Ultrasound echogenicity reveals the response of breast cancer to chemotherapy

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Aims and objectives

Early prediction of pathological complete response (pCR) is a prognostic factor in overall survival and disease-free survival in patients with breast cancer (BC) during neoadjuvant chemotherapy (NAC). NAC is recommended in patients with triple-negative breast cancer(TNBC), Luminal B HER2-positive and HER-positive non-luminal subtype. 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.

The aim of this study was to determine, whether changes in theUS (volume, vasculature, and echogenicity) and sonoelastography during NAC-treated breast cancer patients predict response to treatment.

Methods and materials

Prospective US analysis was performed on 42 malignant tumors in 40 patients, prior to NAC treatment and 7 days after the first four courses of NAC. All women were qualified for NAC at the Oncology Clinic. NAC was administered according to guidelines in the protocol: AC (doxorubicin, cyclophosphamide).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 USscanner (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.Tumors echogenicity was assessed in comparison with fat tissue in the preglandular zones. The following echogenicity levels were assigned to each tumor image: hypoechoic, hypo- and isoechoic (mixed) and

Isoechoic. The 5-point Tsukuba scale has been used to assess the stiffness of the lesions. 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. Tumor vascularization was assessed using color Doppler technique using the following levels: lack of vascularity, peripheral vascularity and central and peripheral vascularity. Changes in volume of the tumor after the n^{th} dose of NAC with respect the volume before NAC were calculated.

All patients underwent a simple mastectomy with lymphadenectomy. After surgery, information on tumor response to treatment, including cellularity (percentage of the resistant malignant cells [RMC], from 0% to 100%) was assessed by a pathologist.

Echogenicity, volume, vascularity, and sonoelastography of the breast tumors were measured and compared with posttreatment pathological results. In histopathological examination after NAC, tumors were classified into two categories: responding tumors (RT) and non-responding (N-RT). In our study, RT included tumors with a reduction in tumor cellularity >30% (<70% RMC), which represented pathological partial response and pCR. N-RT included tumors with a reduction in tumor cellularity <30% (persisting over 70% RMC). The correlation analysis and a logistic regression model were used in statistical analysis.

Results

Changes in the echogenicity of tumors after the 3rd course of NAC had the statistical correlation with the percentage of residual malignant cells, with the sensitivity of 84%, specificity of 93%, PPV of 84%, NPV of 94% and accuracy of 88%. The Odds Ratio was 60. The decreasing in the stiffness of the lesions after 4th course of NAC and the alteration of the volume of the lesions after the first course of NAC were statistically significant between the RT and N-RT groups ($p< 0.05$).There was no statistically significant difference in the alteration of vascularity (Fig.1-6, Fig.7-13).

Images for this section:

