Elmoghazy *et al. Egypt J Radiol Nucl Med* (2023) 54:119
https://doi.org/10.1186/s43055-023-01065-2

Egyptian Journal of Radiology and Nuclear Medicine

RESEARCH

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The role of shear wave elastography in early prediction of response to neaodjuvant chemotherapy in cases of breast cancer

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Abstract

Background Breast cancer is the most common malignant tumor and the commonest cause of death in female between 35 and 55 years of age. Neoadjuvant chemotherapy (NACT) is used in large scale nowadays in management of breast cancer. Recent studies propose that shear wave elastography (SWE) can early predict tumor therapy response during NACT for invasive breast cancer.

Aim of work To study the ability of SWE to predict pathological complete response (pCR) during NACT as early as first cycle.

Subjects and methods The study analyzed data of 48 patients breast cancer who were scheduled for receiving NACT before surgery. During treatment, SWE examination was done at first four cycles.

Results Forty-eight breast cancer cases were included in the study with one hundred and ninety two examinations done. The cutoff point of stiffness ratio percent change post-first cycle in differentiating pCR and npCR groups was − 20% (AUC 0.755, sensitivity 81.8%, specificity 61.5%). The cutoff point of stiffness ratio percent change post-second cycle in differentiating pCR and npCR groups was − 49% (AUC 0.741, sensitivity 72.7%, specificity 76.9%). The stiffness ratio could predict pCR in early cycles of NACT.

Conclusions US using shear wave elastography is an available, cheap, non-contrast, non-ionizing radiation method that predicts pCR in cases of breast cancer at neoadjuvant setting as early as first cycle.

Keywords Pathological complete response, Breast cancer, Ultrasound

Background

Worldwide, the incidence of female breast cancer cases was about 2.1 million in 2018, accounting for almost one in four cancer cases among women, and 630 000 died of breast cancer [1]. Neoadjuvant chemotherapy is widely used nowadays in management of breast cancer. Neoadjuvant chemotherapy is the treatment of choice for patients with inflammatory breast cancer, unresectable and locally advanced disease aiming respectability with neoadjuvant treatment [2]. Pathological complete response is considered as surrogate marker for neoadjuvant response evaluation in case of breast cancer [3].

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Ultrasonography (US) examination is frequent in addition to initial mammographic imaging in evaluation prior to, during, and after completion of NACT [4]. The shear wave type applies a push pulse, ARFI (acoustic radiation force impulse), which results in shear wave propagation that can be measured as a velocity or pressure [5]. Magnetic resonance imaging (MRI) of the breast is the most sensitive method for assessing treatment responses in NACT patients. Multiple quantitative breast MRI measures are being actively investigated as early indicators of responses to NACT with a reduction in tumor volume being indicated as the most dependable. Breast MRI has various drawbacks, including patient convenience, high expense, lack of uniformity in image acquisition/processing, and clinicians' unwillingness to conduct extra sophisticated investigations [6]. Magnetic resonance elastography has the advantage of being able to monitor tissue deformation in any direction with equal sensitivity and assess the speed and propagation of stimuli. Magnetic resonance imaging is costly, not applicable in many clinical contexts, and requires a longer acquisition time than real-time ultrasound. Ultrasound elastography, a noninvasive imaging technique, is used to evaluate tissue stiffness (elasticity). Ultrasound is the most popular imaging modality due to its low cost, practicability, accessibility, and simple, quick technique. Ultrasound can capture shear wave elastography readings in a matter of seconds, as opposed to MR's lengthy acquisition times [7]. Studies showed that change in elasticity of the tumor can predict response to chemotherapy as early as second and third cycles[8, 9].

Aim of work

To investigate the role and sensitivity of shear wave elastography in breast cancer patients to predict pathological complete response during the period of neoadjuvant chemotherapy administration as early as the first cycle.

Patients

This prospective study was performed in a single breast cancer specialized institute, and all the included cases gave informed consent. The study was approved by institutional Review Board.

Inclusion criteria Breast cancer patients receiving neoadjuvant chemotherapy before surgery.

Exclusion criteria

- breast cancer patients scheduled for upfront surgery
- breast cancer patients proven to be metastatic.

We did 192 examinations for the 48 cases as they were examined pretreatment, post-first cycle, post-second cycle of chemotherapy then fourth cycle.

