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The Role of Ultrasound Elastography in Assessment of the Therapeutic Effect of Breast Cancer after Neoadjuvant Chemotherapy

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ABSTRACT

Background: Breast cancer (BC) is one of the most frequent cancers in women worldwide. Neoadjuvant chemotherapy (NACT) is used nowadays for locally advanced BC, which gives more chances to patients to undergo breast-conservative surgery. Positron emission tomography (PET), conventional ultrasound, mammography, magnetic resonance imaging (MRI), and ultrasound shear wave elastography (SWE) are used to detect the effect of the NACT.

Objective: This study aimed to evaluate the accuracy of ultrasound elastography in assessment of the therapeutic response and residual BC after NACT.

Patients and methods: This prospective study was conducted on female patients with histologically proven BC with mean age of 46.06 ± 8.44 years. They were referred from The Surgical and Clinical Oncology Departments to the Radiology Department, Menoufia University Hospital through the period from May 2023 to May 2025.

Results: ultrasound elastography revealed sensitivity of 83.3%, specificity of 75%, PPV of 83%, NPP of 75% and accuracy of 80% in follow-up of BC after NACT. When combined with the Doppler parameters, the sensitivity was 96.7%, specificity was 65%, and accuracy was 93%.

Conclusion: The present study concluded that BC is one of the most common malignancies among females. NACT is currently used in the treatment of BC, aiming at the reduction of size to prepare the patient to undergo conservative surgery. SWE is considered a useful and powerful tool in the assessment of BC after NACT

Keywords: BC, NACT, Ultrasound Doppler, Ultrasound Elastography.

INTRODUCTION

Breast cancer (BC) is the most common kind of cancer and the second leading cause of cancer-related deaths among women globally [1]. Using immunohistological methods, invasive BC may be classified into four main molecular subgroups according to the human epidermal growth factor receptor 2 (HER2), the progesterone receptor (PR), and the estrogen receptor (ER) expression [2].

For the most individualized, secure, and effective therapy, the grade, stage, and BC molecular subtypes are taken into consideration, while choosing a course of treatment [3]. More patients can have breast-preserving surgery thanks to Neoadjuvant chemotherapy (NACT), a proven treatment approach for operable and locally advanced BCs [4]. PET, conventional ultrasonography, mammography, MRI, and SWE are currently available methods for tracking response to NACT [5]. When assessing the size of a tumor that remains after treatment, conventional mammography and ultrasonography are not very reliable. SWE is a new low-cost imaging method that measures tissue stiffness quantitatively, noninvasively, and with good consistency [6].

PATIENTS AND METHODS

The present study was conducted at the Radiodiagnosis Department, Menoufia University and included 100 patients with malignant BC. Between May 2023 and May 2025, 100 female patients with histologically proven BC was managed with NACT followed by surgery.

All patients were subjected to the following:

a) Full detailed history (age, complaint, medical history, surgical history etc.).
b) Laboratory data or previous results of fine needle aspiration cytology (FNAC) histopathology (pathological type, ER, PR, KI67 & HER2) or other imaging studies (mammography and ultrasonography).
c) SWE was done for all patients at different points of time.
d) Patients were operated on after completion of NACT (breast conservative surgery or modified radical mastectomy).
e) Correlation with the histopathological findings of the specimen and surgical data, whenever possible.

Inclusion criteria: Patients with locally advanced BC confirmed by biopsy (stage II and III). Patients who were treated with NACT. Patients who underwent surgery after completion of NACT.

Exclusion criteria: Patients with recurrent disease. Patient who was not be operated on after NACT. Patients with inflammatory BC. Patients who refused to be part of the study. Patients with contraindications to NACT.

The ultrasound examination was done using a digital ultrasound scanner (LOGIC E 10, GE system, General Electric company, Boston, USA), equipped with a 9–12 MHz linear transducer. Evaluation of the criteria of the lesion was done first using the B-mode ultrasound (echogenicity, borders &

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microcalcifications) with measurement of the maximum diameter of the lesion.
Examination of the axilla to examine the lymph nodes status.