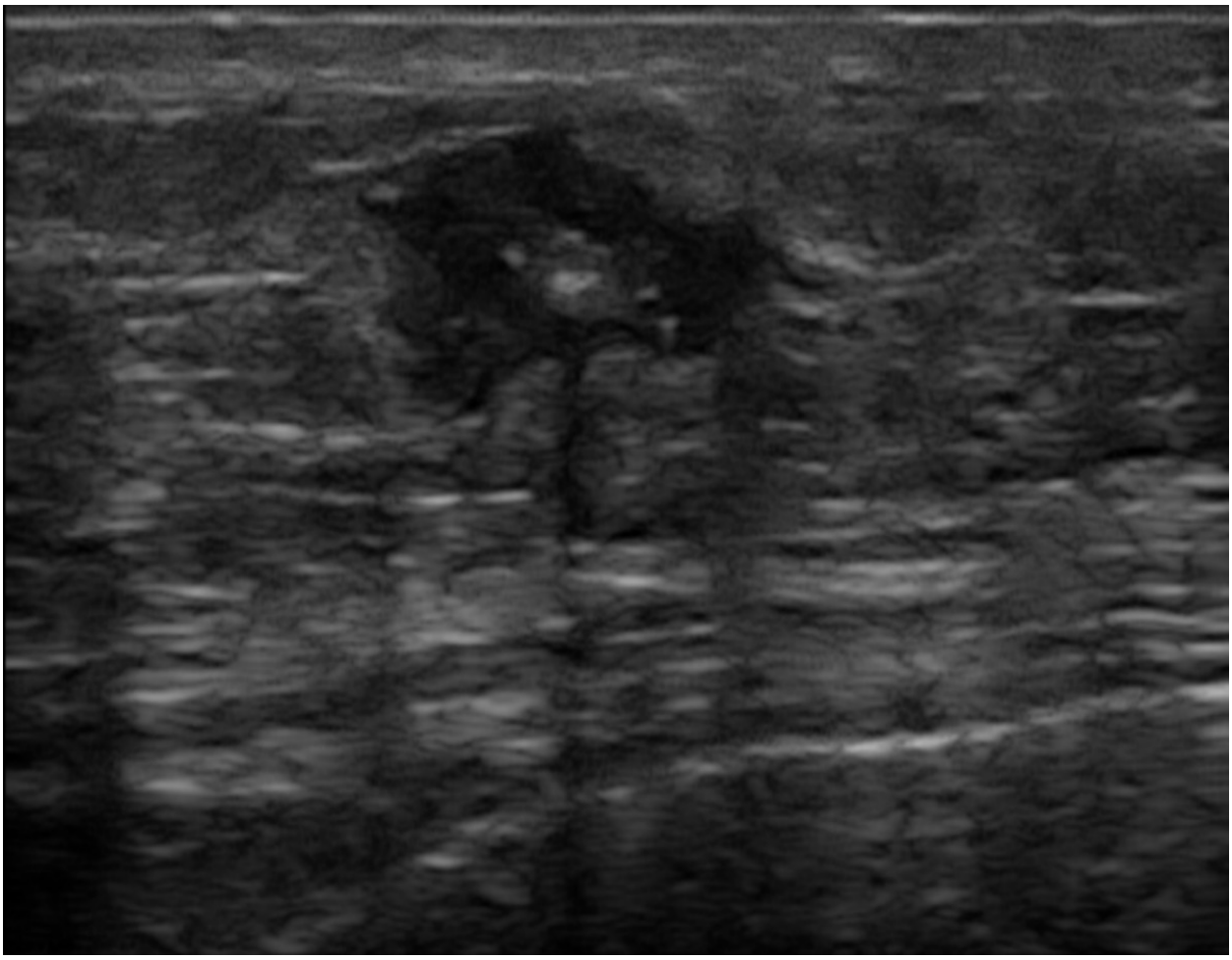

Fig. 1: Ultrasound examination in 65-year patient with breast cancer (carcinoma invasivum apocrinale, Grade 3, TNBC, Ki 67-20%). In B-mode examination before treatment the tumor was hypoechoic.

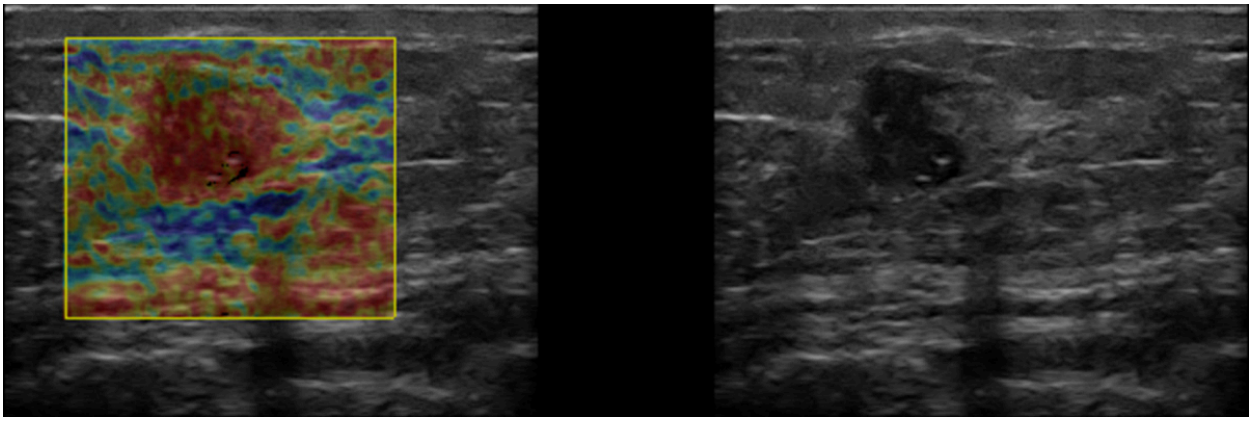

Fig. 2: Ultrasound examination in 65-year patient with breast cancer (carcinoma invasivum apocrinale, Grade 3, TNBC, Ki 67-20%). In B-mode examination before treatment the tumor was stiff in SE (Tsukuba4).

