of breast cancer; LB was the most common subtype, and accounting for 62.5% of breast cancers, and no significant relationship was found between the patient age and molecular

Table 1. Clinicopathological features for four subtypes of breast cancer

Variable	LA n (%)	LB n (%)	HER2+ n (%)	TN n (%)	Total n (%)	p-value *
Age						
<40	1 (10%)	7 (15.5%)	2 (40%)	3 (25%)	13 (18.1%)	0,449
≥40	9 (90%)	38(84.5%)	3 (60%)	9 (75%)	59 (81.9%)	
Palpable abnormality						
Positive	6(60.0%)	31(68.9%)	5(100%)	9(75%)	51(70,8%)	0,422
Negative	4(40.0%)	14(31.1)	0(0,0%)	3(25%)	21(29,2%)	
Cancer type						
IDC	7(70.0%)	41(91.1%)	5(100%)	12(100%)	65(90.3%)	0,072
ILC	2(20.0%)	0(0.0%)	0(0.0%)	0(0.0%)	2(2.8%)	
Other	1(10.0%)	4(8.9%)	0(0.0%)	0(0.0%)	5(7.0%)	
Size of invasive cancer						
<20	6(60.0%)	14(31.1%)	1(20%)	2(16.6%)	23(31.9%)	0,154
≥20	4(40.0%)	31(68.9%)	4(80%)	10(83.4%)	49(68.1%)	
Histologic grade						
Low grade	4(40.0%)	18(40.0%)	0(0.0%)	0(0.0%)	22(30,6%)	0,020
High grade	6(60.0%)	27(60.0%)	5(100.0%)	12(100.0%)	50(69,4%)	
LVI						
Present	4(40.0%)	15(33.3%)	2(40.0%)	6(50.0%)	27(37.5%)	0,759
Absent	6(60.0%)	30(66.7%)	3(60.0%)	6(50.0%)	45(62.5%)	
Axillary lymph node						
Positive	5(50,0%)	37(82,2%)	5(100,0%)	10(83,3%)	57(79,2%)	0,077
Negative	5(50,0%)	8(17,8%)	0(0,0%)	2(16,7%)	15(20,8%)	

*: Chi-Square test, LA; luminal A subtype, LB; luminal B subtype, HER2+; human epidermal growth factor receptor 2-positive subtype, TN; triple-negative subtype. IDC: Invasive ductal cancer ILC: Invasive lobular cancer. LVI: Lymphovascular invasion

subtype. (Clinicopathological features for four subtypes of breast cancer are given in Table 1).

In a comparison of the B-mode US characteristics of molecular subtypes, the vast majority of the subtypes showed hypoechoic and complex echogenicity, and often nonparallel orientation and an irregular shape in general. LA and LB were often seen to be spiculated and microlobulated, and TNBC most commonly showed circumscribed and microlobulated margins, although the distribution of these US characteristics did not show significant difference across the subgroups (figure (fig) 1a, 1b, 1c). The HER2+ subgroup showed calcification at a rate of 80% ($p=0.01$), and the 70% posterior enhancement in the TNBC subgroup was statistically significant when compared to that of the other subgroups ($p=0.01$) (fig.2). An echogenic rim was present in all molecular subtypes, aside from TNBC, and the difference was statistically significant ($p=0.02$) (fig. 3a and 3b) (Table 2).

The Ki-67 index was higher than 14% in 59 patients (81.9%), 46 (78%) of whom had high-grade lesions ($p=0.02$). Mean SWV value of high grade lesions was higher than low grade lesions. If we accept the SWV as 5.1 m / s according the ROC curve analysis, 64% specificity and 96% sensitivity rates found between high grade breast cancer and low grade breast cancer (Under of Curve: 0.835, $p=0.00$). In addition, 96% positive

predictive value (PPD) and 72% accuracy rates were obtained with this cutt-of value.

Patterns 1 and 2 were not observed in VTTI. The frequency of pattern 3 increased with increasing lesion size and palpability, and pattern 4b was more common in lesions measuring less than 2 cm in size ($p<0.05$). SWV was found to be significantly increased with increasing lesion size if Ki-67 was $\geq 14\%$ and the histological grade was high ($p < 0.05$) (Table 3).

