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Ultrasound echogenicity reveals the response of breast cancer to chemotherapy

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ABSTRACT

Purpose: To evaluate the ultrasound (US) response in patients with breast cancer (BC) during neoadjuvant chemotherapy (NAC).
Methods: Prospective US analysis was performed on 19 malignant tumors prior to NAC treatment and 7 days after each first four courses of NAC in 13 patients (median age = 57 years). Echogenicity, size, vascularity, and sonoelastography were measured and compared with posttreatment scores of residual cancers burden.
Results: Changes in the echogenicity of tumors after 3 courses of NAC had the most statistically strong correlation with the percentage of residual malignant cells used in histopathology to assess the response to treatment (odds ratio = 60, $p < 0.05$). Changes in lesion size and elasticity were also significant ($p < 0.05$).
Conclusions: There is a statistically significant relationship between breast tumors' echogenicity in US, neoplasm size, and stiffness and the response to NAC. In particular, our results show that the change in tumor echogenicity could predict a pathological response with satisfactory accuracy and may be considered in NAC monitoring.

1. Introduction

In the past, neoadjuvant chemotherapy (NAC) was reserved for patients with locally advanced breast cancer and inflammatory breast cancer. Currently, it is also indicated in patients with triple-negative (TNBC) and HER-2–positive cancers [1,2]. Such an approach can inhibit metastases and micrometastases to distant organs. Moreover, it reduces the tumor size, enables breast-conserving surgery, decreases the number of patients with local recurrence, and reduces mortality. The best outcome of NAC is pathologic complete response (pCR), which is a prognostic factor in overall survival and disease-free survival [3,4].

At the moment, clinical breast examination, mammography, B-mode ultrasound (US) imaging, and magnetic resonance imaging (MRI) are used to monitor patients receiving NAC; however, diagnostic standards have not yet been established [5]. US is considered a more precise tool than clinical breast examination or mammography in assessing tumor size and monitoring residual lesions, whereas MRI is generally the most accurate [5,6]. The latest studies and meta-analyses confirm that contrast-enhanced MRI has high specificity and diffusion-weighted imaging MRI has high sensitivity in predicting pCR after NAC [7]. Unfortunately, MRI is not widely accessible, and its use is limited in certain groups of patients.

US sonoelastography (SE) is a modern approach used to monitor the effectiveness of treatment. The first published results suggest that a reduction in tumor stiffness observed by shear wave elastography (SWE) allows prediction of the response to NAC [8,9]. Using SWE, Evans et al. [9] demonstrated that a decrease in breast cancer stiffness, evaluated after the third course of NAC, was a better predictor of pCR (area under the curve [AUC] 0.82, sensitivity 59%, specificity 85%) compared with the assessment of lesion reduction diameter using MRI (AUC 0.68, sensitivity 50%, specificity 79%). The percentage change in stiffness in combination with change in US diameter was the best parameter (AUC 0.83) for predicting pCR. Similar results have been published with a larger group of patients (n = 80), in which the combination of percentage reductions in E_{mean} (Young modulus mean value) and gray-scale US diameter yielded an AUC of 0.92, similar to the AUC for MRI of 0.96 [10]. In the literature, several studies also using quantitative ultrasound (QUS) techniques for monitoring the response to NAC were published and indicated the importance of planning the tailored treatment [11–13]. Ultrasonic parameters are determined from the scattered echo that can characterize the microstructure of tissues and include echo envelope statistical

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parameters [14,15], texture parameters [16], and backscatter parameters [12]. The first results of clinical trials on a group of 24 tumors in NAC-treated breast cancer patients published by Sadeghi-Naini et al. showed that QUS (with the use of spectral parameters) allows patient response to NAC treatment to be categorized with high sensitivity (100%) and specificity (83.3%) after 4 weeks of treatment [17]. In the most recent paper, Sannachi et al. [16] found that after 4 weeks of treatment in a large cohort of 96 patients, the accuracy was 86% for predicting the response to NAC, based on the texture parameter. However, QUS methods use raw US signals available only in an examination performed with US scanners equipped with a research option, which are not generally available in clinical practice.