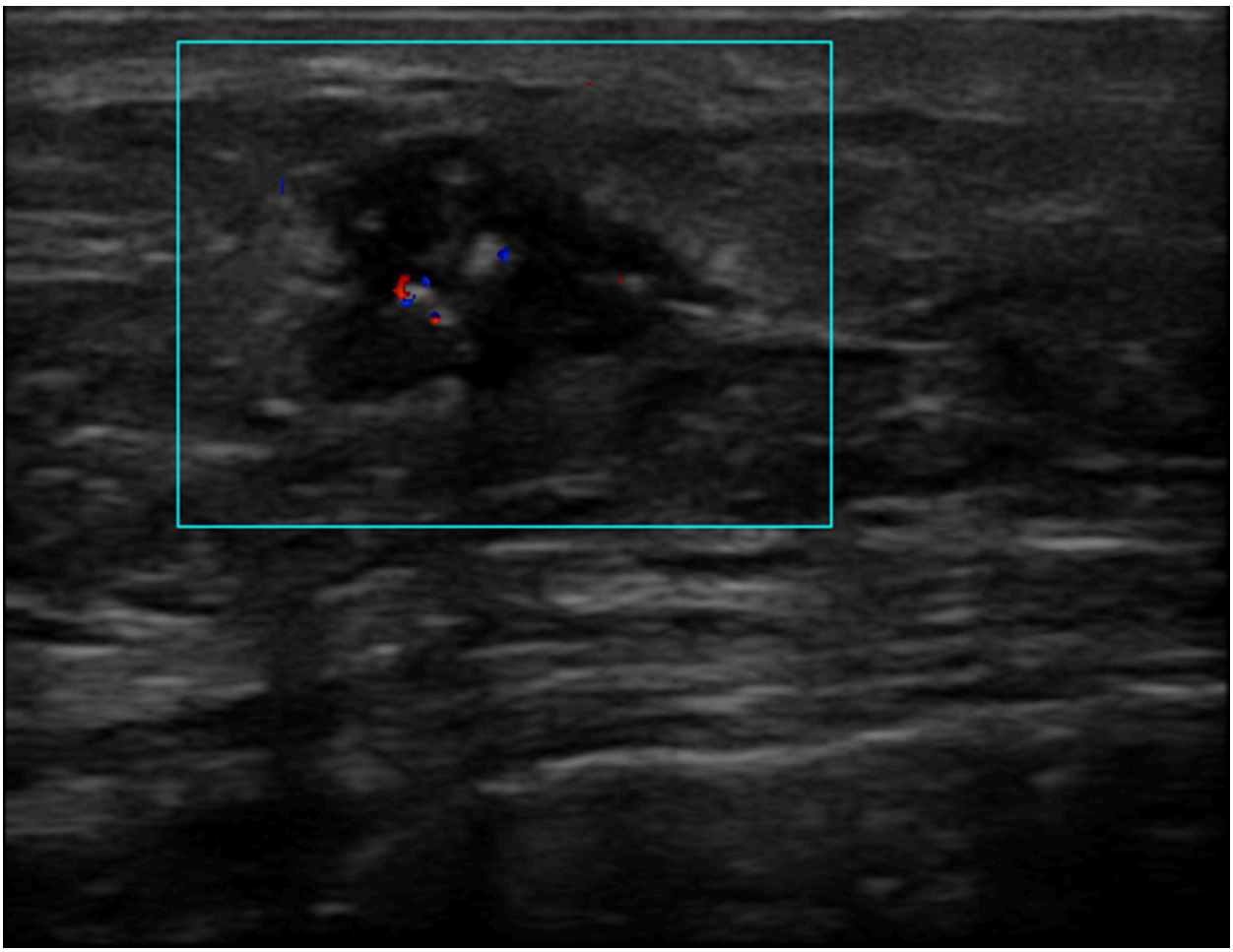

Fig. 3: Ultrasound examination in 65-year patient with breast cancer (carcinoma invasivum apocrinale, Grade 3, TNBC, Ki 67-20%). In B-mode examination before treatment the tumor had increased vascularity.

