



Prediction of Response to Neoadjuvant Systemic Therapy by Shear Wave Elastography in a Case-Series of Patients with Breast Cancer

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Abstract

Background: Neoadjuvant Systemic Therapy (NAST) is used in the treatment of patients with Breast cancer (BC). The available modalities, which are currently available for assessment of response to NAST in patients with BC are imperfect. Previous reports suggest that shear wave elastography (SWE) is useful for prediction of tumor response to NAST. However, little is known about the efficacy of SWE in predicting tumor response to NAST in the Saudi population. Purpose: to evaluate the accuracy of SWE in the prediction of pathology response to NAST.

Materials and Methods: We conducted a retrospective cross-sectional study on a case-series of female patients with BC who received NAST from January 2017 to June 2018 collected. The tumor stiffness in kilopascal (kPa), as measured by Q-Box Mean, was assessed for patients before and after receiving NAST, and was compared to pathology response. We compared mean change in tumor stiffness pre- and post- NAST using the paired t-test. We also assessed percent of agreement between SWE response and pathology response and assessed concordance by calculating the Kappa statistic. We also assessed specificity and sensitivity of SWE in detecting tumor response.

Results: Sixteen patients were included, with a mean age of 54 years (sd=12.4). After three cycles of NAST, tumor diameter as measured by ultrasound significantly reduced by 8.9 mm (sd=8.6) (t-test=4.13, df=15, p-value < 0.001). Similarly, the stiffness of tumor was significantly lower by 57.4 kpa (sd=84.7) (t-test=2.54, df=13, p-value=0.025). There was good agreement between SWE response and pathology response (81.25%) and good concordance (Kappa=0.61, p-value=0.01). Additionally, the sensitivity of SWE response was 83.33% while specificity was 80%.

Conclusion: SWE is a useful proxy for prediction of the response to NAST in our population, with high sensitivity and specificity. Further research on a larger and more representative sample is needed.

Keywords: Breast Imaging, Shear Wave Elastography, Breast Cancer, Neoadjuvant therapy, Pathology response.

Summary Statement

The accuracy of Shear Wave Elastography in the prediction of pathology response to neoadjuvant systemic therapy was assessed through comparing the change in tumor stiffness to pathology assessment among a case-series of patients with breast cancer, which showed good concordance (Kappa=0.61, p-value=0.01).

Key Results

- On average the stiffness of the tumor measured by SWE significantly regressed following chemotherapy.
- There is a good percentage of agreement (81.25%) in tumor response assessed by change in stiffness and assessed by pathology examination.
- Using -36.1% as optimal stiffness threshold, change in stiffness represents a useful predictor for response to NAST in patients with BC with high sensitivity (83.33%) and specificity (80%).

Abbreviations

NAST= Neoadjuvant Systemic Therapy,

BC= Breast cancer,

SWE= Shear wave elastography,

kPa= Kilopascal, IDC,

NOS= Invasive ductal carcinoma not otherwise specified,

ER= Estrogen receptor, PR= Progesterone receptor,

HER2= Human epidermal growth factor receptor 2,

ROI= Region of interest

Introduction

Breast cancer (BC) is the most common cancer in females. In Saudi Arabia, the number of new cases of cancer is 2741 including about 19.9% of breast cancer in women (1). Locally advanced breast cancer, which is commonly called the most advanced stage of non-metastatic breast cancer, represents over 40% of all non- metastatic breast cancer in Saudi Arabia (2).

Neoadjuvant systemic therapy (NAST) has been widely used in early and locally advanced breast cancer. NAST is used in the care of BC patients for three major reasons: to improve the surgical options, to determine the response to NAST, and to obtain long-term disease-free survival (3). Early detection of chemotherapy-resistant tumors avoid unnecessary exposure to therapy-related complications and helps in obtaining more information on response to optimize therapy (4). Palpation and most appropriate imaging methods are routinely used to assess clinical complete response.

Magnetic resonance imaging (MRI) accurately detects residual tumor (5). MRI is a useful tool to identify non- responders as early as after 2 cycles of therapy (6). Although it is significantly more accurate than mammography, (5) its higher cost and the potential advantage of clinical examination and ultrasound in terms of accessibility suggest that the combination of these latter two methods may be a reasonable alternative to MRI in clinical practice.