Methods

All the patients ($n=48$) were subjected to bilateral mammography, ultrasound and core needle biopsy for histopathological examination and immunohistochemistry for ER, PR, HER 2 and Ki67, in addition to metastatic work-up including CT chest, abdomen and pelvis and/or PET CT. Treatment decision was taken by multidisciplinary team including breast surgeon, medical oncologist, radiation oncologist, breast radiologist and a pathologist.

Imaging timing

Ultrasound examination was done pretreatment, post-first cycle of chemotherapy, post-second cycle and fourth cycle.

Handheld ultrasound technique

Gel is applied to breasts and ultrasound examination was done using radial and anteradial techniques using GE logic E9 device with 9L-D linear probe with frequency range of 2–9 MHz. It had a footprint FOV 44 mm.

Image analysis

The technique was used to assess the stiffness of tumor tissue. The shell-shaped ROI were placed in tumor and in surrounding normal tissue. Three images using shear wave elastography were obtained. The maximum shear wave elasticity in Kpa, minimum shear wave elasticity and mean shear wave elasticity were calculated.

The stiffness ratio was calculated by the maximum stiffness in lesion to the stiffness in normal tissue.

Shear wave elasticity was calculated post-first cycle, and then change in shear wave elasticity was calculated (including maximum shear wave elasticity in Kpa, minimum shear wave elasticity and mean shear wave elasticity) compared to baseline measurements as follows:

$$\begin{aligned}&\text{SWE max, min , mean post-first cycle absolute change}\\&= \text{SWE max, min, mean post-first cycle}\\&\quad - \text{SWE max, min, mean baseline}\end{aligned}$$

$$\begin{aligned}&\text{SWE max, min, mean post-first cycle percent change}\\&= \text{SWE max, min , mean post-first cycle}\\&\quad - \text{SWE max ,min, mean baseline}\\&\quad / \text{SWE max, min, mean baseline} \times 100\%\end{aligned}$$

Post-treatment evaluation

Correlation of response to chemotherapy was done by pathological examination of the postoperative specimen. Grading on response was based on RCB (residual cancer burden).

Statistical analysis

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) versus 28. For independent groups, the Student t test was used to compare numerical variables that were normally distributed. Receiver operating characteristic (ROC) curve analysis was used to calculate the area under the curve (AUC) and determine the cutoff values, as well as the corresponding sensitivity and specificity. The optimal cutoff was defined as the point closest to the point (0, 1) on the ROC curve. $P < 0.05$ was considered statistically significant.

Results

The current prospective study analyzed data of 48 cases with breast cancer who were scheduled for receiving neoadjuvant chemotherapy before surgery. Their ages ranged from 25 to 66 years (mean age: 43 ± 10 SD years).

Pathological types: Regarding pathological type and grading, 28 cases (58.2%) were IDC grade 2, 17 cases (35.4%) were IDC grade 3, one case medullary carcinoma (2.2%), 2 cases cribriform carcinoma (4.2%).

Molecular subtypes: According to molecular subtypes, 8 cases (16.7%) were luminal A, 6 cases (12.5%) were luminal B1, 16 cases (33.3%) were luminal B2, 8 cases (16.7%) were Her2 enriched, and 10 cases (20.8%) were triple-negative breast cancer.

TNM staging: Regarding the T stage, 4 (8.3%) patients were T1, 36 were T2 (75%), and 8 cases were T3 (16.7%). Regarding the N stage, 14 (29.2%) cases are N0, 24 cases were N1 (50%), 8 cases (16.7%) were N2, 2 cases (4.2%) were N3. All the cases included in the study were essentially M0.

Clip was inserted in 32 cases (66.6% of Cases) before starting treatment.

Treatment regimens: Regarding the treatment regimens, 26 cases (52%) received four cycles of adriamycin and cyclophosphamide and twelve cycles of taxol, 18 cases (36%) received four cycles of adriamycin and cyclophosphamide and twelve cycles of taxol and herceptin, and four cases (8%) received fluorouracil methotrexate and cyclophosphamide.

Surgical management: Breast conserving surgery was done for 28 cases (58.3%), and modified radical mastectomy was done for 20 cases (41.7%).

Post-treatment post-surgical pathological analysis: We divided the outcome of the cases into two groups, those who achieved complete pathological response pCR (22 cases) 45.8% and those who had residual disease (could not achieve pCR) (26 cases) 55.2% according to the post-operative pathology results.