Using the Doppler mode to detect the vascularity and recording the PSV (peak systolic velocity) and RI of the lesion. Examination of the mass lesion using the SWE mode and recording the EMAX value (we should ensure good image quality by asking the patient to hold breathe and no movement was allowed).

Color map of SWE (the deep red color denoting hard lesions and the blue color denoting soft lesions) was displayed on the gray image. The region of interest (ROI) for the images was determined to include both the lesion and the surrounding normal tissue. If the lesion was large, a portion of it was incorporated along with the surrounding normal tissue. The Emax values in kilopascals were calculated, and ratio between the mass and surrounding tissue was calculated (E2/E1).

Tumor stiffness was assessed before chemotherapy [Dmax (mm), E2/E1 & Emax (Kpa)]. Doppler parameters include PSV (m/s) and RI, after 4th cycle of chemotherapy (Dmax1 (mm), E2/E1and Emax1 (Kpa). Doppler parameters include PSV1 (m/s) and RI1 and after completion of chemotherapy (Dmax2 (mm), E2/E1 and Emax2 (Kpa). Doppler parameters include PSV2 (m/s) and RI2 The relative percentage changes in tumor stiffness were determined as follows:

Δ D max=Dmax-Dmax2/D max 100.
Δ Emax=Emax-Emax2/Emax X100.
Δ E2/E1= E2/E1 -E2/E12/E 2/E1X100.
Δ PSV=PSV-PSV2/PSVX100
Δ RI=RI-RI2/RI x100

Then the radiological response was evaluated according to RECIST 1.1.

1. Complete response: Almost no lesion was detected and a reduction of the SWE to approximate the surrounding normal tissue.
2. Partial response: Reduction of the malignant lesion with a reduction in the value of the SWE.
3. Non-response (stationary, progressive): Either no changes or an increase in the size and value of SWE.

Pathology and immunohistochemistry:

The two primary phases of the pathological assessment method were as follows:

First: Patients had tumor biopsies performed under ultrasound guidance for histological evaluation. To detect the histopathological type of the mass (IDC or other types) and grade (I, II or III). Also, to detect the phenotype of the mass (ER, PR, KI67 or HER 2).

Second: After surgery, NACT responses were assessed using the residual cancer burden (RCB) method on the specimens (breast and axillary lymph nodes). RCB0, RCB1, RCB2and RCB3. Where the responding group include (RCB0 and RCB1) while the non-responding group include (RCB2 and RCB3).

Ethical approval: Menoufia Faculty of Medicine's Ethics Committee approved this study. All participants signed their consent after receiving all the information. The Helsinki Declaration was followed throughout the whole investigation.

Statistical analysis

The gathered data were tabulated and analyzed using SPSS version 26.0. Quantitative data were expressed as Mean ± SD and compared using Student's t-test or one-way ANOVA with Tukey's post-hoc test. Categorical variables were analyzed with X^2- test or Fisher's exact test. ROC curves were examined using the DeLong technique to quantify the diagnostic performance of parameters and establish the appropriate cut-off value for predicting NAC. The ideal cut-off value was determined by maximizing the Youden index. The performance of the appropriate cut-off value for total points was evaluated using sensitivity, specificity, and diagnostic accuracy. AUC more than 0.9 indicated an excellent diagnostic value, whereas AUC greater than 0.7 suggested a moderate diagnostic value. A p-value ≤ 0.05 denoted statistical significance.

RESULTS

Most of the patients (58%) were ER positive, 58% were PR positive, 16% were HER2 positive, and 48% had high Ki-67. There were statistically significant lower mean values of SWE parameters from baseline to post-treatment measurements. The mean age of the studied patients was 46.06±8.44, ranging from 32 to 64 years. 68% of them were Premenopausal and 32% Postmenopausal. 58% have no comorbidities, 30% of them had hypertension, 2% were diabetic, and 10% had Hypertension& DM. (Table 1).