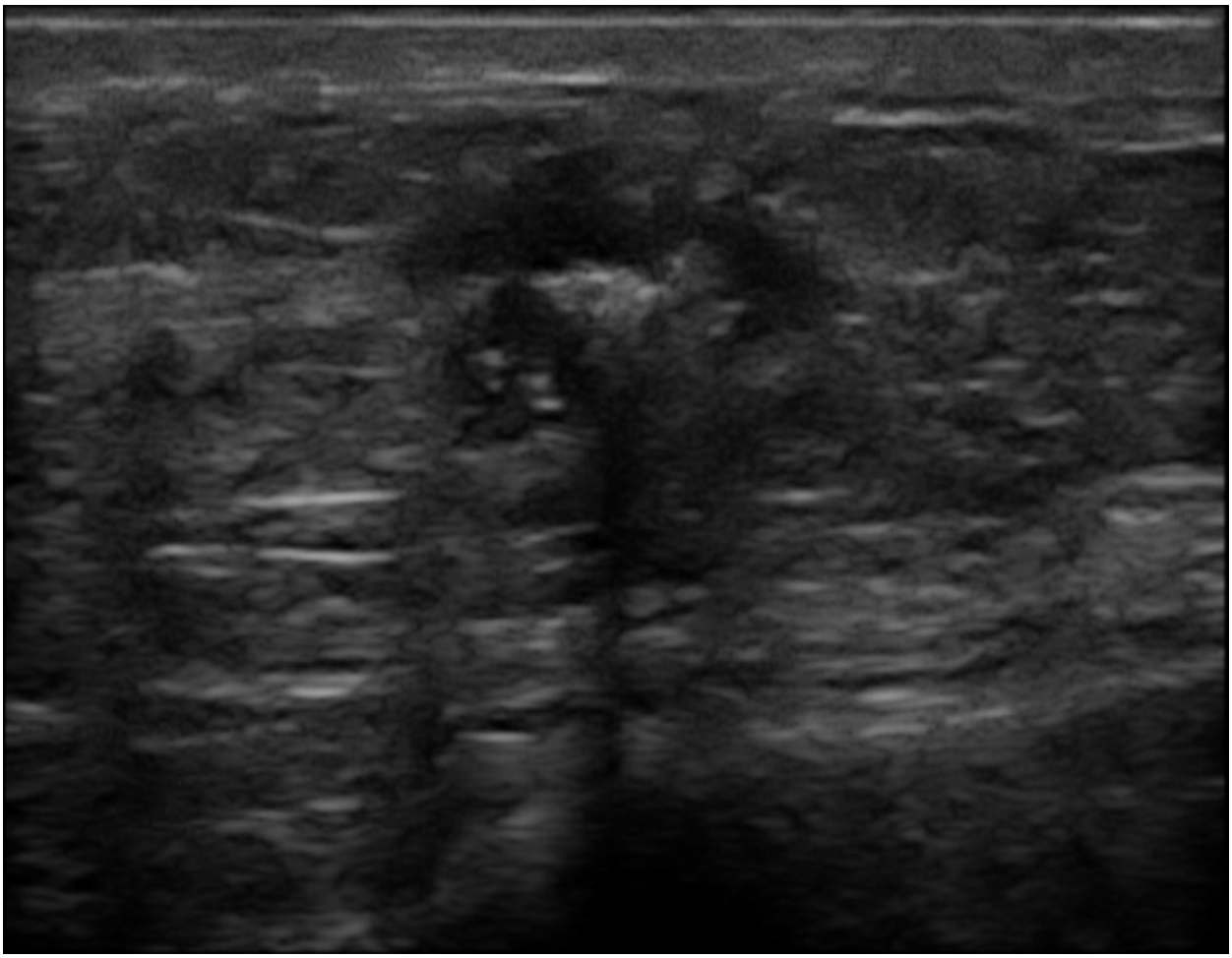

Fig. 4: After 3-rd course of the NAC, the echogenicity, remain unaltered (histopathological verification: N-RT).

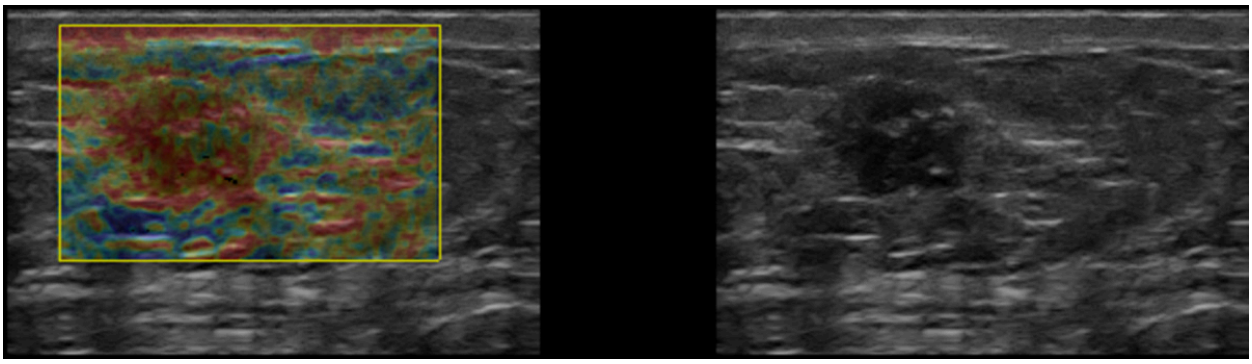

Fig. 5: After 3-rd course of the NAC stiffness remain unaltered (histopathological verification: N-RT).