Discussion

It was found in the present study that ARFI elastography and B-mode US characteristics can help in the diagnosis of the subtype of some breast cancers that mimic with benign lesions and present with high-grade tumor. In addition, it was found that the degree of tumor can be evaluated with high sensitivity by ARFI elastography at the time of diagnosis.

All patients in the TNBC and HER2+ subgroups were evaluated as high-grade ($p=0.02$). An increase in tumor mass can be expected alongside an increase in histologic grade due to higher rate of mitosis in high-grade tumors (12). In the present study, lesions larger than 2 cm were found to be associated with high tumor grade ($p=0.04$). Similar to our study, Kim et al (13). found higher rate of high-grade invasive cancer in the HER2+

Table 2. Sonographic features for four subtypes of breast cancer

Variable	LA (10) n (%)	LB (45) n (%)	HER2+ (5) n (%)	TN (12) n (%)	Total(72) n (%)	p-value *
Echopattern						
markedly hypoechoic	1(10,0%)	8(17,8%)	0 (0,0%)	3(25,0%)	13(16,7%)	
hypoechoic	4(40,0%)	16(35,6%)	1(20,0%)	6(50,0%)	27(37,5%)	
isoechoic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0,253
hyperechoic	1(10,0%)	0(0%)	0 (0%)	0 (0%)	1(1,4%)	
complex	4(40,0%)	21(46,7%)	4(80,0%)	3(25,0%)	32(44,4%)	
Orientation						
Parallel	3 (30%)	14(31,1%)	2(40%)	2(16,7%)	21(29,2%)	0,735
Not parallel	7(70%)	31(68,9%)	3 (60%)	10(83,3%)	51(70,8%)	
Shape						
Irregular	10(100%)	36(80,0%)	5(100%)	9(75%)	60(83,3%)	0,266
Oval/round	0(0%)	9(20,0%)	0(0%)	3(25%)	12(16,7%)	
Margin						
Circumscribed	0(0,0%)	6(13,3%	0(0,0%)	5(41,7%	11(15,3%)	
Indistinct	1(10,0%)	2(4,4%)	0(0,0%))	3(4,2%)	
Angular	3(30,0%)	12(26,7%)	2(40,0%)	0(0,0%)	17(23,6%)	0,050
Microlobulated	2(20,0%)	12(26,7%)	2(40,0%)	0(0,0%)	23(31,9%)	
Spiculated	4(40,0%)	13(28,9%)	1(20,0%)	7(58,3%)	18(25,0%)	
				0(0,0%)		
Calcification						
Present	0(0%)	21(46,7%)	4(80%)	4(33,3%	29(40,3%)	0,010
Absent	10(100%)	24(53,3%)	1(20%)	8(66,7%)	43(59,7%)	
Posterior features						
Nonenhancement	1(10,0%	10(22,2%)	1(20,0%)	0(0,0%)	12(16,7%)	
Mixt	3(30,0%)	13(28,9%)	0(0,0%)	2(16,7%)	18(25,0%)	0,010
Enhancement	2(20,0%)	6(13,3%)	1(20,0%)	9(75,0%)	18(25,0%)	
Shadowing	4(40,0%)	16(35,6%)	3(60,0%)	1(8,3%)	24(33,3%)	
Boundary						
Abrupt interface	3(30%)	12(26.6%)	0(0.0%)	8(66.6%)	23(31.9%)	0,020
Echogenic rim	7(70%)	33(73.3%)	5(100%)	4(33.3%)	49(68.1%)	

*: Chi-Square test, LA; luminal A subtype, LB; luminal B subtype, HER2+; human epidermal growth factor receptor 2-positive subtype, TN; triple-negative subtype

and TNBC molecular subtypes. The tumors in the LA subtype were largely low-grade (13). A spiculated mass lesion with a posterior shadow on US is more likely to be a low-grade tumor (12). The LA subtype was mostly related to lesions with spiculated contours and post-acoustic shadow (14).