Shear wave results analysis during treatment: Three images using shear wave elastography were obtained. The maximum shear wave elasticity in Kpa, minimum shear wave elasticity and mean shear wave elasticity were calculated.

Shear wave elasticity was calculated post-first cycle, and then change in shear wave elasticity was calculated (including maximum shear wave elasticity in Kpa, minimum shear wave elasticity and mean Shear wave elasticity) compared to baseline elasticity ratio the change in elasticity ratio percent.

Stiffness ratio

Post-first cycle, mean tumor stiffness ratio post-first cycle was significantly different (0.002) between the patients with pCR and npCR. The absolute change in tumor stiffness ratio post-first cycle was significantly different (0.04) between the patients with pCR and npCR as well as the percent change in the tumor stiffness ratio post-first cycle. So the decrease in tumor stiffness ratio and

Table 1 Stiffness ratio in relation to pathological outcome

	Pathological outcome				*p*-value
	pCR		npCR		
	Mean	Standard deviation	Mean	Standard deviation	
Mean tumor stiffness ratio post-first cycle (kpa)	4.2	2.8	7.2	3.3	**0.002**
Stiffness ratio delta first cycle (kpa)	−8.5	16.6	−1	6.9	**0.04**
Stiffness ratio change percent first cycle (%)	−42.9	44.5	120	315	**0.02**
Mean tumor stiffness ratio post-second cycle (kpa)	2.9	2.1	6.5	3.2	**< 0.001**
Stiffness ratio change post-second cycle (kpa)	−9.7	18.3	−1.7	6.9	**0.044**
Stiffness ratio change percent post-second cycle (%)	−33.1	92	89.4	282.5	**0.058**
Stiffness ratio post-fourth cycle (kpa)	3.3	2.5	6.2	3.4	**0.002**
Stiffness ratio change post-fourth cycle (kpa)	−9.4	17	−2	7	**0.052**
Stiffness ratio change percent post-fourth cycle (%)	−25.6	88.47	88	284	0.078

Bold values indicate significant *p* value ≤ 0.05

the percent change in the tumor stiffness ratio post-first cycle were able to predict the pCR.

Similar results apply to the second and fourth cycles of chemotherapy. This is described in Table 1. The cut-off point of the mean tumor stiffness ratio post-first cycle between the pCR and npCR group was 4.5 (AUC0.769, sensitivity 72.7%, specificity 84.6%, NPV 84%, PPV 72%, accuracy 79%). This is illustrated in Fig. 1. The cutoff point in change in mean stiffness ratio post-first cycle in differentiating pCR and npCR groups was − 1.3 (AUC 0.671, sensitivity 72.7%, specificity 61.5%). The cutoff point in change in stiffness ratio delta change percent post-first cycle in differentiating pCR and npCR groups was − 20% (AUC 0.755, sensitivity 81.8%, specificity 61.5%, PPV 64%, NPV 80%, accuracy 70.8%). The cutoff point of the mean tumor stiffness ratio post-second cycle between the pCR and npCR group is 3.9 (AUC0.811, sensitivity 72.7%, specificity 66.9%, NPV 80%, PPV 72%, accuracy 75%). The cutoff point in change in stiffness ratio post-second cycle in differentiating pCR and npCR groups is − 2 (AUC 0.664, sensitivity 63.6%, specificity 61.5%). The cutoff point in change in stiffness ratio delta change percent post-second cycle in differentiating pCR and npCR groups is − 49% (AUC 0.741, sensitivity 72.7%. specificity 76.9%, PPV 70%, NPV 77%, accuracy 70.8%).