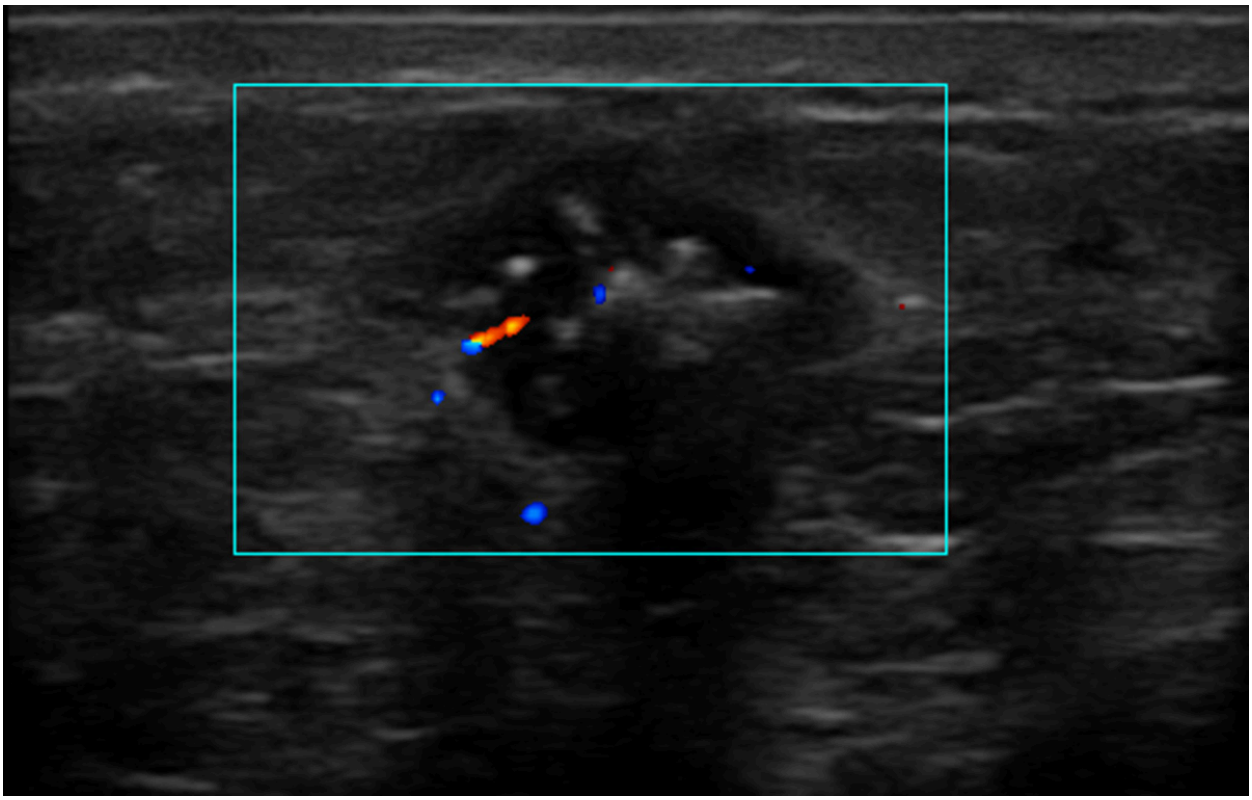

Fig. 6: After 3-rd course of the NAC vascularity remain unaltered (histopathological verification: N-RT).

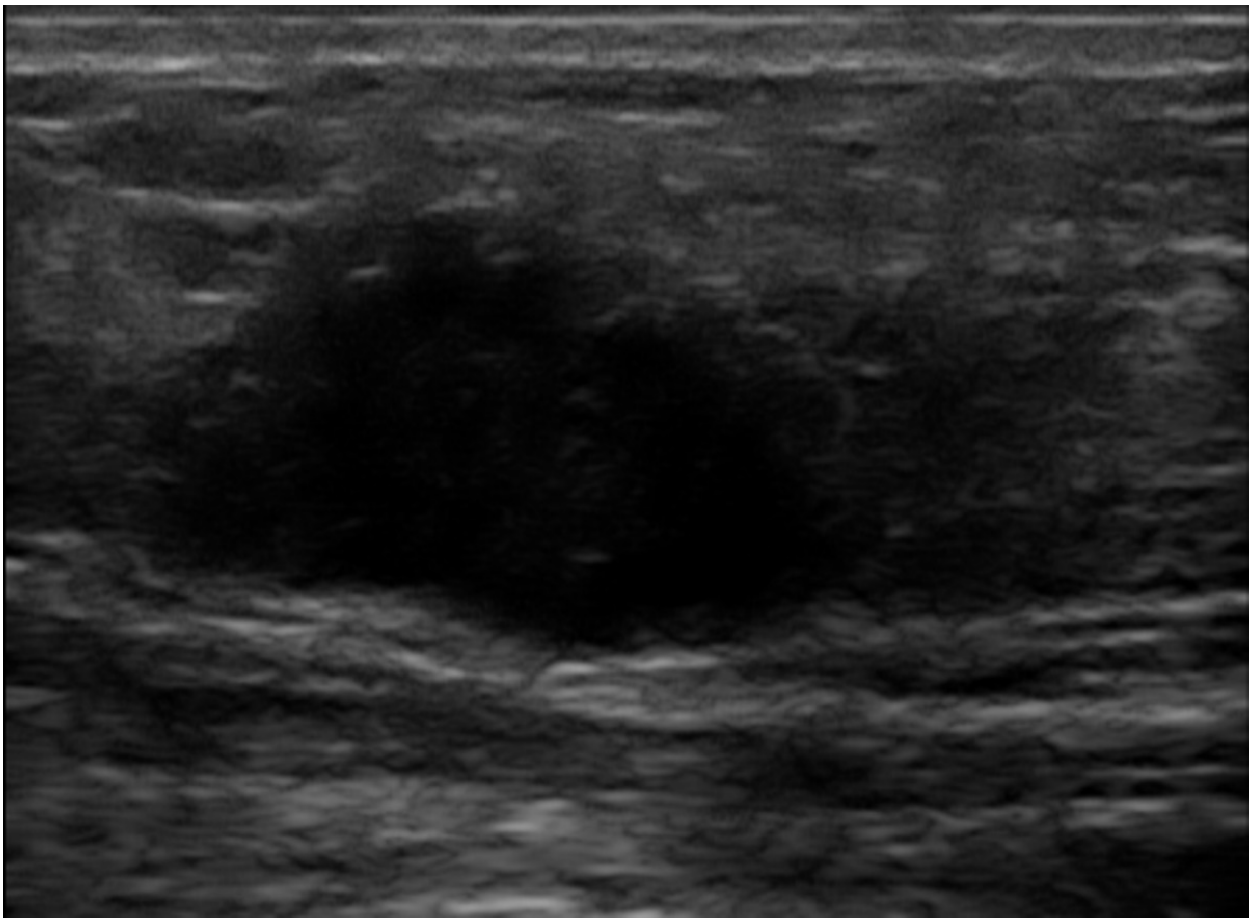

Fig. 7: Ultrasound examination in 56-year patient with breast cancer (NST Grade3 with CDIS, ER-25%, PGR-10%, HER 2-3+, Ki 67-30%). In B-mode examination before treatment the tumor was hypoechoic.