TNBCs mostly appeared as hypoechoic or markedly hypoechoic, although the difference was not statistically significant. Although hypoechoicity and a complex echo pattern in malignant lesions were the most significant among the other subtypes in literature, TNBCs were found to be markedly more hypoechoic than other

subtypes (6,14). The margin is one of the most useful features when describing breast masses and making biopsy decisions. An ill-defined lesion margin is characteristic of malignant lesions, as benign lesions often show well-defined margins (7). Previous studies evaluating the relationship between US imaging findings and molecular subtypes have found TNBC to have better-defined margins than luminal lesions (4,14,12,15). It is also shown that, paradoxically, high-grade invasive ductal carcinomas may show a posterior enhancement that is typical of benign breast masses (10).

Table 3: ARFI elastography features for four subtypes of breast cancer

Variable	Total n (%)	Mean SWV (m/s) Mean ± SD	p- value##+	VTTI			P- value *
				Patern 3 n (%)	Patern 4a n (%)	Patern 4b n (%)	
Palpable abnormality							
Positive	51(70,8%)	5,81±1,57	,001	29(56,9%) 7(33,3%)	5(9,8%) 1(4,8%)	17(33,3%) 13(61,9%)	,08
Negative	21(29,2%)	4,47±1,16					
Cancer type							
Ductal	65(90,3%)	5,60±1,54 3,77±0,70	,04	34(52,3%) 2(70%)	3(4,6%) 3(60%)	28(43,1%) 2(70%)	,01
Other	7(9,7%)						
Size							
<20 mm	23(31,9%)	4,23±0,97	,00	7(30,4%) 29(59,2%)	3(13,0%) 3(6,1%)	13(56,5%) 17(34,7%)	,07
≥20 mm	49(68,1%)	6,02±1,47					
Histologic grade							
Low grade	22(30,6%)	4,19±0,84	,00	10(45,5%) 26(52,0%)	3(13,6%) 3(6,0%)	9(40,9%) 21(42,0%)	,54
High grade	50(69,4%)	6,09±1,58					
Ki 67							
<14%	13(18,1%)	4,48±1,36	,01	5(38,5%) 31(52,5%)	1(7,7%) 5(8,5%)	7(53,8%) 23(39%)	,68
≥14%	59(81,9%)	5,74±1,63					
LVI							
Absent	45(62,5%)	5,26±1,55	,25	22(48,9%) 14(51,9%)	5(11,1%) 1(3,7%)	18(40,0%) 12(44,4%)	,54
Present	27(37,5%)	5,70±1,61					
Molecular subtype							
LA	10(13,9%)	4,89±1,26	,57	3(30,0%) 26(57,8%) 2(40,0%) 5(41,7%)	1(10,0%) 5(11,1%) 0(0,0%) 0(0,0%)	6(60,0%) 14(31,1%) 3(60,0%) 7(58,3%)	,35
LB	45(62,5%)	5,40±1,75					
HER2+	5(6,9%)	5,80±1,64					
TNBC	12(16,7%)	5,78±1,06					

*: Chi-Square test, #: One-Way ANOVA, Independent t test, SD: Standard Deviation, LA; luminal A subtype, LB; luminal B subtype, HER2+; human epidermal growth factor receptor 2-positive subtype, TN; triple-negative subtype. VTTI: Virtual Touch(TM) Tissue Imaging, Mean SWV: Mean Shear wave velocity, LVI;

Similar to previous researches, spiculated contours were observed mostly in luminal lesions in the present study, and TNBCs showed circumscribed and microlobulated margins. Well-defined margins observed on a B-mode US may misguide clinicians into deciding upon a biopsy for TNBCs, and discourage us from performing biopsy (15). Due to the contour characteristics of TNBCs, evaluation into a possible benign category may lead to a delayed diagnosis. Radiologists working in breast imaging should be well aware that most TNBCs can be misdiagnosed as benign lesions at

B-mod US, and such tumors are more likely to be diagnosed as high-grade tumors in subsequent histological examinations (10). Posterior shadowing is a result of the decreased conduction of sound waves through the lesion, and the presence of acoustic shadowing in some malignant tumors is considered to be caused by the increased desmoplasia that is also responsible for spiculation (6). In previous studies in literature, luminal tumors were found to be associated with a posterior shadow, and the TNBC subtype was