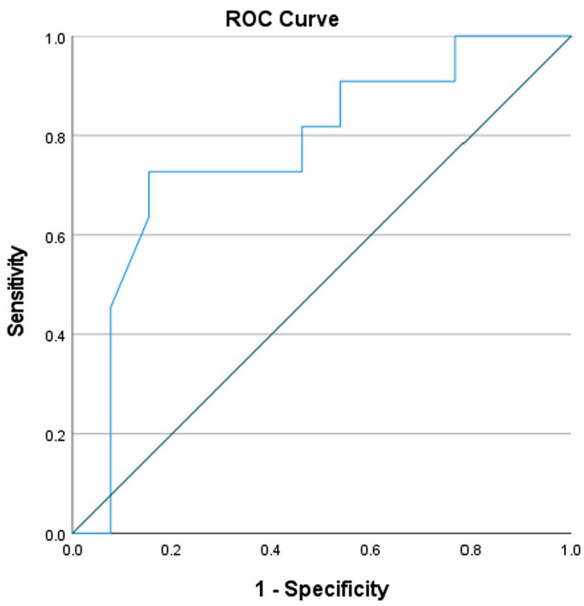


Fig. 1 ROC curve stiffness ratio post-first cycle with pathological outcome

SWE min

The decrease in absolute SWE min and the percent change in the SWE min post-first cycle of chemotherapy were not able to predict pCR as described in Table 2. In contrast, the mean SWE min value, absolute change in SWE min post-second cycle and the percent change in SWE min were able to predict pCR. The cutoff point of the mean tumor SWE min between the pCR and npCR group is 61 (AUC 0.678, sensitivity 81.8%, specificity 69.2%, NPV 81%, PPV 69%, accuracy 75%). This is illustrated in Fig. 2**.**

The cutoff point of change in SWE min post-second cycle in differentiating pCR and npCR groups is − 25 (AUC 0.720, sensitivity 72.7%, specificity 69.2%). The cutoff point in SWE min percent change post-second cycle in differentiating pCR and npCR groups is − 28% (AUC 0.741, sensitivity 81.8%, specificity 69.2%, PPV60%, NPV77.7%, accuracy 66.67%).

Table 2 SWE min correlation with pathological outcome

	Pathological outcome				*p*-value
	pCR		npCR		
	Mean	Standard deviation	Mean	Standard deviation	
Mean tumor SWE min first cycle (kpa)	69.6	34	75.9	47.3	0.609
SWE min delta first cycle (kpa)	−33.38	25	−17	61	0.255
SWE min change percent first cycle (%)	−34	28.8	63.4	274	0.104
Mean tumor SWE min post-second cycle (kpa)	51.4	31.7	79	44.5	**0.019**
SWE min change post-second cycle (kpa)	−51.56	37.9	−14	61.36	**0.016**
SWE min change percent post-second cycle (%)	−50.6	34	70.3	314.2	**0.009**
SWE min post-fourth cycle (kpa)	52	39	74	54	0.11
SWE min change post-fourth cycle (kpa)	−51	37	−18	77	0.08
SWE min change percent post-fourth cycle (%)	−50.6	34	70	314	0.07

Bold values indicate significant *p* value ≤ 0.05

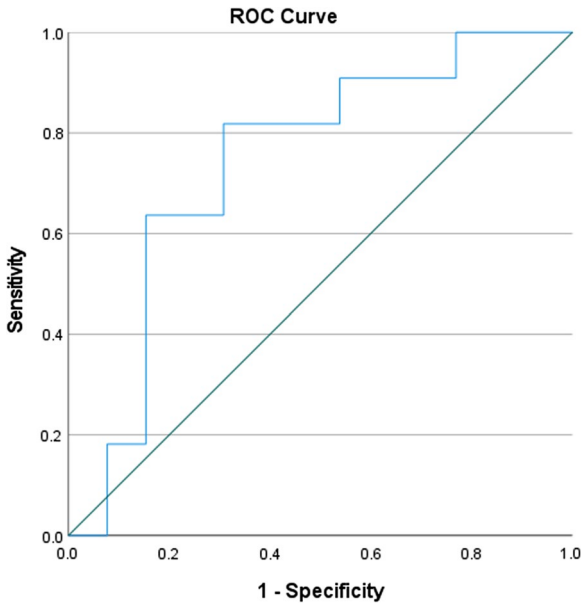


Fig. 2 ROC curve SWE min post-second cycle with pathological outcome

SWE max

The decrease in absolute SWE max and the percent change in the SWE max post-first cycle, post-second and fourth cycles of chemotherapy were not able to predict the pCR. The results are shown in Table 3.

SWE mean

The decrease in absolute SWE mean and the percent change in the SWE mean post-first cycle, post-second and fourth cycles of chemotherapy were not able to predict the pCR. The results are shown in Table 4.

SWE images of One case which achieved pCR is illustrated in Fig. 3, two cases which had residual disease (could not achieve pCR) are illustrated in Figs. 4 and 5.

