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Tumor Echogenicity Alteration: Can it Help Early Prediction of Pathological Complete Response to Neoadjuvant Chemotherapy in Cases of Breast Cancer?

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Abstract

Background: Locally advanced breast cancer is defined as breast cancer with large tumor size (T2 or higher stage), high regional lymph node burden, or direct invasion of the skin or underlying chest wall. Neoadjuvant chemotherapy (NAC) is the standard care option for locally advanced breast cancer patients. Quantification of echogenic changes can predict pCR of breast cancer lesions after NAC.

Aim of Study: To investigate the role of change in echogenicity at the B mode ultrasound in the assessment of response in breast cancer patients after neoadjuvant chemotherapy administration.

Patient and Methods: We did 192 ultrasound examinations for the 48 cases as they were examined before pretreatment, post-first cycle, post-second cycle of chemotherapy then post fourth cycle. The correlation of response to chemotherapy was done by pathological examination of the postoperative specimen. Grading on response was based on RCB (residual cancer burden).

Results: The cases with complete pathological response pCR were (22 cases) 45.8% and those who could not achieve complete pathological response (26 cases) 55.2%. The change in echogenicity could predict response to treatment as early as first cycle (*p*-value=0.012).

Conclusion: The breast cancer echogenicity can predict p CR in cases of breast cancer in neoadjuvant status as early as first cycle. Hence, we recommend using of lesions echogenicity to predict pCR and to monitor response to neoadjuvant chemotherapy. Further interventional studies are needed to modify the treatment plan according to the predicted response by the US as early as the first cycle.

Key Words: *Breast cancer – Neoadjuvant chemotherapy – Tumor response – Breast ultrasound – Tumor echogenicity.*

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Introduction

LOCALLY advanced breast cancer is defined as breast cancer withalarge tumor size (T2 or higher stage), high regional lymph node burden, or direct invasion of the skin or underlying chest wall **[1]**.

Neoadjuvant chemotherapy (NACT) is the standard care option for locally advanced breast cancer patients. It is used to decrease the tumor volume and to test for treatment response in-vivo. This enables in operable patients to be treated with operable ways or operable patients converting from mastectomy to breast-conserving therapy **[2]**.

Quantification of echogenic changes can predict pCR of breast cancer lesions after NACT in patients with triple negative breast cancer (TNBC) **[3]**. Other studies correlated back scatter from the lesions with the response to NACT namely the residual viable cells **[4-6]**.

Aim of work:

To investigate the role and sensitivity of change in echogenicity at the B mode ultrasound in the assessment of response in breast cancer patients after neoadjuvant chemotherapy administration.

Patients and Methods

This prospective study was performed in the breast imaging unite of the National Cancer Institute, starting from August 2020 till August 2021. All the included cases gave informed consent. The study was approved by institutional Review Board & ethical comity. We did 192 examinations for the 48 cases as they were examined pretreatment, post first cycle, post second cycle then after fourth cycleof chemotherapy.

Inclusion criteria: Breast cancer patients receiving neoadjuvant chemotherapy before surgery.

Exclusion criteria:

1- Breast cancer patients scheduled for up front surgery.

2- Breast cancer patients proven to be metastatic.

Methods:

All the cases (n=48) were subjected to pretreatment diagnosis with mammography, ultrasound and core needle biopsy to detect the tumor pathological type and well as luminal subtype (including ER, PR, HER2 and Ki67%). Treatment decision was taken by Medical disciplinary team including breast consultant surgeon, medical oncology consultant, Radiation oncology consultant and breast radiologist. During treatment Ultrasound examination was done pretreatment, post first cycle of chemotherapy, post second cycle and fourth cycle.

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

Handheld ultrasound technique:

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

Image analysis:

The echogenicity of the lesions was assessed after first, second and fourth cycles of chemotherapy then finally correlated with the postoperative pathology response.