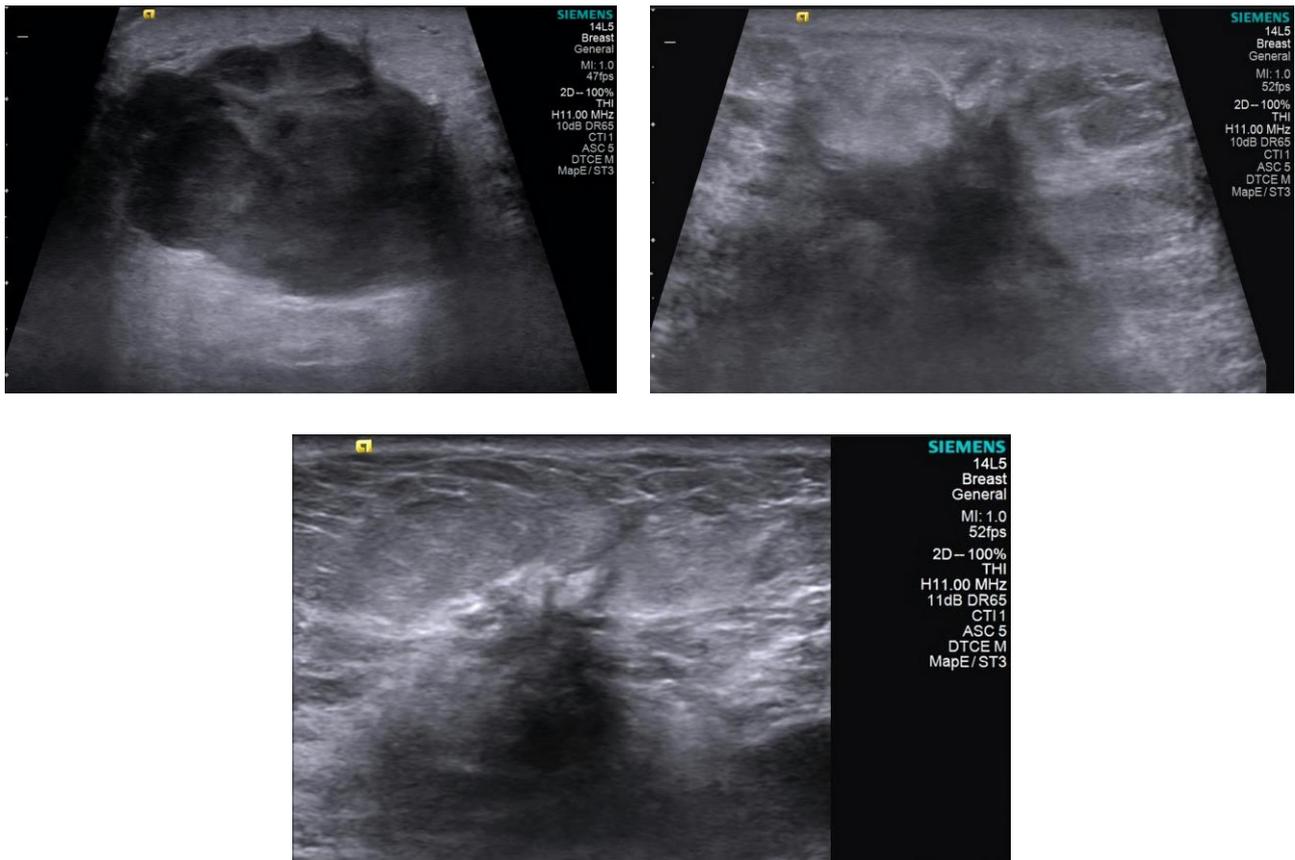


Fig. 1. a. Triple-negative breast cancer showing a lobulated/microlobulated margin and posterior enhancement. b, c. Luminal A and luminal B breast cancer showing a spiculated, angulated, indistinct margin and posterior shadowing