There is a need for a new diagnostic method that will discriminate responders from nonresponders more accurately, noninvasively, and at earlier stages of NAC therapy. The objective of our study was to determine whether monitoring changes via US in breast cancer patients undergoing NAC treatment (size, strain in SE, vasculature, and echogenicity) allows for the prediction of the effectiveness of therapy with regard to postoperative pathological verification after completion of chemotherapy.

2. Materials and methods

2.1. Patients

This prospective study protocol was approved by the institutional review board and ethics commission of the Maria Skłodowska–Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland. All patients gave their written consent to participate in the study.

From April 2016 to November 2017, 65 US breast examinations in 13 patients were performed with a total of 19 lesions (two women had bifocal lesion and two women had trifocal lesion). All women were qualified for NAC at the Oncology Clinic and had US examinations before NAC and 7 days after first four NAC courses. NAC were administered according to international guidelines in protocol: AC (doxorubicin, cyclophosphamide) and taxol and trastuzumab with/without were used. In one patient with a history of breast cancer, AT (doxorubicin, docetaxel) was used (1). All patients underwent a simple mastectomy with lymphadenectomy.

2.2. Histology

All patients underwent core needle biopsies after administration of 2% lidocaine, using a biopsy gun needle (14G diameter, Pro-Mag) before treatment. Three to five cores were taken from each lesion. After surgery (simple mastectomy) and following NAC therapy, surgical specimens were immediately fixed in 10% buffered formalin. Representative sections from these samples were processed and routinely stained for hematoxylin and eosin for histopathological (microscopic) examinations. All tumor samples were evaluated by the same pathologist. Based on the pathological assessment of breast tissue from core needle biopsies, the grade of malignancy, cancer subtype, and immunohistochemistry results were obtained. After surgery, information on tumor response to treatment, including cellularity (percentage of the resistant malignant cells [RMC], from 0% to 100%), degree of cell damage, and residual tumor size, was obtained (Tables 2 and 3) using the recommendation on residual tumor burden assessment [18].

In histopathological examination after NAC, tumors were classified into two categories: responding tumors (RT) and non-responding (N-RT).

- RT included tumors with reduction in tumor cellularity > 70% (< 30% RMC), which represented pathological partial response and pCR.
- N-RT included tumors with reduction in tumor cellularity < 70% (persisting over 30% RMC)

3. Registration of ultrasonic data

B-mode US examinations with breast SE were performed at the Department of Ultrasound, Institute of Fundamental Technological Research Polish Academy of Science in Warsaw, using an US scanner (Ultrasonix Sonix Touch-Research, Ultrasonix Medical Corporation, Richmond, BC, Canada) with a linear array transducer L14-5/38 and the transmitted frequency set at 10 MHz.

Each patient underwent at least five US examinations: before the treatment and 1 week after first four courses of chemotherapy. The breast cancer data were recorded from four cross sections (radial, radial + 45°, anti-radial, anti-radial + 45°). The period of participating patient monitoring was 4 to 5 months. The radial and anti-radial projection was used to compute the volume of the tumor.

The assessment of focal lesions in the breast was based on the guidelines of the American College of Radiology (BI-RADS lexicon) and the standards of the Polish Ultrasound Society [19,20]. US examinations were done by a single radiologist with an experience of 19 years in breast imaging and 8 years in performing SE.

Before NAC treatment and after each dose during the treatment, we assessed the size of the tumor and its echogenicity, vascularity and stiffness.

3.1. Echogenicity of the tumors

Tumor echogenicity was assessed basing on gray-level standard B-mode images of lesions and the fat tissue in the preglandular zones used as a reference. One of the three following echogenicity levels was assigned to each tumor image:

1. hypoechoic;
2. hypo- and isoechoic (mixed);
3. isoechoic.

3.2. Volume of the tumors

The volume, X, of the tumor was calculated using the tumor dimensions assessed from B-mode images applying the following equation:

$$V(n) = (X(n) - X(0))/X(0)$$

where n is the number of the NAC course and n = 0 corresponds to the measurement before NAC therapy.

Changes in volume V(n) of tumor after the nth dose of NAC with respect to X (0) before NAC, were calculated from the equation: $V(n) = (X(n) - X(0)) / X(0)$.

3.3. Tumor's stiffness

The SE technique was used to assess the stiffness of tumor tissue according to guidelines from the World Federation for Ultrasound in Medicine and Biology [21]. The Tsukuba scale has been used to quantify estimation. The Tsukuba scale is a 5-point scale of classification, ranging from Tsukuba 1, when strain is presented in the entire lesion, to Tsukuba 5, when no strain is measured in the lesion or surrounding tissue.