Statistical analysis:

Data management and analysis was performed using Statistical Package for Social Sciences (SPSS) vs. 28. The Chi square test was used to compare categorical data as needed.

Results

The prospective study was conducted on 48 patients presented with breast cancer and were scheduled for receiving neoadjuvant chemotherapy before surgery starting from August 2020 till August 2021.

Their ages ranged from 25 to 66 years (mean age: 43 ± 10 SD years).

Regarding our gold standard we divided the outcome of the cases into two groups, those with complete pathological response pCR (22 cases) 45.8% and those who could not achieve complete pathological response (26 cases) 55.2%. Regarding the lesions echogenicity we assessed them pretreatment, post first cycle of Adriamycin and cyclophosphamide, post second cycle and post fourth cycle. The change in echogenicity could predict the pCR as early as first cycle then throughout rest of the cycles as shown in the Tables (1-3).

Table (1): Echogenicity vs pathological response (PCR) post first cycle.

	Pathological outcome		Total	*p*-value
	npCR	pCR		
Echogenicity Post first cycle:				
Hypoechoic:				
Count	20	14	34	0.012
Heterogeneous:				
Count	6	2	8	
Isoechoic:				
Count	0	6	6	
Total:				
Count	26	22	48	

Table (2): Echogenicity vs pCR post second cycle.

	Pathological outcome		Total	*p*-value
	npCR	pCR		
Echogenicity post second cycle:				
Hypoechoic:				
Count	14	6	20	0.002
Heterogeneous:				
Count	8	2	10	
Total:				
Isoechoic:				
Count	4	14	18	

Table (3): Echogenicity vs pCR post fourth cycle.

	Pathological outcome		Total	*p*-value
	npCR	pCR		
Echogenicity post fourth cycle:				
Hypoechoic:				
Count	4	16	20	<0.001
Heterogeneous:				
Count	2	6	8	
Isoechoic:				
Count	16	4	20	
Total:				
Count	22	26	48	