Discussion

In this study, we were exploring the potential capability of ultrasound examination with one of its recent advanced applications which is shear wave elastography measured in kilopascal (kpa) in early prediction of breast cancer response to neoadjuvant chemotherapy (NACT). Categorizing the patients into pCR and npCR or responders and non-responders may change the therapeutic plan or help future modification of treatment plans. The study done by Gu et al. [10] revealed that the cutoff point in change in stiffness ratio delta change percent post-first cycle in differentiating pCR and npCR groups is − 8% (AUC 0.658, sensitivity 77.3%, specificity 71.4%), while the second cycle is − 26% (AUC 0.842, sensitivity 68.2%, specificity 100%). In the current study, the cutoff point in change in stiffness ratio delta change percent post-first cycle in differentiating pCR and npCR groups is − 20% (AUC 0.755, sensitivity 81.8%, specificity 61.5%), while the second cycle was − 49% (AUC 0.741, sensitivity 72.7%. specificity 76.9%).

In a study done by Jing et al. [9], the cutoff value of stiffness percent change was −36.1% post-second cycle with sensitivity of 72.92% and specificity of 85.71%. In the current study, the cutoff point in SWE min percent change post-second cycle in differentiating pCR and npCR groups was − 49% (AUC 0.741, sensitivity 72.7%, specificity 76.9%).

The non-significant difference in the stiffness ratio post-fourth cycle percent change in the current study is likely due to hypoxia, which is associated with increased

Table 3 SWE max correlation with pathological outcome

	Pathological outcome				*p*-value
	pCR		npCR		
	Mean	Standard deviation	Mean	Standard deviation	
Mean tumor SWE max first cycle	108.3	52.6	124.7	60.6	0.329
SWE max delta first cycle	−4.8	35.2	−6.3	95.38	0.946
SWE max change percent first cycle (%)	−4.3	44.5	99	303	0.120
Mean tumor SWE max. post-second cycle	99.6	50.8	126	55.8	0.094
SWE max change post-second cycle delta	−13.5	52	−4.7	88.3	0.684
SWE max change percent post-second cycle (%)	−4.7	59.6	78.3	220	0.093
SWE max post-fourth cycle	96.8	45.8	121	61	0.132
SWE max change post-fourth cycle	−16.3	45.8	−9.9	97.8	0.778
SWE max change percent post-fourth cycle (%)	−9.4	45	76.8	222	0.08

Table 4 SWE mean correlation with pathological outcome

	Pathological outcome				*p*-value
	pCR		npCR		
	Mean	Standard deviation	Mean	Standard deviation	
Mean tumor SWE mean post-first cycle (kpa)	88.8	44.3	101.7	52.1	0.365
SWE mean delta first cycle (kpa)	−18.2	30.3	−9	68.5	0.564
SWE mean change percent first cycle (%)	−20.5	33.9	74.8	272.7	0.110
Mean tumor SWE mean post-second cycle (kpa)	80.6	37.4	103	47.4	0.078
SWE mean change post-second cycle (kpa)	−26.4	36.9	−7.6	65.3	0.238
SWE mean change percent post-second cycle (%)	−23	37	70.7	247.4	0.085
SWE mean post-fourth cycle (kpa)	72.3	37	98.5	56	0.067
SWE mean change post-fourth cycle (kpa)	−34.7	34.8	−12	79.8	0.226
SWE mean change percent post-fourth cycle (%)	−12.2	79.8	69.5	249.5	0.065

