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**ORIGINAL ARTICLE**

## Role of Sonomammography in Detection of Locally Advanced Breast Cancer Response to Neoadjuvant Chemotherapy

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**ABSTRACT:**

**Background:** Locally advanced breast cancer (LABC) can be caused by a variety of breast neoplasms. The use of mammography with sonography to estimate pathological complete response (PCR) after neoadjuvant chemotherapy (NAC) has a good degree of precision. **Aim of work:** To evaluate the precision of breast sonomammography in determining LABC response to neoadjuvant chemotherapy. **Subjects and methods:** A total of 54 female patients with locally advanced breast cancer were included in the study, which was conducted prospectively from August 2019 to May 2020, they were sent to the Zagazig University Radiology Department and hospitals by the General Surgery and Oncology Departments. A thorough medical history (personal, past, present, and family) was collected, as well as a thorough physical examination. All subjects had bilateral digital mammography as well as a traditional B-mode ultrasonography examination. Before neoadjuvant treatment, a sonomammographic evaluation of the tumour size and morphometric criteria was performed. Biopsy processes were done for suspected breast masses. after finishing the NAC 1:4 weeks previous to surgery, a sonomammographic evaluation of the tumour size and morphological criteria was conducted. **Results:** There was significant association between post chemotherapy diameters and different breast subtypes in radiological assessment. HR-/HER2- were the most subtype to show radiological response followed by HR+/HER2- while none of HR+/HER2+ show response to NAC. **Conclusion:** In patients with LABC, mammography and breast ultrasonography are regarded more reliable techniques for assessing tumour size and nodal staging of breast cancer subtypes prior to or after treatment.

**Keywords:** Sonomammography, Chemotherapy, LABC, Radiology, Breast.

**INTRODUCTION:**

Locally advanced breast cancer can be caused by a variety of breast neoplasms and accounts for 10% to 20% of all recently discovered cancers of the breast [1]. In the industrialized world, LABC is

a rare occurrence, responsible for approximately five to twenty percent of cases. However, in the developing countries, it accounts for roughly half of all cases [2]. Aggressive local treatment, like surgery or radiation, played a little impact in improving survival rates, but it did so at the expense

of higher consequences. The occurrence of distant metastases is the most common pattern of failure in LABC [3]. The standard of therapy for the management of locally advanced cancer is neoadjuvant chemotherapy (NAC) [4]. Patients benefit from better pathological complete response (pCR), incidence of breast-conserving surgery, disease-free survival, and loco-regional recurrence-free survival before loco-regional surgery [5].

Because of the prognostic details given by the molecular test, recent reviews give little concrete information on response to targeted and documented therapy, such as endocrine and trastuzumab therapy for tumors expressing human epidermal growth factor receptor 2 (Her2) proteins or estrogen receptor/progesterone receptor (ER/PR). The immunohistochemistry (IHC) categorization can help with both treatment and prognosis [6].

Breast cancer classification by the status of hormonal receptor (HRs) and human epidermal growth factor receptor-2 (HER2) create the basis of recent systemic treatment planning and prediction of long-standing prognosis. It is well-known that the rate of pCR after traditional NACT differs significantly by breast cancer subtype. [7].

HR-/HER2-tumor patients had the lowest overall survival rate. The prognosis for patients with HR-/HER2+ malignancies is poor. HR+/HER2-carcinomas respond infrequently, but they have a good prognosis. HR+/HER2+ co-expressing carcinomas have a favorable prognosis and a strong response rate to neoadjuvant anthracyclines/taxanes treatment [8].

After the last cycle of neoadjuvant chemotherapy, 1-4 weeks before surgery, a diagnostic imaging was used to assess tumor size. Physical exam and conventional breast imaging are used to measure tumor size and compare it to the tumor size prior to definitive surgical treatment in patients managed with neoadjuvant chemotherapy [9]. Mammography, breast ultrasonography, and magnetic resonance imaging have all been used to evaluate the outcome of neoadjuvant chemotherapy [10].

Mammography is one of 2 major methods for determining primary tumor size at diagnosis, with ductal neoplasia and low-grade cancers seems to be the most precise [11]. Mammography seems to be

the "gold standard" in breast assessment and is the principal imaging technique for mammary neoplasm screening and diagnosis [12]. In patients with LABC, breast ultrasonography is thought to be a more reliable tool for determining tumor size and nodal staging before or after treatment [13]. The use of mammography with sonography to estimate pCR after Neoadjuvant chemotherapy has a good degree of precision. The correlation between mammography and sonography residual tumour size and pathologic residual tumor size was considerable up to eighty percent [14&15].

#### AIM AND OBJECTIVES:

To evaluate the precision of breast sonomammography in determining LABC response to neoadjuvant chemotherapy.

#### SUBJECTS AND METHODS:

Technical design: A total of 54 female patients with a range age of 51 years (mean: 37–72 years) diagnosed with locally advanced breast cancer were included in the study, 6 cases were suffered from bilateral breast cancer and 1 were suffered from multiple breast lesions with all lesions examined and included. The cases were conducted prospectively and included clinical examination, mammography, and breast ultrasound. From August 2019 to May 2020, they were sent to the Zagazig University Radiology Department and hospitals by the General Surgery and Oncology Departments. Patients in the research were over 30 years old and had a breast malignant tumour confirmed by histology with immunohistochemistry. They were also eligible for Neoadjuvant chemotherapy. Patients who were not appropriate for NAC, were under the age of 30, or were pregnant or nursing were excluded from the trial.