Changes in tumor stiffness E(n) were calculated according to the following expression:

$$E(n) = (T(n)–T(0))/T(0),$$

where T(n) is the stiffness of the tumor expressed on the Tsukuba scale determined after the nth NAC course.

3.4. Vascularization of the tumors

Tumor vascularization was assessed using color Doppler technique.

Three levels of vascularization were assumed:

1. lack of vascularity;
2. peripheral vascularity;
3. central and peripheral vascularity.

4. Statistical analysis

Statistical analysis was completed with the STATISTICA v 13.1 software package. A significance level of $\alpha = 0.05$ was used for testing the statistical hypothesis. In the analyzed material, for each continuous variable, the arithmetic mean, standard deviation, median, minimum, and maximum values were calculated. Due to the limited number of tumors, we used different statistical tests to determine the statistical significance of the differences between the groups of RT and N-RT to NAC therapy. To compare means, the Student's *t*-test, Cochran-Cox test, one-way analysis of variance, Mann-Whitney test, median test, and Kruskal-Wallis test were used. For each discrete variable, the structure index was calculated. For the contingency table, the Fisher-Freeman-Halton test was used. In the correlation analysis, the Spearman and Gamma coefficients were used. In regression analysis, a logistic regression model was applied. The classification matrix obtained in this model allowed for calculation of the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and odds ratio.

5. Results

The mean age of 13 patients with 19 breast cancers of nonspecified type (NST) was 57 years (range, 32–83 years; median, 56 years). Histopathological examination after final NAC and surgery revealed 10 RT (4/10 pCR, 6/10 tumors with 1%–30% malignant cells persist), and the remaining 9 were N-RT (in 5/9, resistance of 100% of pathological cells). The average age of patients with responding tumors was statistically lower as compared with patients in the nonresponder group ($p = 0.024$, Student *t*). Lesions were verified as invasive carcinoma NST G2 (12), G3 (6), and G1 (1). There were 5 luminal A cancers, one luminal B Her2+, 10 luminal B Her 2−, two TNBC, and one HER2+.

5.1. Echogenicity of the tumors

Before treatment, all lesions appeared hypoechoic in gray scale US compared to fat tissue. After four courses of NAC, only 4 tumors with an RMC value of 100% (determined after the mastectomy) were persistently hypoechoic in gray scale US. Changes in echogenicity of the tumors in subsequent cycles of NAC therapy ranked (Y axis) according to the RMC value are presented at Fig. 1.

The correlation between RMC (average value) after NAC treatment and the change in echogenicity (Echo) after 1 to 4 successive courses of NAC are presented in Table 1.

After the first course of NAC, the average RMC calculated for tumors in the hypoechoic group (n = 16) was 47.25, compared with 100.00 (in 5 lesions) after 4 courses of NAC. In tumors in which the echogenicity become isoechoic, the average RMC value after NAC treatment was 19.57 (n = 7).

The statistical significance of the correlation between RMC and the increase (changing from 1 to 2 and 3) of the echogenicity after 3 and 4 courses of NAC treatment was obtained. The results are presented in Table 2.

5.2. Tumor size

The mean lesion volume for all the tumors calculated in the B-mode examination before the treatment was 9583 mm^3 (median, 5915; range, 80–51,660 mm^3; SD, 12,676), and after the treatment (intravenous [IV] course of NAC), it was 2529 mm^3 (median, 1360 mm; range, 64–20,520 mm; SD, 4750). The arithmetic mean value of the alteration of the tumor volume in the two groups (RT, N-RT) is presented in Table 3.