Breast elastography, real-time tissue or shear wave-based, is used to improve the specificity of B-mode ultrasound (US) for evaluation of tumors, using the same superficial probe. It adds only 2 to 5 minutes to routine US evaluation (7) and inherits the advantages of US imaging as low cost, accessibility and lack of use intravenous contrast agent. Shear wave elastography (SWE) has been applied for treatment monitoring of ablative therapies which induces degeneration in the form of fibrosis and inflammation, which then, changes the stiffness of ablated tissue (8). Similarly, chemotherapy can substantially alter the biomechanical properties of malignant tissues and studies suggest that SWE can be used in early prediction of tumor response to NAST in patients with BC (9) (10).

Little is known about the usefulness of SWE as a prognostic tool for BC tumor response to NAST in our region. We needed to investigate the application of SWE as possible alternative imaging modality to MRI in routine monitoring of response to NAST at our institution.

The aim of this study was to evaluate the accuracy of SWE in the prediction of pathology response to NAST, among a case-series of patients with BC. We hypothesized that through SWE we will identify the same patients identified as responders to NAST through histopathological assessment.

Materials and Methods

Study Design and Setting

Institutional ethics committee approval was given and written informed consent obtained. We conducted a cross-sectional study on data from a case-series of patients, which was collected retrospectively by reviewing hospital charts and the radiology archiving system, at Prince Sultan Military Medical City, Riyadh, Saudi Arabia. We included all female patients diagnosed with BC and who received NAST between January 1st 2017 and June 31st 2018. Patients who already received therapy or were known to have inflammatory breast cancer were excluded.

Identifying Breast Cancer

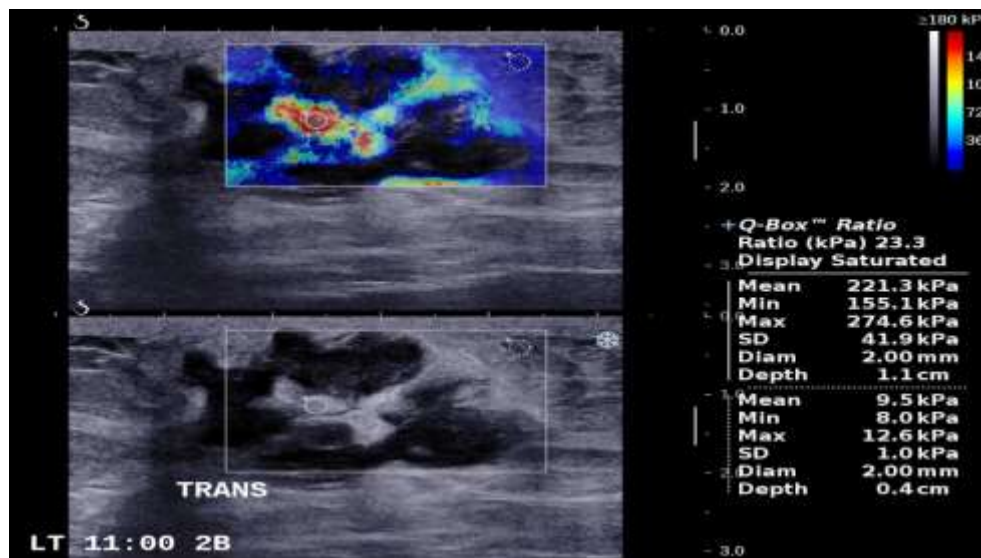
Cancer was identified in patients based on mammography and US investigation besides histopathological examination of the lump core biopsy. Based on histopathological examination, we recorded tumor Scarf Bloom Richardson tumor grade, histological subtype (invasive ductal carcinoma not otherwise specified (IDC, NOS), apocrine carcinoma, papillary carcinoma, cribriform carcinoma, metaplastic carcinoma) and immunohistochemistry expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2).