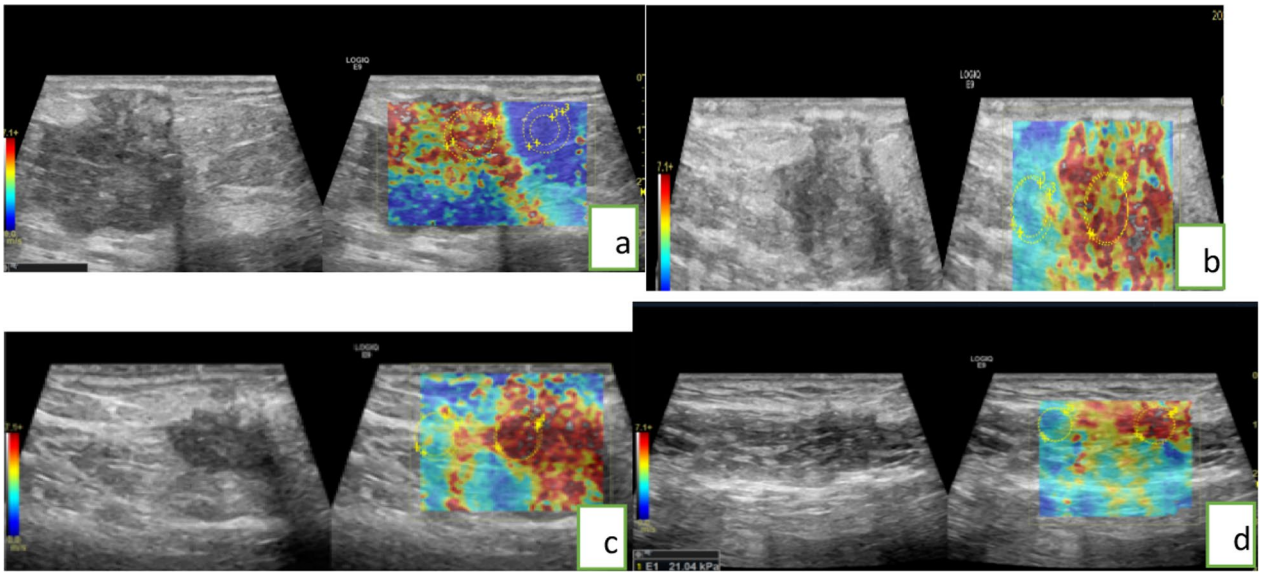
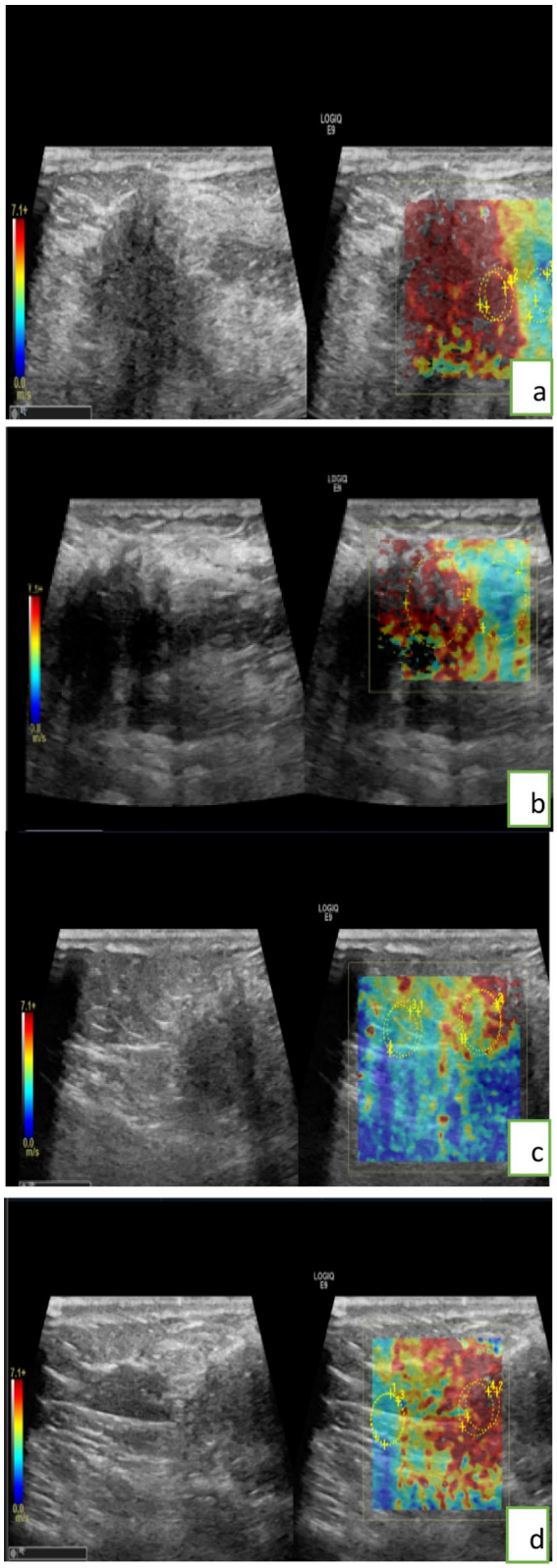