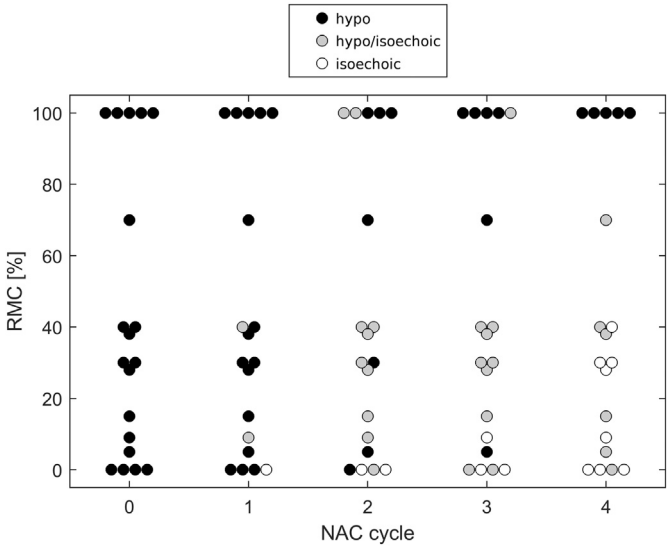

Fig. 1. Alteration of the tumors echogenicity in subsequent cycles of NAC therapy.
0 - echogenicity determined before the start of therapy, and 1,2,3,4 after subsequent NAC courses.

In the N-RT group, the mean volume of the tumors increased after the first NAC dose, then in both groups, the tumors volume continued to decrease until the last NAC course.

A statistically significant difference in the mean change in tumor volume in the N-RT and RT group was observed after the first and fourth NAC courses.

5.3. Tumor stiffness

Assessing the tumor stiffness according Tsukuba scale, only after the fourth NAC course was a statistically significant difference in the decrease in tumor stiffness observed between the N-RT and RT groups. The mean value of the alterations in tumor stiffness in the two groups of lesions is presented in Table 4.

5.4. Vascularization of the tumors

There was no statistically significant difference between groups in the variation of vascularity (Student *t*, Cochran-Cox, Mann-Whitney tests; $p > 0.05$).

6. Discussion

The intention of our study was to analyze specific US features to assess their predictive power in the assessment of the pathologic response of tumors to NAC, being mindful of that the traditional US is noninvasive, widely available and is a first-line examination in breast disease imaging. In our study, we examined patients using the same US machine and the same setting and assessed the lesions in four planes. Our results demonstrated that the change in echogenicity (from hypoechoic to iso- or mixed) after the third course of NAC has excellent accuracy and a very high odds ratio in distinguishing between N-RT and RT (Figs. 2, 3). After the third treatment, only one of the RT tumors remained hypoechoic and only one of the N-RT tumors changed echogenicity to hypoechoic/isoechoic (Fig. 1). To the best of our knowledge, this is the first study assessing the alteration of the echogenicity in breast cancer tissue during NAC treatment.

Table 1
Average value of RMC in relation to echogenicity during successive NAC treatments.
The avg-mean value of RMC in correlation to echogenicity and subsequent courses of NAC. Echo: 1, hypoechoic; 2, hypo- and isoechoic (mixed); 3, isoechoic; SD indicates standard deviation; n, number of cases

Echo.	NAC 1	RMC	RMC	NAC 2	RMC	RMC	NAC 3	RMC	RMC.	NAC 4	RMC	RMC
	n	avg	SD	n	avg	SD	n	avg	SD	n	avg	SD
1	16	47.25	40.87	7	57.86	45.45	6	79.17	38.26	5	100.00	0.00
2	2	24.50	21.92	10	40.00	34.37	10	32.10	28.18	6	28.00	26.42
3	1	0.00	0.00	2	0.00	0.00	3	3.00	5.20	7	19.57	16.25
All	19	42.37	39.69	19	42.37	39.69	19	42.37	39.69	18	44.72	39.45

The change in the stiffness of the lesions after 4 courses of NAC and the alteration of the size of the lesions after 1 course of NAC allowed for statistically significant differentiation between the RT and N-RT groups. We used SE, which has a diagnostic performance comparable to SWE, for predicting the response to NAC, as reported by Evans et al. [22]. Those authors concluded that both methods exhibited similar performance for predicting favorable NAC responses after a second course (AUCs of 0.90 and 0.93, respectively), but SWE was superior to SE for predicting NAC resistance (AUCs of 0.92 and 0.78, respectively).

Tumor stiffness and echogenicity depends on many factors including location of the lesion, surrounding tissue stiffness, the examination technique, and tissue properties such as desmoplasia, tissue fibrosis, and cellularity of the nodules. Tissue US image echogenicity results also from the US scattering on tissue structures and its intensity depends on the number and physical properties of the scatterers.