Table (1): Socio-demographic and clinical characteristics of studied patients

Sociodemographic characteristics		**Total(n=100)**	
		No.	**%**
Age (years)	Mean ± SD	46.06± 8.44	
	Range	32-64	
Menstrual state	Premenopausal	68	68.0
	Postmenopausal	32	32.0
Complaints	Mass	84	84.0
	Discharge	14	14.0
	Pain	2	2.0

Most of the patients (88%) had IDC and 12% had other types. According to tumor grading, 4% were grade I, 72% grade II, 14% grade III, and 10%grade II/III.27% had complete response, 33% partial response and 40% had no response (Table 2).

Table (2): Pathological characteristics of studied patients

Pathological characteristics		Total(n=100)	
		No.	%
Pathological type	IDC	88	88.0
	Other	12	12.0
Grading	Grade I	4	4.0
	Grade II	72	72.0
	Grade III	14	14.0
	Grade II/III	10	10.0
Response	Complete response	6	6.0
	Partial response	54	54.0
	No response	40	40.0

There were significant differences between responders and non-responders, regarding Dmax (mm), Emax (KPa), E2/E1, PSV (mm/s), and resistive index (RI) (Table 3).

Table (3): Comparison of SWE parameters between response and non-response groups post-treatment of NAC

Change rate of Parameters (%)	Responder (n=60)	Non responder (n=40)	test	P value
	Mean ± SD	Mean ± SD		
Δ Dmax (mm)	-70± 20	-44± 3 1	U=4.254	<0.001**
Δ Emax (KPa)	-58± 12	-27± 23	U=6.362	<0.001**
Δ E2/E1	-58± 11	-27± 22	U=6.488	<0.001**
Δ PSV (mm/s)	-48± 11	-38± 14	U=3.186	<0.001**
Δ RI	-22±6	-17± 9	U=3.125	0.002*

U=Mann-Whitney's test, *: Significant, **: Highly significant.

Δ D-max (mm) with the optimal cut-off value set at -68 had an AUC value of 0.752(0.652 -0.852) indicating a diagnostic sensitivity of 73% and a specificity of 70%. Δ E max (KPa) with the optimal cut-off value set at -48 had the AUC value of 0.877(0.807-0.946) indicating a diagnostic sensitivity of 83.3% and a specificity of 75%, respectively. Δ E2/E1with the optimal cut-off value set at -45 had the AUC value 0.884(0.818-0.946) indicating a diagnostic sensitivity of 87% and a specificity of 70%, Δ PSV (mm/s) with the optimal cut-off value set at -42 had the AUC value of 0.688(0.576- 0.8) indicating a diagnostic sensitivity of 70% and a specificity.

of 65%. Δ RI with the optimal cut-off value set at -42 had the AUC value of 0.685(0.571-0.79) indicating a diagnostic sensitivity of 80% and a specificity of 40%. Upon combination, the sensitivity increased to 96.7% (Table 4).

Table (4): Diagnostic performance of SWE parameters in the prediction of response after NAC.

Elasticity indices(kPa)	AUC% (95%CI)	P value	Cut-off values	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Δ Dmax (mm)	0.752(0.652 - 0.852)	<0.001**	-68	73%	70%	79%	64%	72%
Δ Emax (KPa)	0.877(0.807- 0.946)	<0.001**	-48	83.3%	75%	83%	75%	80%
Δ E2/E1	0.884(0.818- 0.946)	<0.001**	-45	87%	70%	81%	78%	80%
Δ PSV (mm/s)	0.688(0.576- 0.8)	<0.001**	-42	70%	65%	75%	59%	68%
Δ RI	0.685(0.571- 0.799	0.002*	-15	80%	40%	67%	57%	64%
Combination	0.904(0.842- 0.966)	<0.001**	0.63	96.7%	65%	94%	93%	93%

****:** Highly significant, AUC, areas under the ROC curve; PPV, positive predictive value; NPV, negative predictive value.