Chemotherapy

Different chemotherapy regimens were used for these patients. These included Doxorubicin and cyclophosphamide, 5-Fluorouracil, epirubicin and cyclophosphamide, Docetaxel, Docetaxel and Herceptin, Docetaxel, pertuzumab and Herceptin, and docetaxel, doxorubicin combined with cyclophosphamide. Routine US investigations were scheduled for patients three to four weeks before therapy and two to four weeks after the third cycle of chemotherapy. Surgery for cancer excision was conducted three to four weeks following the last cycle of the chemotherapy.

Cancer Imaging

Ultrasound B-mode and SWE data were collected three to four weeks before the start of therapy and follow up visit after 3rd cycle of therapy. In each visit we used super linear 4-15 MHz linear transducer and Aixplorer-Ultimate Ultrasound Diagnostic System, Aix-en-Provence, France to obtain series of B-mode US images. The tumor size was measured in two orthogonal planes and the longest dimension was recorded. In addition, four two-dimensional SWE images in two orthogonal planes were obtained for each lesion, while holding the transducer without pressure to allow the image to build up over about 10 seconds. In each image, the grayscale and SWE images were displayed simultaneously. Semitransparent color-coded SWE images were obtained by placing the rectangular region of interest (ROI) to include the lesion and the surrounding normal tissue. Tissue elasticity was measured in kilopascals (kPa) for each pixel in real-time with the elasticity scale configured at 180 kPa. The color range in the ROI was from blue (indicating low stiffness tissue) to red (indicating high stiffness tissue). Tumor elasticity was measured by placing 2 mm circular ROI over its stiffest part, including the immediately adjacent stiff tissue or halo. Four elasticity parameters were automatically calculated, including the mean (Q-Box Mean), maximum (Q-Box Max), minimum (Q-Box Min), and standard deviation (Q-Box SD). Second similar size dotted circular ROI was placed on the adjacent fatty tissue



to obtain the elasticity ratio, as illustrated in figure 1. We selected the images with highest elasticity scores and Q-Box Mean value was recorded for data analysis. A dedicated breast imaging sonographer performed the examination with direct supervision of a breast consultant radiologist (with at least 3 years of experience in breast imaging and elastography).

Figure 1a: Images show grade 3 IDC, NOS with complete pathology response after NAST. In a and b SWE (top) and B-mode images (bottom). A. baseline assessment shows irregular mass in left breast at 11:00 with heterogenous, predominantly red elasticity. The mean, minimum, maximum and standard deviation of elasticity values were measured in kPa by placing the region of interest (ROI) in the stiffest

part of the lesion (circle). B. after two months of therapy, same lesion shows significant interval reduction in elasticity. It appears homogenously not different from the color around the lesion. The mean, minimum, maximum and standard deviation of elasticity values were measured by placing ROI interiorly.