Fig. 3 66-year-old patient presented with grade 3 IDC TNBC planned to receive AC (adriamycin and cyclophosphamide) 4 cycles and 12 cycles of taxol. **a**–**d** SWE baseline, post-first, second, and fourth cycles, respectively. The stiffness ratio in the lesion, their change, and percent change were post-first cycle 9.6, −57.4, and −85.6%, respectively. Post-second cycle, the stiffness ratio, change in stiffness ratio, and percent change were 3.9, −63.1, and −94%, and post-fourth cycle the stiffness ratio, change in stiffness ratio, and percent change were 8.4, −58, and −87%. Postoperative pathology revealed pCR

matrix stiffness in the non-necrotic area of the tumors [11]

In the study done by Ma et al. [12], it was found that the change in the shear wave elasticity maximum post-one cycle of chemotherapy was not significant in predicting pCR, while the change in the shear wave elasticity mean post-one cycle of chemotherapy was significant. In contrast, the change in stiffness post-second cycle was significant (maximum and mean) between the responders and non-responders. In the current study, the decrease in SWE mean and the percent change in the SWE mean post-first cycle of chemotherapy were not able to predict the pCR. Also the decrease in SWE max and the percent change in the SWE max post-first cycle of chemotherapy were not able to predict the pCR. This is similar to post-second cycle SWE max, and SWE mean could not predict pCR post-chemotherapy. These results are different from the Ma et al.'s study.



◀ **Fig. 4** 31-year-old patient presented with grade 2 IDC ER positive, PR negative, Her2 positive planned to receive AC (adriamycin and cyclophosphamide) 4 cycles and 12 cycles of taxol and herceptin. **a**–**d** SWE baseline, post-first, second, and fourth cycles, respectively. The stiffness ratio in the lesion, their change, and percent change were at first cycle 5.7, – 3.7, and – 39%. Post-second cycle, the stiffness ratio, the change in stiffness ratio, and percent change were – 7.5, 1.9, – 20%, and post-fourth cycle, the stiffness ratio, the change in stiffness ratio, and percent change were 2.5, – 6.9, – 73%. Postoperative pathology revealed npCR (RCBII)

In the current study, the cutoff point of the mean tumor SWE min between the pCR and npCR group is 61 (AUC0.678, sensitivity 81.8%, specificity 69.2. %, NPV81%, PPV 69%, accuracy 75%). The cutoff point of change in SWE min post-second cycle in differentiating pCR and npCR groups is – 25 (AUC 0.720, sensitivity 72.7%, specificity 69.2%). The cutoff point in SWE min percent change post-second cycle in differentiating pCR and npCR groups is – 28% (AUC 0.741, sensitivity 81.8%, specificity 69.2%). Ma et al. study didn't calculate the SWE min, so we could not compare our cutoff value.

The points of strengths of the study were being prospective, involving heterogeneous group of different molecular subtypes of breast cancer, being of the few studies that assess early response during treatment to chemotherapy in cases of breast cancer rather than final assessment of response to chemotherapy that is usually studied paving the road for future studies that can personalize the management plan according to the predicted response pattern, assessing the role of ultrasound which is a cost effective method that can be used in low middle income countries rather than expensive methods as MRI and molecular imaging and using the concept of multi parametric ultrasound.

The point of weakness in the study is the small sample size, so individual assessment of each molecular subtype is difficult to done, few studies that used ultrasound to early assess response to chemotherapy hinder the ability to compare our results to other studies, the involvement of different molecular subtypes causes involvement of rather different treatment planes, and clipping of the lesion was thought to affect imaging; however, we accused images in cuts different from the clip level, also lack of standardization of radiological reporting for assessment of breast cancer in post-neoadjuvant setting, lack of standardization of acquisition of shear wave elastography either whole lesion, using single and multiple region of interest (ROI) as well as lack of single method in reporting pathological response.