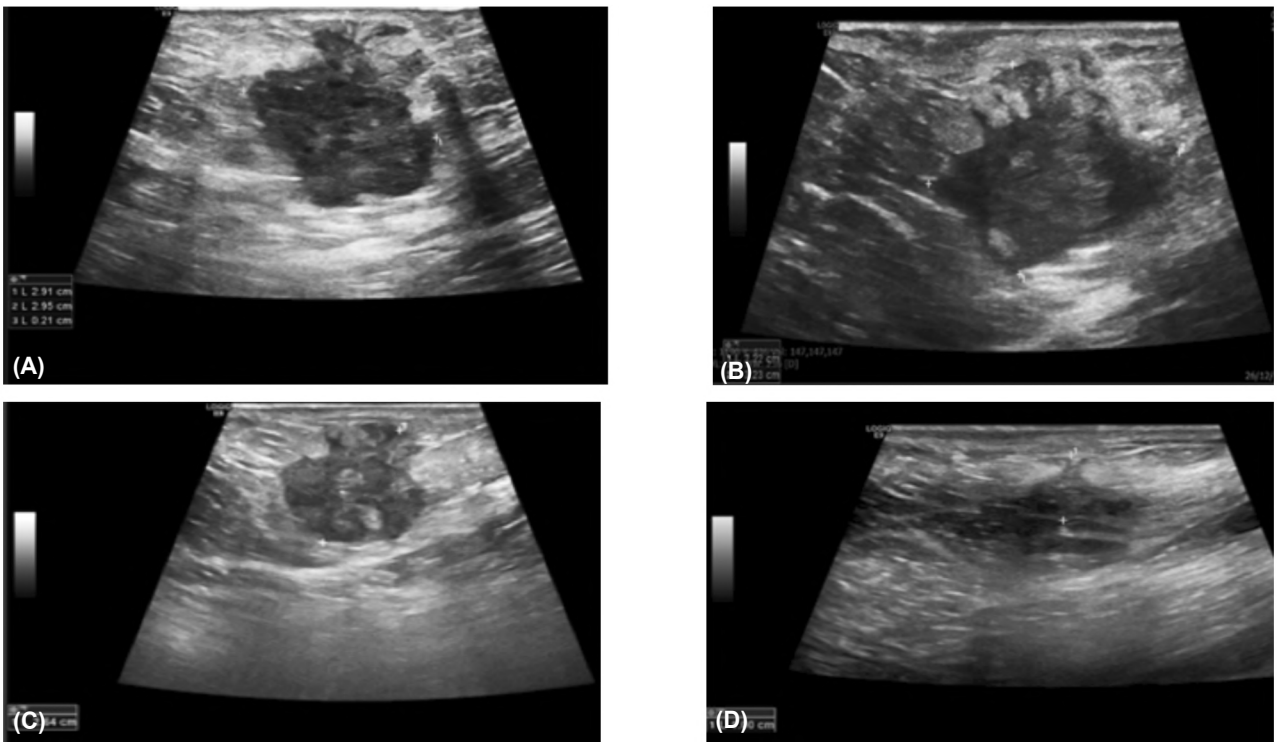

Fig. (1): 66 years old patient presented with grade 3 IDC TNBC planned to receive four cycles of AC (Adriamycin and cyclophosphamide) and 12 cycles of taxol. The mass showed changes in echogenicity allover the cycles from hypoechoic (A&B) to heterogeneous (C) to isoechoic (D). Postoperative Pathology revealed: A pathological complete response.