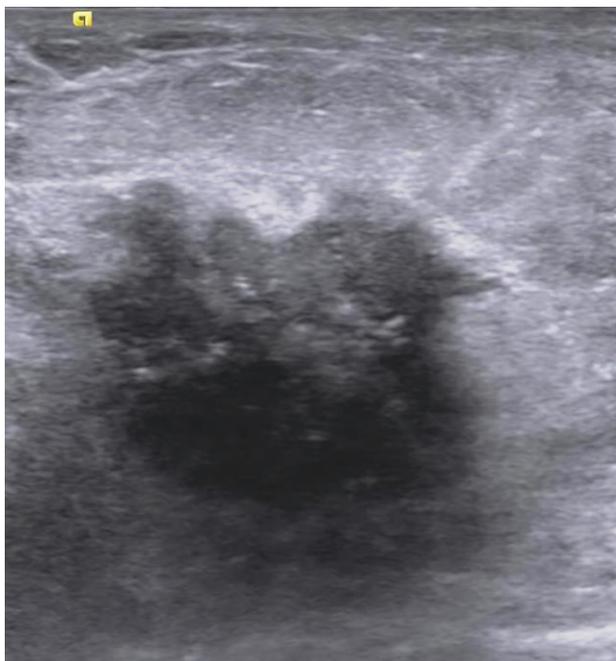


Fig. 2. Her 2+ breast cancer showing a lobulated/microlobulated margin and microcalcifications

found to be associated with posterior enhancement (3, 14, 15).

Calcifications one of the findings that can correctly guide clinicians in the diagnosis of malignant masses. The present study identified no calcification in the LA group, whereas calcification was present in 80% of the cases in the HER2+ molecular subgroup. In similar studies, mass lesions with irregular margins and calcification were found to be associated with the HER2+ molecular subgroup (6,14,12). An overexpression of the HER2/neu gene has been associated with several negative prognostic indicators, such as large tumor size, high tumor grade, presence of axillary lymph node metastasis and absence of hormone receptors (16). All patients in the HER2+ group in the present study had high-grade tumors and lymphadenopathy. In view of the present findings, the presence of calcification may be related to the prognosis of the patient.

Stromal reaction has been held responsible for spiculations and an echogenic rim in US. Low-grade ductal breast carcinomas, and frequently luminal cancers, have been linked to stromal

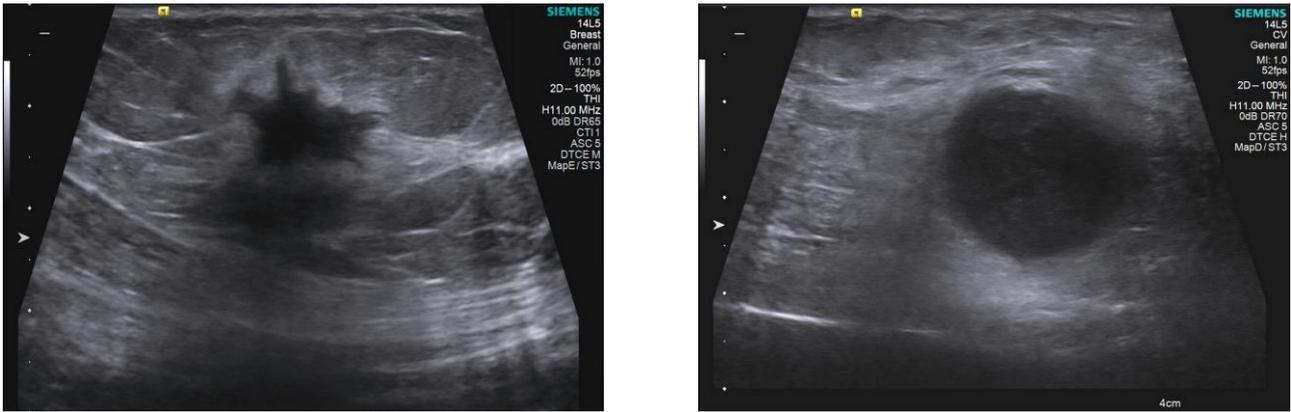


Fig. 3. a,b. A spiculated, ill-defined margin luminal cancer with echogenic rim, and an oval/round well-defined triple negative breast cancer with an abrupt interface