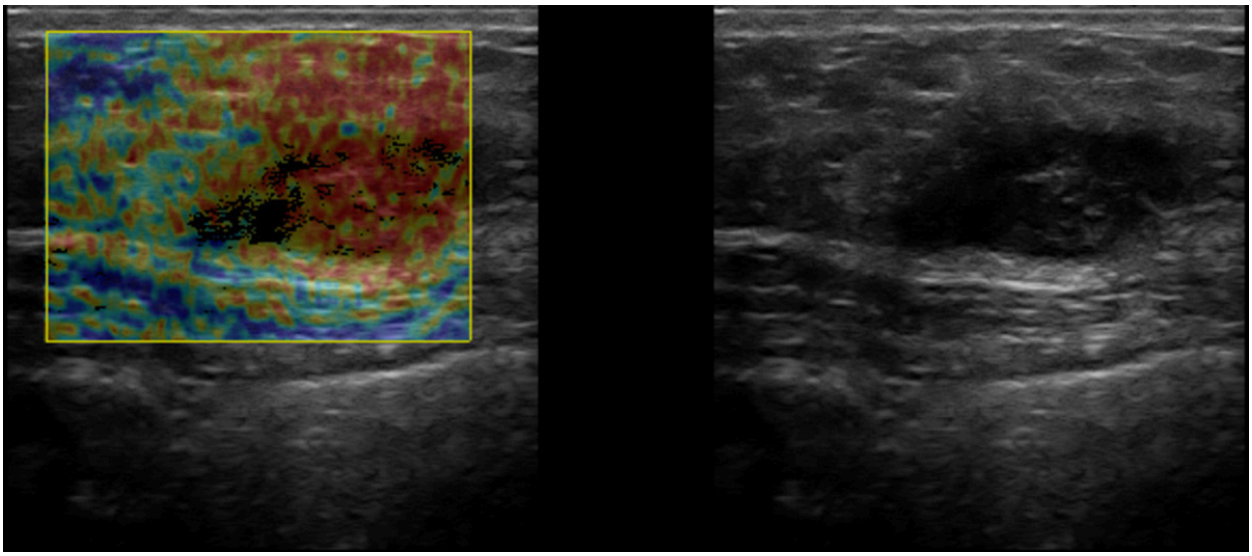

Fig. 8: Ultrasound examination in 56-year patient with breast cancer (NST Grade3 with CDIS, ER-25%, PGR-10%, HER 2-3+, Ki 67-30%). In B-mode examination before treatment the tumor was stiff in SE (Tsukuba4).