Before treatment, most neoplasms are rich in cellularity (carcinomatous cells or inflammatory cells), transmit sound better than normal breast tissue, and appear as hypoechoic. On the other hand, spiculated lesions that contain desmoplastic tissue tend to cause acoustic shadowing [23]. The changes observed in the echogenicity of tumors in patients responding positively to NAC treatment are likely to result from changes in neoplasm tissue occurring at the cellular level.

It has been proven that condensation of cell nuclei, which occurs during apoptosis of cells, results in an increase in ultrasonic backscatter signal intensity [24]. The size of a single cell is much smaller than the wavelength used in ultrasonography. Thus, it is not possible to observe changes in a single cell, but it is possible when the changes occur in a large number of cells. Analogously to the creation of the so-called speckle patterns in the US image, a large number of small scatterers with changing properties causes changes in the amplitude of the signal and, as a result, changes in echogenicity of the image. As a result of the NAC, changes occur in whole-cell assemblies. These are changes in the nuclear structures of cells as well as in their elasticity, viscosity and density [25]. As a consequence, the acoustic properties of cancer tissue change.

Another factor that can affect the US scattering characteristics of chemotherapy-treated tissues is the change in scattering structures. As a result of the interaction of NAC at the site of the primary lesion, composed mainly of tumor cells, fibrosis, collagenization, and microcalcifications in the stroma occur. Structures appear, the size and mechanical properties of which indicate that they are characterized by strong US scattering, which consequently translates into an increase in echogenicity [26].

Matsuda et al. published results similar to ours. Their study was based on 52 patients with TNBC, and they used changes in the brightness of the tumor images in relation to the brightness of the subcutaneous fat to calculate ratios of neoplasms to fat echogenicity (T/F). Based on this T/F assessment before and after NAC therapy, they achieved an AUC of 0.8 for classifying patients into RT and N-RT groups [27]. It is worth noting that, in our study, we prospectively examined the echogenicity of the tumors after each course of NAC. Our results are

Table 3
Arithmetic mean value of the alteration of the tumor volume in both groups of patients. N-RT, non-responding tumors; RT, responding tumors; p. test, parametric tests, Student *t*; np. test, nonparametric tests, Mann-Whitney; V avg, mean alteration in volume of tumor.

NAC	N-RT	RT	p. test	np. test
	V avg	V avg	*p*	*p*
1	0.159	−0.378	0.011	0.018
2	−0.425	−0.588	0.090	0.102
3	−0.427	−0.617	0.120	0.149
4	−0.496	−0.808	0.023	0.015

Table 4
Arithmetic mean value of alteration of the tumor stiffness in both groups (N-RT and RT).
N-RT, nonresponding tumors; RT, responding tumors; p. test, parametric tests, Student *t*; np. test, nonparametric test, Mann-Whitney; E_{avg}, mean alteration of the tumor stiffness

NAC	N-RT	RT	p. test	np. test
	E_{avg}	E_{avg}	*p*	*p*
1	0.194	0.044	0.429	0.323
2	0.161	−0.064	0.143	0.210
3	−0.131	−0.290	0.229	0.152
4	0.031	−0.333	0.041	0.041

Table 2
Correlation between RMC and echogenicity during treatment.
The logistic regression model calculated from the tumors' echogenicity after the third course of NAC was determined, where the sensitivity was 83.33% (43.65%–96.99%), specificity was 92.31% (66.69%–98.63%), PPV was 83.33% (43.65%–96.99%), NPV was 92.31% (66.69%–98.63%), and accuracy was 89.47%. The odds ratio was 60 (3.07–1173.64). There was only one false-positive case and one false-negative case

NAC	n	Spearman	Spearman	Gamma	Gamma	ANOVA	K-W	Median	F-F-H
		R	*p*	*R*	*p*	*p*	*p*	*p*	*p*
1	19	−0.259	0.285	−0.435	0.171	0.433	0.363	0.622	0.678
2	19	−0.381	0.108	−0.457	0.046	0.189	0.113	0.351	0.207
3	19	−0.667	0.002	−0.760	0.000	0.005	0.018	0.049	0.005
4	18	−0.715	0.001	−0.712	0.000	0.000	0.005	0.014	0.001