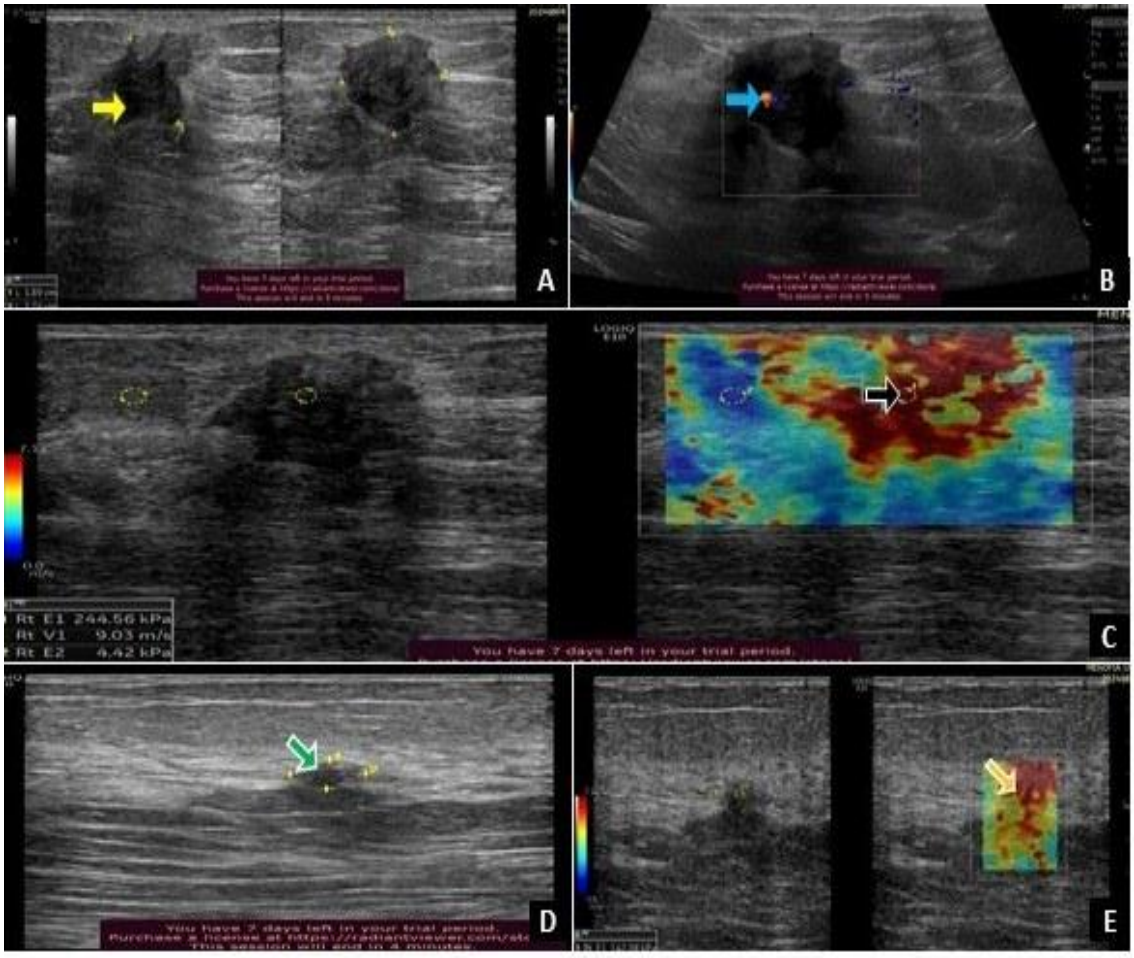

Figure (1): Female patient 50years old presented to us by bleeding per nipple, histopathology was IDC grade II, negative ER and PR, positive HER2 and KI67 was high. A) Base line US yellow arrow showed an ill-defined irregular showed hypoechoic speculated mass lesion measuring about 29 mm. B) Doppler US (base line) blue arrow central vascularity PSV 16m/sec RI0.74. C) Elastography before NAC. (C): Black arrow showed deep red color with Emax 244 kap & E2/E2 12. D) Post NACT US: Decreased size of the mass 5 mm being isoechoic (green arrow). E) Elastography post NAC: The color became mixed red and yellow color, Emax 79 & E2/E1 2.1 (orange arrow). The patient underwent BCS and pathological response was RCB1.