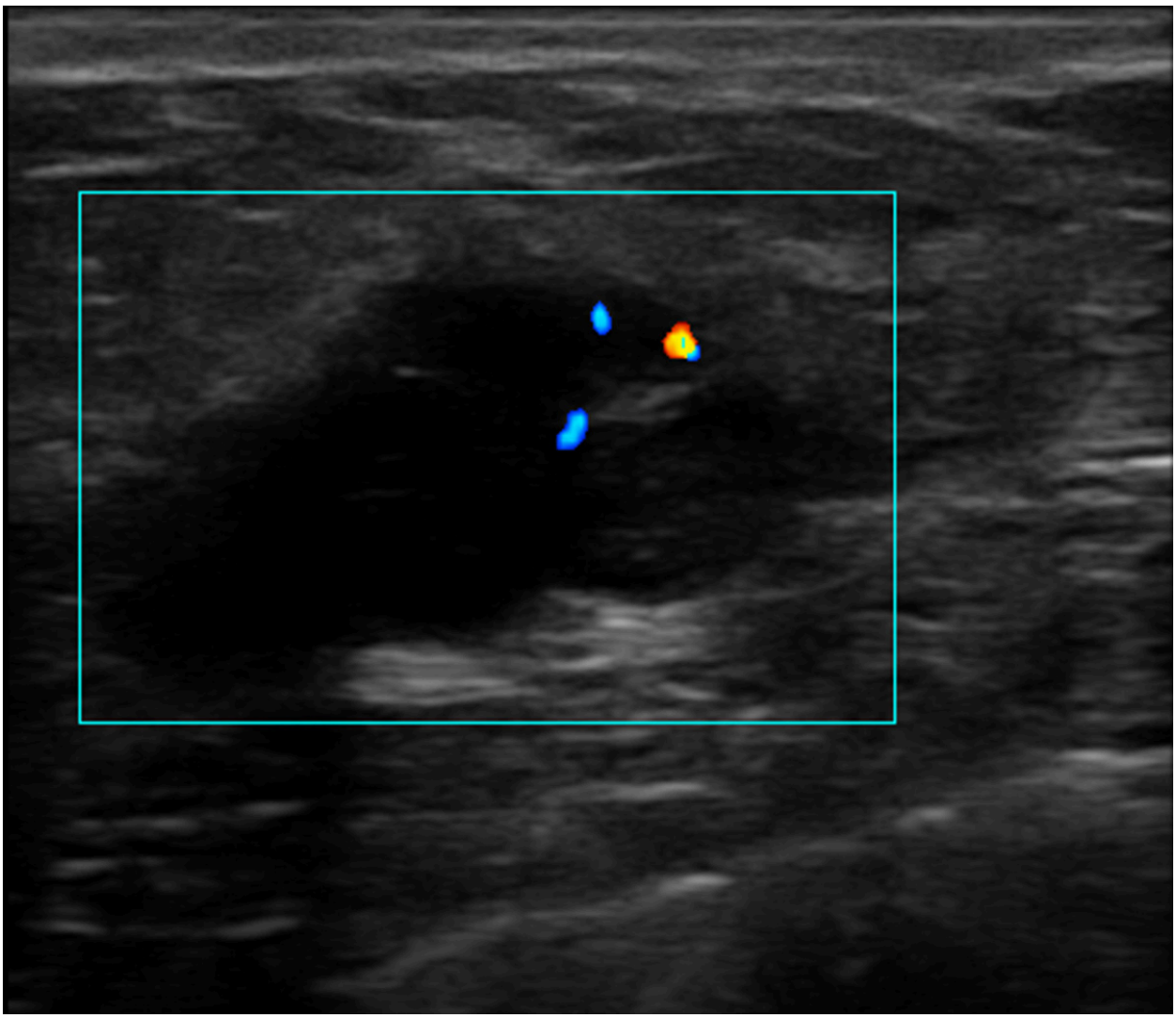

Fig. 9: Ultrasound examination in 56-year patient with breast cancer (NST Grade3 with CDIS, ER-25%, PGR-10%, HER 2-3+, Ki 67-30%). In B-mode examination before treatment the tumor had increased vascularity.

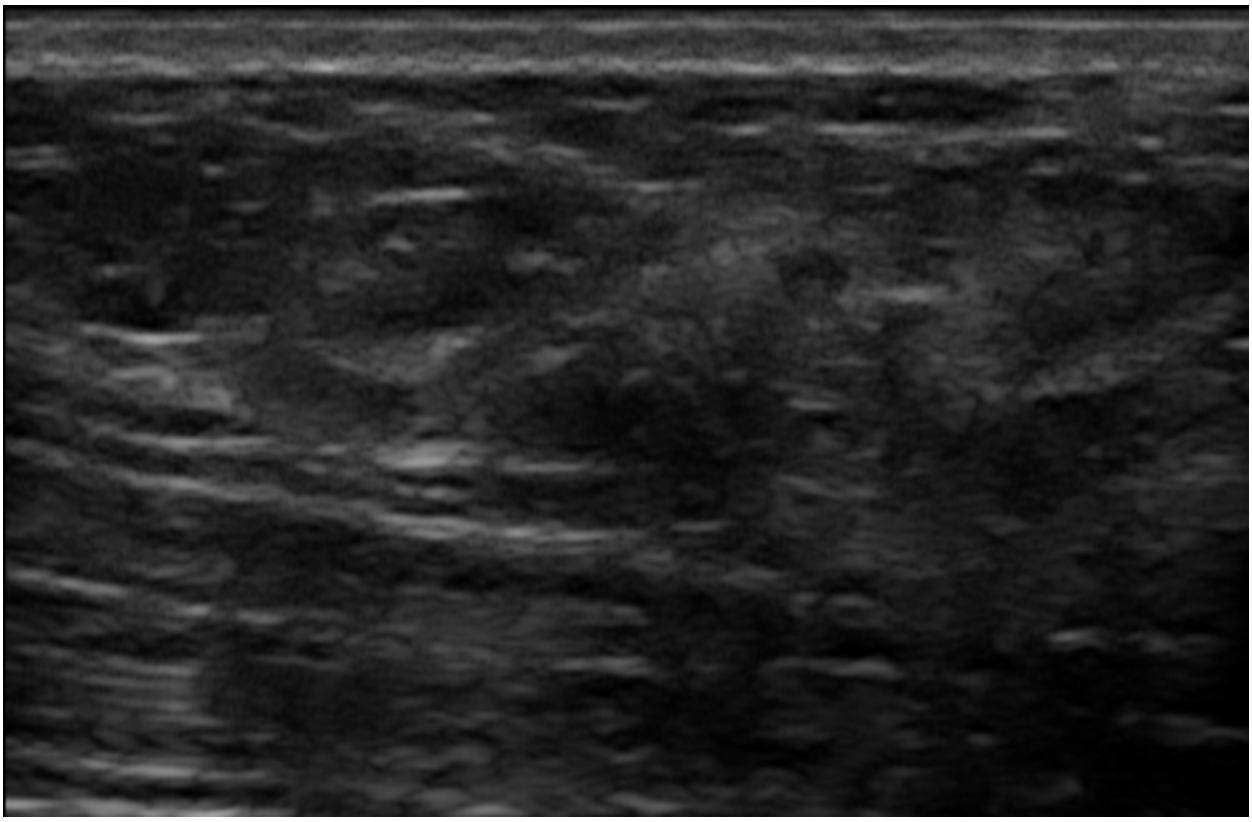

Fig. 10: After 3-rd course of the NAC, the echogenicity increase.