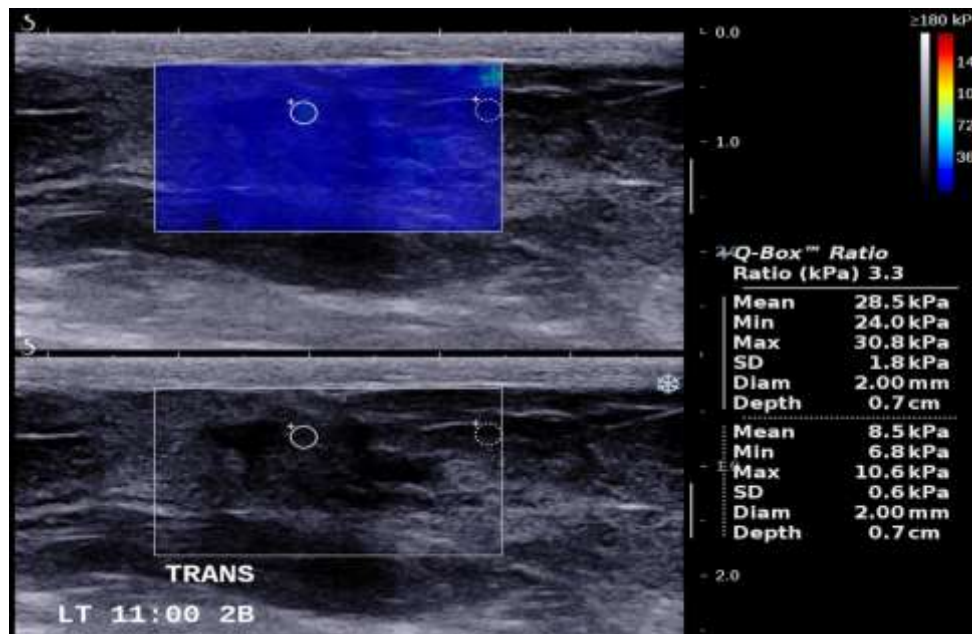


Figure 1b: images show grade 3 IDC, NOS with complete pathology response after NAST. In a and b SWE (top) and B-mode images (bottom). A. baseline assessment shows irregular mass in left breast at 11:00 with heterogenous, predominantly red elasticity. The mean, minimum, maximum and standard deviation of elasticity values were measured in kPa by placing the region of interest (ROI) in the stiffest part of the lesion (circle). B. after two months of therapy, same lesion shows significant interval reduction in elasticity. It appears homogenously not different from the color around the lesion. The mean, minimum, maximum and standard deviation of elasticity values were measured by placing ROI interiorly.

Response to Chemotherapy

Changes in the Q-Box Mean values using SWE from baseline were collected. Based on findings reported by Jing H, et al. (10), we specified the change in stiffness threshold to distinguish responders from non-responders to NAST as -36.1%. Patients with greater than 36.1% reduction in stiffness on follow up assessment were considered “positive responders” to NAST. Surgical specimens were examined for the presence of an invasive tumor or insitu carcinoma in addition to size and cellularity if present. Patients were categorized after histopathologic assessment as responders versus non-

responders based on the presence of residual disease in surgery bed. Breast tissue with complete response to therapy i.e. without residual malignant epithelial cell and without microscopic evidence of invasive cancer in axillary specimens (Sataloff T-A/N-A or T-A/N-B classification [Table 1]) were considered “responders” based on histopathological examination.

Statistical Analysis

Descriptive analyses were conducted for baseline characteristics of patients before initiation of NAST. These characteristics included age, family history of breast cancer, side of the tumor, type of tumor, hormone response status, and tumor grade based in Bloom-Scraff-Richardson system. We reported count and percentages for categorical variables and means and standard deviation for continuous variables. We also estimated the mean US tumor diameter pre- and post-chemotherapy, besides the Q-Box Mean values (stiffness) pre- and post-chemotherapy, for which we reported mean and standard deviation. Additionally, we calculated the mean change in US tumor diameter and Q-Box Mean value after the third cycle of therapy and tested the significance in change (comparing pre- and post-measures) using the paired t-test.

We created a measure called “Q-Box Mean Δ ” which reflected the response to NAST. It was calculated using the formula introduced by Jing and colleagues: $[\text{tumor Q-Box Mean after the third cycle of chemotherapy}/\text{tumor Q-Box Mean at baseline}]-1] \times 100\%$ (10). We also used the same cut-off point of -36.1% for the Q-Box Mean Δ that was identified by (10). If the Q-Box Mean Δ value was smaller than -36.1% we categorized the patient as “positive responder” to NAST. However, if the Q-Box Mean Δ value was -36.1% or more, the patient was categorized as “negative responder”. We calculated the percentage of responders as measured by Q-Box Mean Δ and by histopathological assessment. We also compared concordance of these response rates as measured by Q-Box Mean Δ and that confirmed by histopathological assessment, by calculating the percentage of agreement and the Kappa statistic. Percentage of the agreement was calculated by adding the concordant counts for positive and negative response to tumor among patients divided by the total number of patients. Finally, we estimated sensitivity and specificity of Q-Box Mean Δ in identifying response to NAST, using histopathological assessment as the standard. All statistical analyses were conducted using SAS 9.2 (SAS Institute, Carry NC). A p-value of 0.05 or less was considered statistically significant in this study.