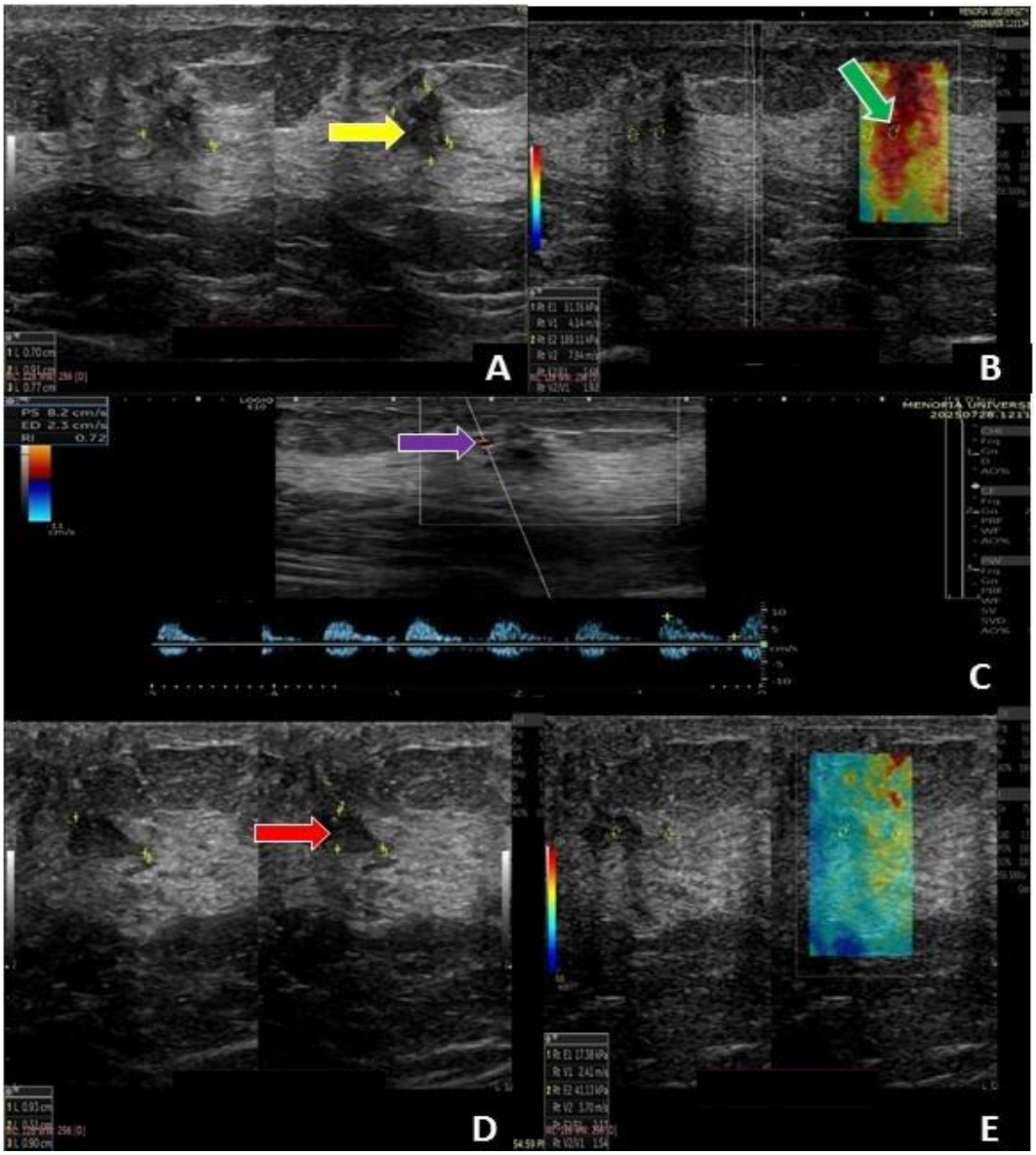

Figure (2): Female patient 39 years old presented with breast lump, histopathology was IDC grade II, negative ER & PR, positive HER2. A) Yellow arrow revealed ill-defined speculated hypoechoic mass lesion measuring about 11 mm. B) Green arrow SWE showed deep red color with Emax 190 Kpa. c) Doppler purpel arrow were PSV 16 m/sec and RI 0.74. D) Red arrow post-management, the mass was decreased in size and became less hypoechoic measuring about 8 mm. E) post NAT SWE showed light blue color with Emax was 41 kap. This patient underwent BCS, histopathology reveled cPR, which matched radiological results.

DISCUSSION

Globally speaking, BC is regarded as one of the most prevalent cancers that affect women. 1,700,000 new BC diagnoses are reported annually, according to the most recent data. BC accounts for around 25% of cancer diagnoses in women [7, 8].

Targeted therapy, hormone therapy, radiation therapy, surgery, and chemotherapy are some of the various management techniques employed. Enhancing life quality and survival rate is usually the goal of care for patients with distant metastases [9]. NACT, which is intended to be utilized prior to surgical removal of a tumor, has gained substantial interest. NACT is currently available to individuals with locally advanced BC as well as those who may benefit from size reduction prior to conserving treatment. As a result, assessing the degree of responsiveness to NACT has a significant influence on patient selection and follow-up therapy, as well as determining patient prognosis [10].

Clinical examination, breast imaging investigations, and, finally, pathological analysis of the post-treatment material can all be used to evaluate response to NACT. Ultrasound and mammography are two breast imaging techniques that are thought to be insufficient for quantifying changes in tumor size. Nevertheless, it has been demonstrated that more modern tools like SWE, MRI, and PET may accurately predict treatment response and offer a better evaluation of tumor response to NACT [11]. In order to reduce patient toxicity and postpone surgical treatment for patients who are not responding to NACT, this evaluation is vital [12].