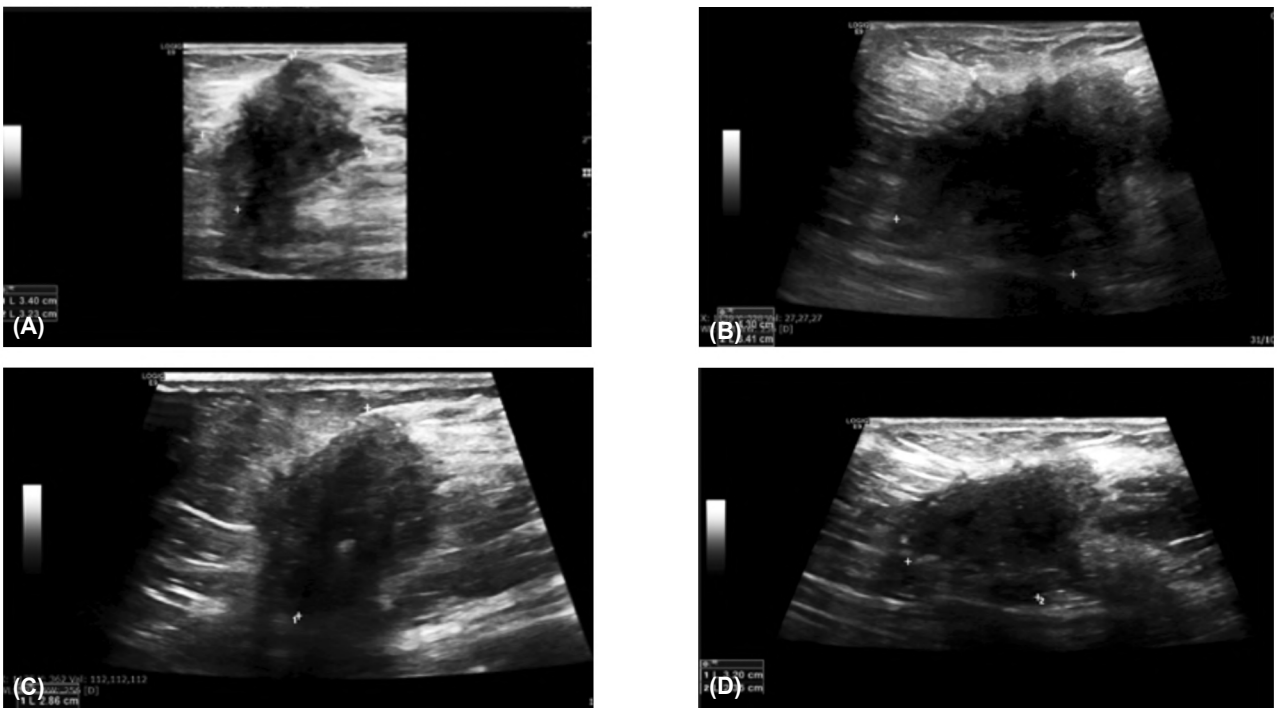

Fig. (2): A 31 years old patient presented with IDC grade 2 ER-positive PR negative, Her-2 positive scheduled for neoadjuvant chemotherapy. The mass echogenicity was stable all over the cycles as being hypoechoic. Postoperative Pathology revealed: RCB I (npCR).

Discussion

In this study we are exploring the potential capability of greyscale ultrasound examination with its 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. We found that echogenicity of the tumors was significantly altered after receiving NACT in pCR category while no significant change was detected in patient with npCR.

The study done by Dobruch-Sobczak in 2019, revealed that changes in the echogenicity of tumors after 3 courses of NACT 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, $p<0.05$) [4].

The same author published a study in 2021 that showed echogenicity change using quantitative measure which is the in herit backscatter correlated with residual malignant cancer cells [5].

In our study the change in echogenicity was able to predict the response. Another study revealed that the quantitative change in echogenicity was different between the pCR and npCR groups in cases of triple negative breast cancer [3].

In 2018, Naoko Matsuda et al., conducted Ultrasound studies to determine effects of neoadjuvant chemotherapy on breast cancer. They aimed to predict pCR to NACT using echogenicity changes in US region of interest (ROI) in patients with TNBC. Of the 52 patients they included in their study, 20 (38.5%) achieved pCR, which was significantly associated with change in ROI ratio ($p<0.01$). The cut-off values for ROI ratio and ROI difference were 0.8 and 0.3. Sensitivity and specificity were 73.7 and 81.8% for ROI ratio, and 70.0 and 81.3% for ROI difference. Area under the curves (AUCs) for ROI ratio and ROI difference were 0.80 [95% confidence interval (CI) 0.67-0.92] and 0.78 (95% CI 0.64-0.92), respectively [7].

Recent studies suggested the further use of quantitative methods and artificial intelligence to classify tumors to pCR and npCR groups [8].

Conclusion:

The breast cancer echogenicity can predict pCR in cases of breast cancer in neoadjuvant status as early as first cycle.

Recommendation:

We recommend use of lesions echogenicity to predict pCR and to monitor response to neoadjuvant chemotherapy. We recommend interventional studies to modify treatment plan according to the predicted response by US as early as first and second cycle, in order to modify treatment guidelines in the future.

References

1- LEE J., KIM S.H. and KANG B.J.: Pretreatment prediction of pathologic complete response to neoadjuvant chemotherapy in breast cancer: Perfusion metrics of dynamic contrast enhanced MRI. Sci. Rep., 8: 1-8, 2018.

2- HUANG Y., et al.: Prediction of treatment responses to neoadjuvant chemotherapy in breast cancer using contrast-enhanced ultrasound. Gland Surg., 10: 1280-1290, 2021.

3- MATSUDA N., et al.: Change in sonographic brightness can predict pathological response of triple-negative breast cancer to neoadjuvant chemotherapy. Breast Cancer, 25: 43-49, 2018.

4- DOBRUCH-SOBCZAK K., PIOTRZKOWSKA-WRÓBLEWSKA H., KLIMONDA Z., ROSZKOWSKA-PURSKA K. and LITNIEWSKI J.: Ultrasound echogenicity reveals the response of breast cancer to chemotherapy. Clin. Imaging, 55: 41-46, 2019.