Results

Baseline characteristics of patients

This study included a total of 16 patients with BC. The mean age of patients was 54 years (sd=12.4). The duration of chemotherapy ranged from 2.1 to 5.1 months (mean=3.9, sd=0.98). The majority of patients had a positive family history of BC (93.33%), had a tumor on the left side (56.25%), and had a high tumor grade (68.75%). The most common tumor type was IDC, NOS (68.75%). Additionally, most patients were either ER/PR positive, HER2 positive, or ER/PR positive, HER2 negative (33.33% and 33.33%, respectively) [Table 2].

Change in US and elastography parameters in relation to chemotherapy

Overall, the average diameters and stiffness of tumors were lower following chemotherapy [Table 3]. After testing for change in these parameters using the paired t-test, it appeared that tumor diameter as measured by B- mode the US has significantly reduced by 8.9 mm (sd=8.6) after chemotherapy (t-test=4.13, df=15, p-value < 0.001). Similarly, the stiffness of tumor as measured by Q-Box Mean was significantly lower by 57.4 kpa (sd=84.7) following chemotherapy (t-test=2.54, df=13, p-value=0.025).

Concordance between elastography and pathology examination for tumor response

Overall, six patients (37.5%) had a positive response based on histopathological assessment. However, seven patients (43.8%) were identified as positive responders by Q-Box Mean Δ . There was a good agreement in tumor response assessment between Q-Box Mean Δ and histopathological assessment among patients [Table 4]. Thus, the percentage of agreement in tumor response was 81.25%. Additionally, when we tested for concordance using the Kappa statistic, there appeared to be good concordance between the two modes of assessment (Kappa=0.61, p-value=0.01). Furthermore, Q-Box Mean Δ seemed to be a good method for identifying response to NAST, with high sensitivity (83.33%) and specificity (80%).

Primary Tumor		Axillary Lymph Nodes	
T-A	Total or near total therapeutic effect	N-A	No nodal metastasis and evidence of therapeutic effect
T-B	>50% therapeutic effect	N-B	No nodal metastasis or therapeutic effect
T-C	<50% therapeutic effect	N-C	Nodal metastasis present with therapeutic effect

T-D	No therapeutic effect	N-D	Nodal metastasis present without evidence of therapeutic effect
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Table 1. Pathologic response classification in tumor and axillary lymph nodes, according to Sataloff criteria

Characteristic	N=16 Count (%)
Age, mean (sd)	54 (12.4)
Family history of breast cancer	
Yes	1 (6.67%)
No	14 (93.33%)
Tumor side	
Left	9 (56.25%)
Right	7 (43.75%)
Cancer type	
Invasive ductal carcinoma (IDC)	
<i>Not otherwise specified (NOS)</i>	11 (68.75%)
<i>Apocrine</i>	1 (6.25%)
<i>Papillary</i>	1 (6.25%)
Invasive lobular carcinoma (ILC, classic)	2 (12.50%)
Metaplastic carcinoma	1 (6.25%)
Hormone receptor status	
ER/PR positive, HER2 positive	5 (33.33%)
ER/PR negative, HER2 negative	4 (26.67%)
ER/PR negative, HER2 positive	1 (6.67%)
ER/PR positive, HER2 negative	5 (33.33%)
Tumor Grade*	
Low grade	2 (12.50%)
Intermediate grade	3 (18.75%)
High grade	11 (68.75%)

* Tumor grade was based on the Bloom-Scarff-Richardson (BSR) grading system, which was assessed at baseline, before initiating chemotherapy.

Table 2. Baseline characteristics of patients with breast cancer (prior to chemotherapy)

Measure	At baseline Mean (sd)	After chemotherapy Mean (sd)	Mean Change Mean (sd)
US-Size (mm) [¥]	34.5 (14.2)	25.7 (13.8)	8.9 (8.6)
Q-Box Mean (kPa) [†]	132.2 (72.2)	99.2 (81.6)	57.4 (84.7)

*The average duration for chemotherapy was 3.9 months (sd=0.98) and ranged from 2.1 months to 5.1 months.

¥US-Size is longest diameter of lesion in mm.

†Q-Box Mean is calculated quantitative elasticity in region of interest measured by SWE in kPa.