This study was conducted on 100 patients with histopathological proven BC. The mean age of the studied patients was 46.06 ± 8.44, ranging from 32 to 64 years. This agrees with **Wang *et al.*** [12] who founded that the average age was 47.98 ± 9.36 years at time of diagnosis. In our study, 68% were premenopausal and 32% were postmenopausal, which agrees with the study done by **Qi *et al.*** [13]. **Evans *et al.*** [14] found that 64% were pre-menopausal and 36% were post-menopausal. According to a study by **Shang *et al.*** [15], premenopausal women who have higher rates of BC are more likely to have lifestyle risk factors (drinking, being overweight and being inactive), reproductive and hormonal risk factors (early menarche, later menopause, higher age at first childbearing, fewer children, reduced breastfeeding, menopausal hormone therapy and oral contraceptives) and a more extensive mammography screening program, all of which aid in the early detection of BC.

Our study showed that the most common complaint was breast swelling by about 84%, discharge was about 14% and 2% was breast pain. This agrees with study done by **Khan and Tirona** [16], which showed that the most frequent manifestation is a palpable breast lump, although other less common presentations included nipple discharge, hemorrhage and pain.

In our study the most common histological type was IDC by about 88% and the most common grade were grade II and grade II/III. This agrees with **Gu *et al.*** [4] who found that the IDC was common by about 90%. Also, this is in agreement with **Peintinger *et al.*** [17] who found that IDC was found in 84 % and ILC in 8 % of the patients?

In our study the molecular subtypes were ER and PR positive in about 56%, HER2 positive about 19% and KI67 was high in about 48% of patient. These are in agreement with **Murakami *et al.*** [18] who found that ER and PR positive were the most common (65.3%) and triple negative represented (18.9 %).