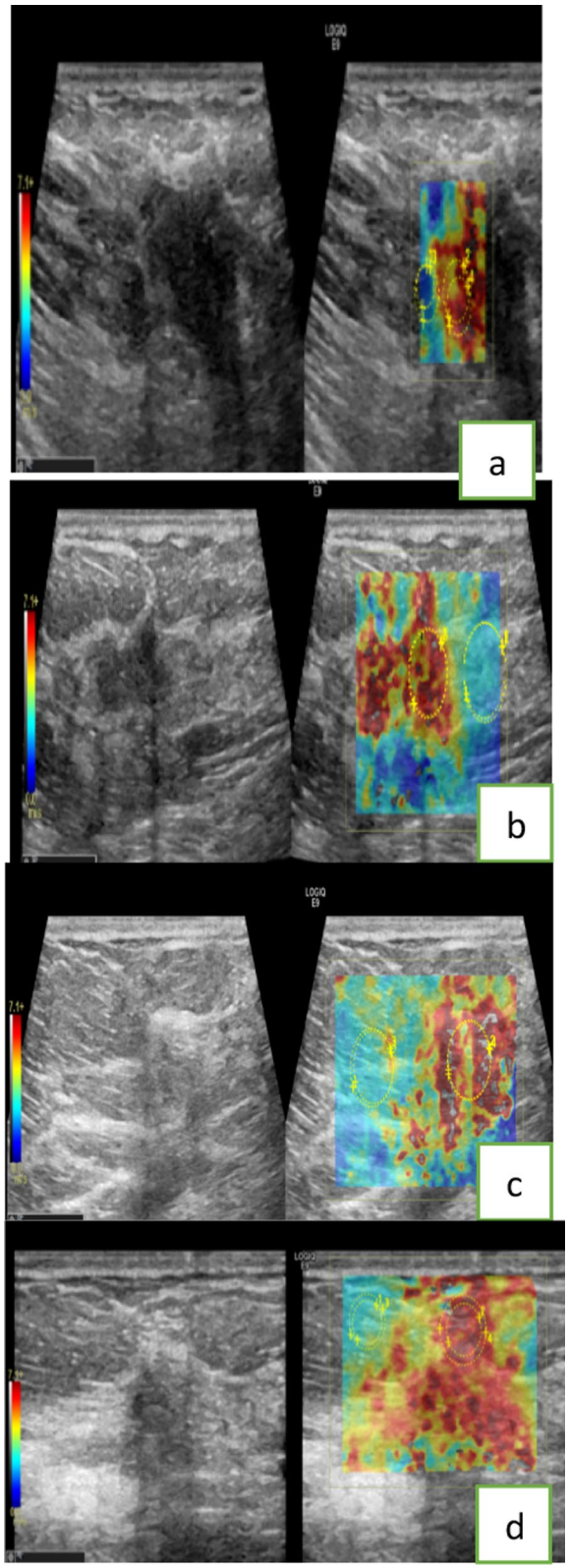


Fig.5 A 41-year-old patient presented with IDC grade 2 ER and PR positive and Her 2 positive planned to receive neoadjuvant chemotherapy and Herceptin. **a**–**d** SWE baseline, post-first, second and fourth cycles, respectively. The stiffness ratio in the lesion, their change, and percent change were 6.2, – 5.7, and 47% post-first cycle. Post-second cycle, the stiffness ratio, change in stiffness ratio, and percent change were 6.9, – 5.1, and – 42%, and post-fourth cycle, the stiffness ratio, change in stiffness ratio, and percent change ratio were 5.1, – 6.8, and – 57%. Postoperative pathology revealed npCR (RCBIII)

Conclusions

The stiffness ratio can predict pCR in cases of breast cancer at neoadjuvant setting as early as first cycle, while the SWE min can predict pCR at the second cycle.

Recommendation

We recommend routine use of shear wave elastography, namely the stiffness ratio to predict pCR after first cycle of chemotherapy. We recommend further studies to modify treatment plan according to the predicted response by shear wave elastography as early as first cycle, in order to modify treatment guidelines in the future.

Abbreviations

pCR	Pathological complete response
LABC	Locally advanced breast cancer
SWE	Shear wave elastography
NACT	Neoadjuvant chemotherapy therapy
ARFI	Acoustic radiation force impulse

Acknowledgements

Thanks to all the staff members in breast imaging unit, NCI, Cairo university.

Author contributions

AM performed the ultrasound examination of the breast, analyzed and interpreted the patient data regarding the breast lesions. AH also performed the ultrasound examination of the breast, and was a major contributor in writing the manuscript. MMR and RE participated in writing the final manuscript. TH proposed the research idea. OM revised the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study is a prospective study that was reviewed by the ethics committee of the NCI and was approved by the review board that is related to our University. Patients included gave informed written consent to use their data in research work. Reference number (approval number201920061.3).

Consent for publication
All the patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests
The authors declare that they have no competing interests.

Received: 24 February 2023 Accepted: 4 July 2023
Published online: 10 July 2023

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