5- PIOTRZKOWSKA-WRÓBLEWSKA H., DOBRUCH-SOBCZAK K. and LITNIEWSKI J.: Quantitative ultrasonography as a tool for the evaluation of breast tumor response to neoadjuvant chemotherapy. J. Ultrason., 22: e86-e92, 2022.

6- SOKBCZAK D., WRÓBLEWSKA H.P., KLIMONDA Z. and KARWAT P.: Multiparametric ultrasound examination for response assessment in breast cancer patients undergoing neoadjuvant therapy. Sci. Rep., 1-9. doi: 10.1038/s41598-021-82141-3, 2021.

7- NAOKO MATSUDA, KUMIKO KIDA, SACHIKO OHDE, KOYU SUZUKI, HIDEKO YAMAUCHI, SEIGO NAKAMURA and HIROKO TSUNODA: Change in sonographic brightness can predict pathological response of triple-negative breast cancer to neoadjuvant chemotherapyDOI: 10. 1007/s 12282-017-0782-z. Breast Cancer, Jan. 2018.

8- WANG J. and WANG B.: A Narrative Review of Ultrasound Technologies for the Prediction of Neoadjuvant Chemotherapy Response in Breast Cancer, 7885-7895, 2021.

تغير الصدى الصوتى للورم بالموجات الفوق صوتية هل يمكن استخدامه كمؤشر مبكر لتحديد استجابة سرطان الثدى للعلاج الكيميائى المسبق

سرطان الثدى هو الورم الأكثر شيوعاً فى السيدات وهو السبب الأكثر شيوعاً للوفاة بين النساء بين ٣٥ و ٥٥ عاماً من العمر. يستخدم العلاج الكيميائى المسبق على نطاق واسع فى الوقت الحاضر فى علاج سرطان الثدى. للتصوير بالموجات فوق الصوتية مزايا كونه غير مكلف ولا يحتاج لصبغة أو أشعة مؤينة. استنتجت الدراسات أنه يمكن التنبؤ مبكراً بحصول استجابة كاملة للعلاج باثولوجيا منذ الجرعة الثانية للعلاج عن طريق نقص حجم وتغير الصدى الصوتى للورم الورم. كان الهدف من الدراسة هو التحقق فى قدرة الموجات الفوق صوتية على التنبؤ بحصول استجابة كاملة للعلاج باثولوجيا . أجريت هذه الدراسة فى وحدة تصوير الثدى بالمعهد القومى للأورام بجامعة القاهرة. أعطت جميع الحالات المشمولة الموافقة المسبقة. أجريت الدراسة على ٤٨ مريضة بسرطان الثدى وكان من المقرر أن يتلقوا العلاج الكيميائى المسبق قبل الجراحة. تم إجراء الفحص بالموجات فوق الصوتية للصدى الصوتى للورم قبل العلاج، وبعد الجرعة الأولى من العلاج الكيميائى، وبعد الجرعة الثانية والجرعة الرابعة. تم إجراء ارتباط الاستجابة للعلاج الكيميائى عن طريق الفحص الباثولوجى لعينة ما بعد الجراحة.

اعتمد تصنيف الاستجابة على (عبء السرطان المتبقى) وتصنيف ميلر باين. استنتجت الدراسة وجود فارق ذو دلالة إحصائية بين الحالات الآتى حدث لها استجابة كاملة للعلاج باثولوجيا والتى لم يحصل لها استجابة منذ الجرعة الأولى من حيث التغير فى صدى الصوت للورم.

\الخلاصة : الموجات الفوق صوتية هى وسيلة متاحة للتصوير الطبى غير المؤين بدون صبغة يمكن أن تتنبأ بحصول استجابة كاملة للعلاج باثولوجيا فى حالات سرطان الثدى فى وقت مبكر منذ الجرعة الأولى.