In the current study, we measured the changes in tumor shape and functionality-related indicators following NAC therapy using conventional ultrasonography, SWE, and SMI methods. We found that Emax, PSV (peak systolic velocity) and the pathological response of tumors to NAC was independently associated with RI (resistive index) and the three measures used together may predict the pathological response to NAC more accurately than using them separately. The same technique was adopted by **Qi *et al.*** [13] who combined the SWE and SMI in assessment of the response chemotherapy, While **Evans *et al.*** [14] used the SWE in assessment of the tumor response to NACT.

Our study showed that the mean tumor diameter before treatment (baseline) was 30.6 ± 12.9 mm). **Yoo *et al.*** [19] found that the mean size of the BC was 21.9 mm (range 8–50 mm). The difference between the diameters of the masses in our results may be due to poor screening program in our governorate, lack of awareness of people about BC and delayed presentation of the cases.

Our study showed that the mean Emax (baseline) was 206.8 ± 77.46 kpa. This is in agreement with **Zhang *et al.*** [20] who found that the mean E max (baseline) was195.0 (143.4–292.9) kpa. This is in disagreement with **Yoo *et al.*** [19] results, which found that the mean E average was 105.5 ± 30.6 kPa (range, 23.5–150.5 kPa; median, 113.4 kPa). This might be due to the default maximum display setting of 180 kPa; on the prototype device, readings greater than 180 kPa were logged as 180 kPa. We used the actual number displayed by the machine. They also used the E average, while we used the Emax in measurement of the elasticity within the lesion.

In our study most of the patients (about 60%) underwent breast conservative surgery (BCS) and 40% underwent modified radical mastectomy (MRM). the study by **Telegrafo *et al.*** [21] reported that most of study population underwent BCS (81%) and the least underwent MRM (19 %).however **Giani *et al.*** [22] reported that 56% of their patients underwent MRM and 44 % underwent BCS. The increased number of the patients who underwent MRM may be due to the far distance of the patient from radiotherapy units, the high cost of radiotherapy post BCS, poor awareness of the patients about the importance of close follow up after BCS.

Our study showed that about 76% showed radiological response and 24% were radiologically non-responding. This agrees with the study done by **Qi *et al.*** [13], which found that fifteen patients (22.06%, 15/68) were non-responders to NAC, whereas 53 patients (77.94%, 53/68) responded. However, **Lee and Chang** [23] found that 24/88 patients (27.27%) showed complete response, while 64/88patients were non responding (72%). The difference between our results and **Lee and Chang** [23] results may be due to that they categorized the patients into two groups responding (pCR) and non-responding groups (partial response and no response). While our study classified the response into responding group (including pCR and partial response) and non-responding group.

Our study showed significant correlation between the pathological response and the radiological response. Tumor stiffness in BC was directly connected to treatment response. The study by **Lee and Chang** [23] have established that changes in tumor stiffness act as early response indicators during therapy.

BC were less likely to react to NACT if they were stiffer at baseline and reduced less throughout NACT. Increasing tumor stiffness causes chemoresistance because it is linked to tumor growth and the aggressive tumor phenotype is linked to invasion and metastasis [24]. Thus, SWE can offer helpful imaging indicators for BC pCR to NACT prediction.

In our study the pathological response was 60% responding and 40% non-responding. The difference between the radiological and pathological response may be due to possibility of SWE in measuring the possibility of residual mass of fibrous tissue post-NAC, which can be measured as tumor residual [8].

Our study showed that there was no significant difference between the responding group as regards age where the mean age in the responding group was 44.9 ± 8 and the mean age in the non- responding group was 47.8 ± 8.6. This agrees with **Qi *et al.*** [13] who found that the mean age in the responding group was 45.83 ± 11.35 and in the non-responding group was 48.20 ± 10.30.

Our study showed that there was no significant difference between the responding and non-responding group as regards the menstrual state. The responding group showed 76.7% pre-menopausal and 23.4% postmenopausal, while the non-responding group showed 60% premenopausal and 40% post-menopausal. This agrees with **Qi *et al.*** [13] study, which revealed that the premenopausal were about 64.7% in responding group and about 66.7% in the non-responding group.