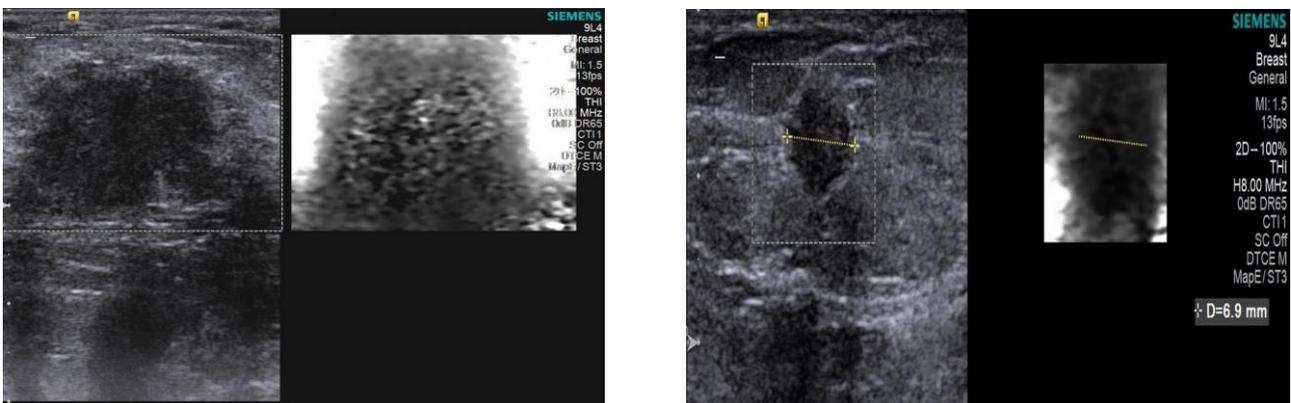


Fig. 4. a. A large luminal type breast cancer observed in VTTI as pattern 3. b. A small triple-negative breast cancer B-mode US shows a hypoechoic mass. The right ARFI VTTI shows a dark area corresponding to an area larger than the hypoechoic mass (pattern 4b)

reaction (12, 13, 15, 17). Echogenic rim is an expression of desmoplastic reaction and inflammation (18). Previous studies have observed a less echogenic rim in TNBCs than in luminal tumors, which is a sonographic correlation of desmoplasia (4,14). In the study by Elkabetset et al (18), however, desmoplasia was found to be a critical prognostic marker of cancer progression that regularly occurs histopathologically in TNBCs. This finding is not surprising, in that TNBCs are often high-grade and aggressive, and associated with poor prognosis (19). Youk et al. (20), and Evans et al. (19) identified a relationship between the mean elasticity features and such clinicopathological data as palpability, size, LVI, high histologic grade and lymph node involvement (19, 20). Youk et al. (20) found no relationship between the molecular subtypes and elasticity values. In addition, breast cancers with higher mean hardness values in SWV were found to be associated with poorer prognostic features (20). Consistent with literature, the present study found SWV to increase with increasing size, palpability

and grade (20, 21). Similar to the findings of the study by Youk et al. (20), the present study observed no difference in elasticity values between the molecular subtypes, and this finding may be associated with the higher rate of high-grade tumors among all subtypes and higher lesion size in all cancer types.

Boisserie-Lacroix et al. (22) reported quantitative SWE results of 15 patients with TNBC who exhibited relatively high mean elasticity values in the perilesional site, ranging between 50 and 232 kPa (22). The TNBC subtype is known to be associated with larger cancer size, higher histologic grade, increased LVI and a higher rate of regional lymph node positivity, leading studies in literature to conclude that an association between mean elasticity values and TNBC could arise from the relationship between mean elasticity and high histologic grade or LVI (20).