Table 3. Average ultrasound and Q-Box Mean measures at baseline and after 3 cycles of chemotherapy for treating breast cancer*

Response as measured by Q-Box Mean Δ	Response as measured by pathology Examination	
	Positive	Negative
Positive	5 (83.33%)	2 (20.00%)
Negative	1 (16.67%)	8 (80.00%)

Notes: Percent agreement for tumor response is 81.25%. Kappa statistic for concordance was 0.61 (p-value=0.01). Sensitivity of Q-Box Δ Mean in identifying responders was 83.33%, while specificity was 80%.

Table 4. Concordance of Shear Wave Elastography Q-Box Mean and pathology examination in identifying response to chemotherapy for breast cancer

Discussion

Using NAST in treatment of BC has become common practice (3). Studies suggest that imaging provides a more accurate assessment of response to therapy than physical examination (11). Although MRI is considered the most effective and specific method in size measurement of residual disease and prediction of pathological complete response, it inherits the traditional drawbacks of MRI examination.

At our institution, we found that physicians and patients were poorly compliant to adding MRI as routine assessment to monitor response to NAST and use SWE instead. We analyzed data from a case series of 16 patients with breast cancer to summarize the changes in SWE parameters after receiving three cycles of chemotherapy. Our findings can be summarized in three points. First, on average the tumors significantly regressed following chemotherapy whether measured by size in B-mode US or stiffness in SWE. Second, of the 16 patients, 7 were identified as positive responders by change in stiffness (Q-Box Mean Δ), while 6 were confirmed as positive responders by pathology examination. Third, the percentage of agreement in tumor response between change in stiffness and pathology examination was 81.25%.

Only a few reports in the literature correlate the relationship between tumor stiffness in SWE and response to NAST in patients with BC. In our study, the tumor showed significant reduction in stiffness after the third cycle of chemotherapy. These results support findings reported by Jing, et al. (10), who used SWE for assessment, and Falou, et al. (9), who used strain elastography to assess stiffness.

Using 36.1% reduction in stiffness as threshold to identify responders to chemotherapy yielded similar findings to what was previously reported. However Jing and colleagues had the advantage of larger study group, 62 patients in comparison to 16 in our study, who were followed up for a similar time period. We found good agreement in tumor response assessment between Q-Box Mean Δ and histopathology assessment (81.25%) with high sensitivity (83.33%) and specificity (80%), suggesting that change in tumor stiffness may be a good indicator for predicting response to NAST in patient with breast cancer. This can guide physicians to more effective regimens and help them avoid unnecessary exposure to therapy in unresponsive patients.

Currently, there is no standard method for assessing histopathological response to therapy (12). Additionally, there is no consensus on how to grade the different degrees of partial histopathological response which represents the majority of patients in our study. Jing and colleagues used Miller- Payne Grading Criteria, which was based on the reduction of tumor cellularity in surgical specimens in comparison to pre-treatment core biopsy, without taking lymph node status into account, and classifying patients with grade 4 and 5 as responders (13). On the other hand, Sataloff's classification assesses microscopically the degree of therapeutic effect on tumor and lymph nodes (14). In our study we classified patients T-A/N-A and T-A/N-B as responders. To decrease the interobserver variability in future studies, consensus to use a comprehensive standardized grading system is needed with additional prognostic information.

The small number of patients in our study is considered a major limitation and subsequently, we could not assess the association between degree of response and other patient characteristics using multivariable analytical methods. In addition, due to our routine clinical practice we monitored the changes after the third cycle of therapy while SWE has been proven to show similar results after the second cycle only. We recommend conducting further research to include more regional institutions with similar demographics. Examining the association of changes in tumor stiffness with tumor immunohistochemistry profile, treatment regimens and prognostic measures is also recommended.

In conclusion, our study confirms the usefulness of the application of SWE for early prediction of the response to NAST in patients with breast cancer which might greatly influence effective treatment strategy and avoid unnecessary complications. From our institution's experience, adding SWE assessment to monitor response at our unit is generally convenient to the patients, operators, and interpreters and does not interrupt our workflow routine.

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