There were no significant difference between responders and non-responders, regarding ER and PR at baseline. However, HER2 and high KI 67was significantly different. This is in agreement with **Wang *et al.*** [12] who found that the responding group had high Ki67 and HER2 was positive compared to non-responder.

There was significant difference between the responding and non-responding regarding the Δ D max (mm), which was about -70 ± 20 in responding and about -44 ± 31 in non-responding. While, **Lee and Chang** [23] found that Δ D max (mm) -19.02 ± 18.45in responding and about -13.90 ± 6.84 in the non-responding group. This difference may be because in our study timing of evaluation was done after completion of the NAC, while **Lee and Chang** [23] evaluated the patients early after the 2nd cycle. **Zhang *et al.*** [20] said that change of elasticity Δ Emax (kPa) in the responder was about − 0.65 (− 0.78 to − 0.47) and the non-responder was −0.43 ± 0.28. This matches our results as the responding was -58 ± 12 and the non-responder was -27 ± 23.

Our study declared that sensitivity of Δ Emax was about 83.3%, specificity was 75 % and cut off value was -48. This agrees with **Zhang *et al.*** [20] who found that the sensitivity of Δ Emax was 81.82, specificity was 80.36 and cut off value was −0.4143.

Our study showed that Δ PSV in the responding group was about -48 ± 11 and in the non-responding group was about -38 ± 14 and Δ RI in the responding was about -22 ± 6 and in the non-responding was about -17 ± 9. While, **Qi *et al.*** [13] founded that Δ PSV in the responding group was about -33.51 ± 16.10 and in the non-responding was about -22.20 ± 9.69 and Δ RI in the responding group was about -20.73 ± 6.34 and in the non-responding was about -13.05 ± 6.64. This difference may be due to the different time of measurement as **Qi *et al.*** [13] measured the PSV and RI as early as 2nd cycle, while we measured the PSV and RI after completion of the NAC. This allowed us to make more changes.

Our study showed that the E ratio (E2/E1), which is the elasticity ratio between the average tumor elasticity and the average elasticity of surrounding fat was significantly higher in the responding (15.7 ± 10.8) and in the non-responding (7.75± 7). Our study declared that sensitivity Δ PSV was about 70%, specificity was 65 % and cut off value was -42, PPV 75%, NPV 59% and accuracy 68%. Our study showed that the sensitivity Δ RI was about 80%, specificity was about 40%, cut off value was -15, PPV6 was 7%, NPV was 57% and accuracy was 64%. This agrees with **Qi *et al.*** [13] who found that the sensitivity of the RI was79% and cut off point was about -15.16. Upon combination of all these parameters the sensitivity reached up to 96.7%, specificity 65%, PPV 94%, NPV 93%, accuracy 94% and cut off value was 0.63

Fernandes *et al.* [25] used the strain elastography and strain ratio as predictive tool for assessment of the tumor response to NACT (sensitivity 95% and specificity 54%), but there were a number of limitations on its use in therapeutic settings. Using the transducer, the operator applies a manual compression force during strain ultrasonography. This approach lacks consistency and repeatability by nature and is non-quantitative.

After NAC, breast MRI is thought to be the most precise imaging technique for determining the size of any remaining tumor [26]. But MRI has some dis advantage as not available in many hospitals, need contrast media administration, claustrophobia, couldn't be used in patient with inserted pace maker and some of metallic implant, high cost, difficult interpretation, couldn't assess the micro calcifications, which may be the only evidence of residual tumor and long scan time. So the SWE may provide a strong tool for evaluation the NACT response in BC with many advantages as it is a simple maneuver, no contrast media administration, ultrasound is a portable device may be used anywhere, no claustrophobia, compatible with pacemaker and metallic implant and low cost.

CONCLUSIONS

SWE is now considered a powerful tool in the evaluation of the response to NACT with many advantages, as it had low cost, no contrast administration, no radiation exposure, no claustrophobia, can be done with portable machines and is compatible with pacemakers and metallic implants.

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