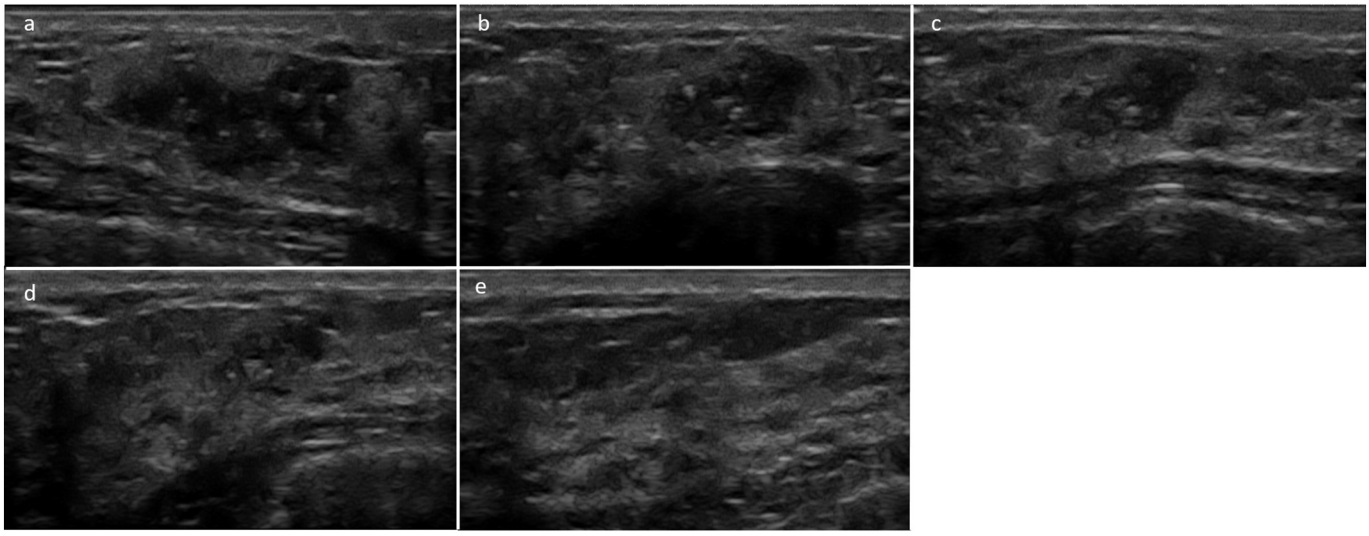

Fig. 2. The B-mode images in responding tumors (5% malignant cell persist) presented as mixed echogenicity after 3 courses of NAC (d) and become isoechoic after four course of NAC (e). Histopathological verified as invasive carcinoma NST.

in agreement with the Matsuda study results in that alteration in tissue echogenicity could predict the response to treatment after 4 courses of NAC. However, the results obtained in our study, in which we performed US examination after each course of NAC, indicate that we could predict the response earlier (after 3 courses of NAC) with a high odds ratio and with only one false-positive and one false-negative case. The one false-negative case concerned one lesion of Luminal B Her-G3 in a young patient with multicentric cancer. Alteration of the echogenicity in this neoplasm was observed after the fifth course of NAC. In one false-positive case (TNBC, G3), mixed echogenicity (iso- and hypoechoic) was observed after 3 courses, but after 4 courses, the tumor was again hypoechoic.

Baumgartner et al. assessed classical gray-scale B-mode US and concluded that this examination is insufficient in predicting pCR with adequate accuracy. In a retrospective study, the authors reported that US-based prediction of pathologic response was most accurate in patients with TNBC cancers, but that overall sensitivity was 60.8% and specificity was 78.0%. The authors did not report the specific timing of the examination during NAC and US features [28].