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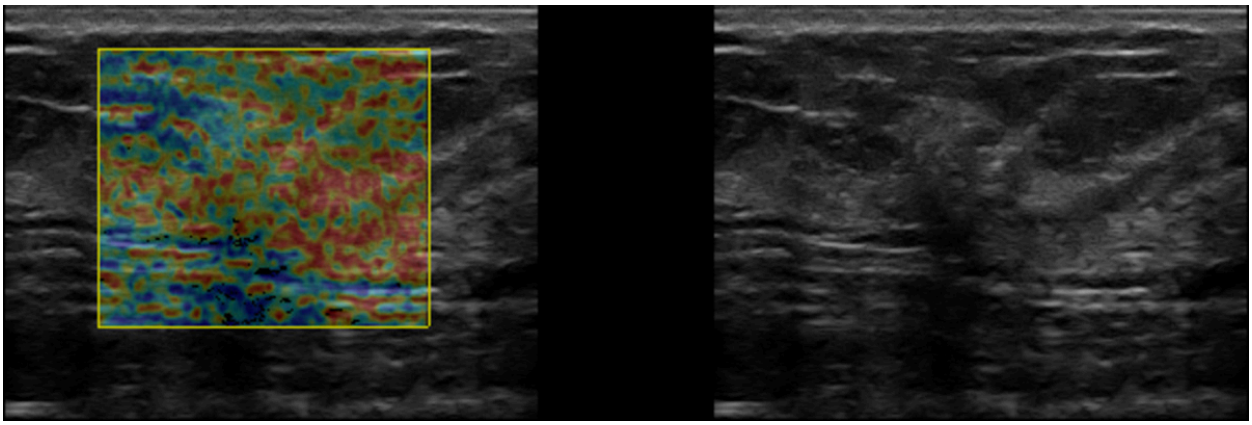

Fig. 11: After 3-rd course of the NAC, the stiffness decrease (histopathological verification: RT).

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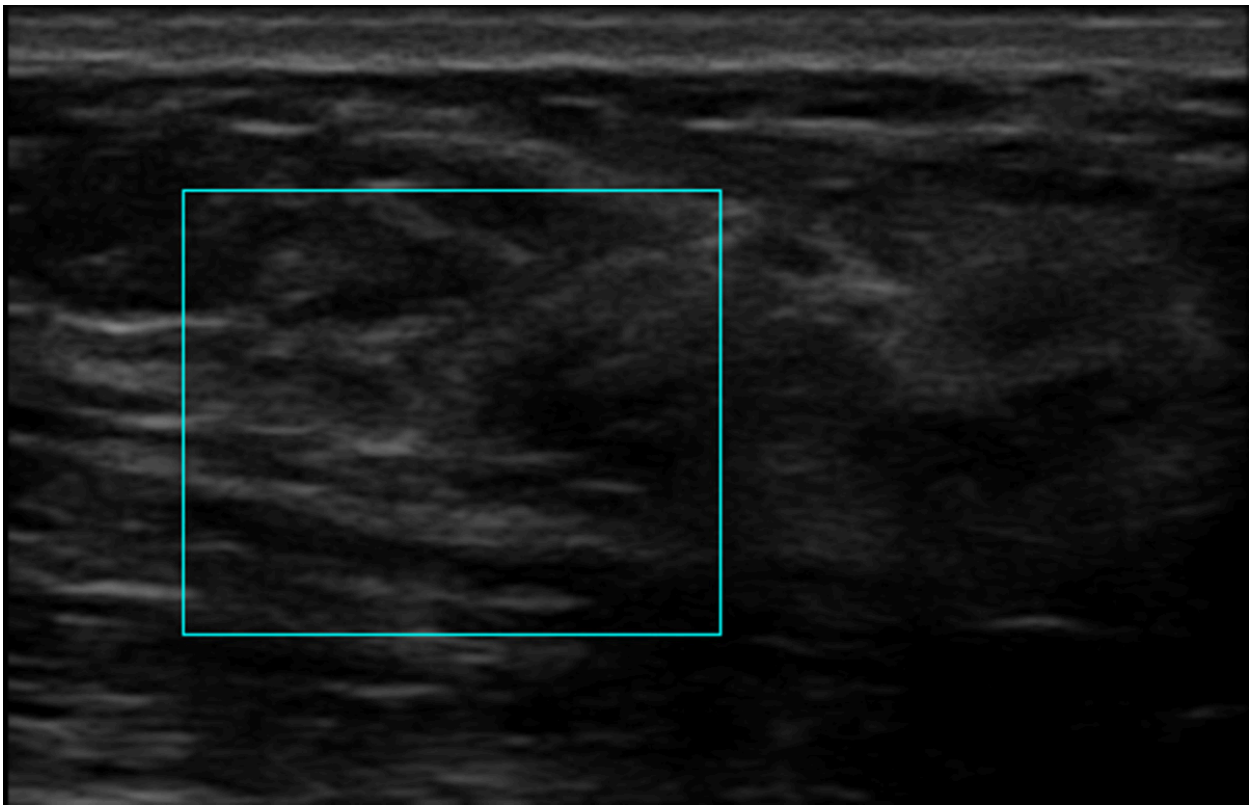

Fig. 12: After 3-rd course of the NAC, the vascularity decrease (histopathological verification: RT).

Conclusion

This is the first preliminary study to present the alteration in echogenicity from hypoechoic to isoechoic as a US feature that can predict breast tumor response to NAC. Our results demonstrated that the change in echogenicity (from hypoechogenic 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 (Fig.1-6, Fig.7-13). Matsuda et al. published results which are in agreement with 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) before and after 4thcourse of NAC therapy. They achieved an AUC of 0.8 for classifying patients into RT and N-RT groups [1].In our study, we prospectively examined the echogenicity of the tumors after each course of NAC. The change in tumor echogenicity in the US after the 3rd course of NAC may be considered useful in monitoring response.

Using SWE, Evans et al. [2]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 a change in US diameter was the best parameter (AUC 0.83) for predicting pCR.

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 and the volume. In addition, SE stiffness reduction and volume reduction could also potentially be useful for predicting the response to NAC.

Personal information

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