Tozaki et al. (5) attempted a VTTI evaluation from ARFI elastographic images and reported a high negative predictive value with the technique in the diagnosis of breast masses. In an individual

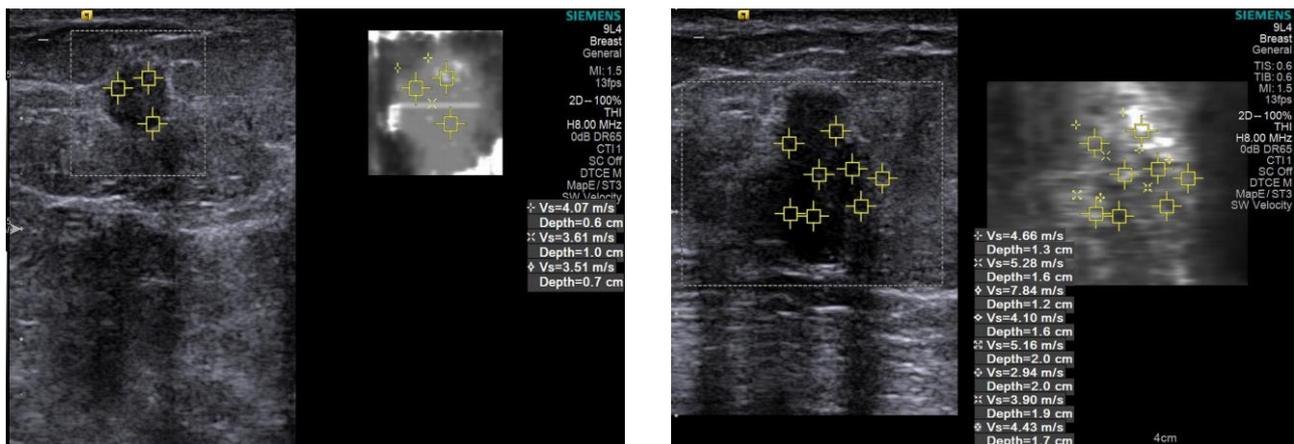


Fig. 5. Mean SWV in TNBC: 3.7 m / s (fig. 5a), 5.7m / s (fig. 5b)

elastographic image, bright sites indicate more elastic (less firm) tissues than black sites. An ARFI image is displayed on a split image with the corresponding conventional B-mode image, however, the margins of the tissue in the ARFI images may differ than those in the B-mode images, as they rely on different tissue contrast mechanisms (5). In a study with ARFI VTTI, Tozaki et al. (5) observed no pattern 1 or pattern 2 in any of the malignant lesions, reporting a negative predictive value of 100%. Although there was no significant difference in VTTI between the molecular subtypes in the present study, no malignant lesion was classified as pattern 1 or pattern 2. The rate of pattern 3 increased with increasing lesion size in our patient group. VTTI images are in grayscale and provide for the qualitative mapping of relative tissue hardness (elastogram) of a defined ROI. Pattern 3 contains both bright and black areas, and the association of pattern 3 with large lesions can be explained by the partial necrosis and softening of the tissue with increasing lesion size (fig.4a and 4b).

Studies in literature have reported a 3.6 m/s cut-off value for SWV in malignant lesions (4). Elasticity values in the present patient group did not differ significantly between the molecular subtypes, and the mean SWV in all molecular subtypes was above 3.6 m/s. The absence of patterns 1 and 2 in all malignant lesions and the SWV being higher than 3.6 m/s are believed to be important findings that elastography operators should take into consideration when differentiating between molecular subtypes with smooth margins and posterior enhancements mimicking benign lesions (fig.5a and 5b).

An upregulated expression of Ki-67 that can be regarded as a marker of cellularity is associated with tumor size, lymph node involvement,

histologic grade and other such negative prognostic factors as LVI (17). In our patient group, there was no significant correlation between the presence of LVI and molecular subtypes and VTTQ-VTTI. That said, Ki-67-positive lesions were found to be firmer than Ki-67-negative lesions. It can be suggested that increased SWV on SWE in association with Ki-67 expression may be related with the number of mitosis reflecting cellularity.

An assessment of archived US images may have brought some limitations to the study in spatial resolution. In addition, the number of assessed patients is not sufficiently high to reach statistical significance. In the field of US radiomics, studies with larger sample sizes are needed to obtain clear data.

The present manuscript provides an alternative radiological perspective to general information in a B-mode and ARFI elastography assessment of breast cancers and has been shown that sonographic features of malignant breast lesions may be associated with molecular subtypes and cancer grade.

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