In our study, alteration of the neoplasm size was an important factor, and the size differences were found to be statistically significant after the first and fourth course of NAC. This is important because, in a

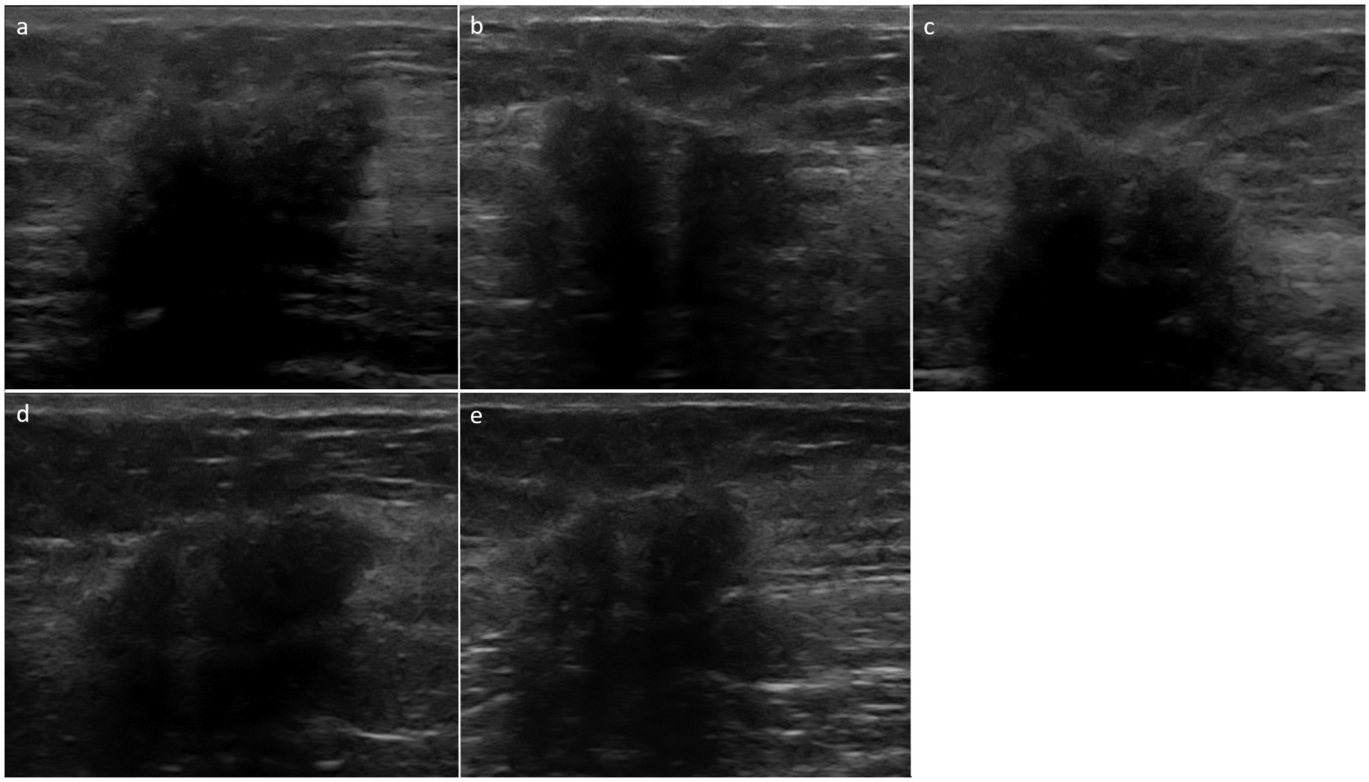

Fig. 3. The B-mode images in non-responding tumor (100% malignant cells persisting) presented as hypoechoic until the (last course before the surgery) course of NAC. Histopathologically verified as invasive carcinoma NST G2.

meta-analysis conducted by Marinovich, which assessed the consistency between MRI, US, and pathologic evaluation of tumor size after NAC, the authors presented comparable performance of both diagnostic methods in cases in which residual tumor was present [29]. Moreover, some studies suggested that MRI could overestimate or underestimate the size of residual tumor [30,31].

7. Conclusions

In summary, this is the first preliminary study to present the alteration in echogenicity from hypoechoic to isoechoic as an US feature that can predict breast tumor response to NAC. We conclude that persistent tumor hypoechogenicity after 3 courses of NAC predicts a poor response to treatment. Echogenicity is a simple and easily accessible parameter that can be used by a radiologist, such as in the case of SE or evaluation of vascularity. In addition, SE stiffness reduction and volume reduction could also potentially be useful for predicting the response to NAC. If the results are confirmed in a larger patient cohort, tracking the changes in tumor US image echogenicity will be an easy and non-invasive method of assessing tumor response to NAC.

8. Limitations

This is a one-institution study on a small group of patients. We conducted further observations using a larger patient cohort.

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