Methods: A thorough medical history (personal, past, present, and family) was collected, as well as a thorough physical examination (either a broad systemic examination or a local examination of the breast). All subjects had bilateral digital mammography as well as a traditional B-mode ultrasonography examination. Before neoadjuvant treatment, a sonomammographic evaluation of the tumor size and morphometric criteria was performed. Biopsy processes were done for suspected breast masses, and the specimens were histopathological analyzed. After finishing the NAC

1:4 weeks previous to surgery, a sonomammographic evaluation of the tumor size and morphological criteria was performed and interpret by the same radiological specialist as shown as an example in **Figure (1), (2),(3)**.

Administrative considerations: Written informed consent was obtained from all participants after clear explanation of the study and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University (Institutional Research Board “IRB”). The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

### STATISTICAL ANALYSIS:

Descriptive statistics for the variables were presented in the form of frequencies and percentages for categorical variables and in the form of mean, standard deviation, for numerical variables. Comparison of response between four tumor groups was done using Chi square exact test for categorical variables while the agreement between the different diagnostic measures and the pathology was done using Fleiss' kappa. Pearson's correlation was done for the correlation between the tumor size as assessed by the pathology and other diagnostic tools. IBM SPSS version 26 for windows software was used for the analysis. A p-value of < 0.05 was considered significant.

### RESULTS

**Table (1)** shows the characteristics of the study sample. Infiltrated ductal carcinoma IDC was the most common type of breast cancer (96.29%), while infiltrated lobular carcinoma was less frequent (3.7%). Pathological tumor grades of the patients: in 2 patients (3.7%) grade I, in 48 patients (88.9%) grade II, in 2 patients (3.7%) grade III. Most of patients present with positive axillary LNs (92.6%). Almost 88.9% of the patients underwent modified radical mastectomy (MRM). Classification and distribution of breast cancer subtypes by ER, PR and HER2 status are demonstrated in **Table (2)**. The most common group was the HR+ / HER2- representing 55.6% of the sample, while each of the other three groups represented 14.8%. **Table (3)** demonstrates a

comparison of the response to treatment using sonomammography and pathology in different tumor subtypes. The sonomammography result shows a statistically significant difference between the groups (p-value=0.046), while the pathology result shows no statistically significant difference in response in the four groups (p-value =0.098). The sonomammography shows that the most common type to show partial response is TN tumors as 6 out of 8 (75 %) while in luminal A shows (60.0 %) as 18 out of 30, in Her+2 type tumors; there is 4 out of 8 (50 %) and none of luminal B type tumors show partial response (0.0%). As regard the stable disease, the most common type is luminal B type as 6 out of 8 (75%), luminal A shows 8 out of 30 (26.7%) while both TNBC and HER+ types show 2 out of 8(25%). most cases that showing progressive disease are HER2+ and luminal B types (25%) as 2 out of 8 while of luminal A there is 4 out of 30 (13.3%). No case of TNBC shows poor response (0.0%). By pathological assessment, in TN tumors 2 out of 8 (25 %) showed complete pathological response while of luminal A type tumors, there is 2 out of 30 (6.7 %). The most common types to show partial response are HER+2 type tumors and TNBC (50%) as 4 out of 8 while 14 cases of luminal A (46.7 %), and none of luminal B type shows partial response (0.0%). Stable disease is fund in 6 out of 8 in luminal B type (75%) and 9 out of 29 in luminal A type (31.03%) while in HR+2 type and TNBC type is 2 out of 8 (25%), progressive disease was showing higher in HER+2 type and luminal B type by 2 out of 8(25%) while 10 out of 30 in luminal A (33.3%), TNBC shows no progressive disease. **Table (4)** clears the mean diameters of pre and post chemotherapy tumor size of different breast subtypes in radiological assessment. There was significant association between post chemotherapy diameters and different breast subtypes in radiological assessment. The least subtype to show downsize of the tumor is HR-/HER2+ with difference between the prechemotherapy and post chemotherapy sizes about -0.575 while HR+/HER2+ is the most subtype to show downsize with difference about 1.550 followed by HR+/HER2- with difference about 1.269 then HR-/HER2- with difference about 1.175. **Table (5)** demonstrates a comparison of the accuracy of different diagnostic methods for different disease groups (Fleiss Kappa) using pathology as reference.

**Table (1):** Characteristics of the study sample:

		Frequency	Percentage
<b>Type</b>	<b>Infiltrated lobular</b>	2	3.7
	<b>Infiltrated duct</b>	52	96.29
<b>Grade</b>	<b>I</b>	2	3.7
	<b>II</b>	48	88.9
	<b>II: III</b>	2	3.7
	<b>III</b>	2	3.7
<b>pre-treatment Sonomammographic assessment of axillary LNs</b>	<b>Negative</b>	4	7.4
	<b>Positive</b>	50	92.6
<b>Operation</b>	<b>MRM</b>	48	88.9
	<b>Bilateral MRM</b>	2	3.7
	<b>LT: MRM, RT: CBS</b>	2	3.7
	<b>RT: MRM, LT: CBS</b>	2	3.7

\*Qualitative data is represented by number and percentage.

CBS: Conservative Breast Surgery

MRM: Modified Radical Mastectomy

LN: Lymph Nodes

**Table (2):** Classification and distribution of breast cancer subtypes by ER, PR and HER2 status:

<b>Groups</b>			<b>N</b>	<b>%</b>
luminal A (HR+ / HER2-)			30	55.6
luminal B (HR+ / HER2+)			8	14.8
HER2 overexpressing (HR- / HER2+)			8	14.8
triple negative (HR- / HER2-)			8	14.8
Total			54	100.00

\*Qualitative data is represented by number and percentage.

HER2: Human Epidermal Growth Factor Receptor 2

HR: Hormone-Receptor

**Table (3):** Comparison of the response to treatment using Sonomammography and pathology in different tumor subtypes.

<b>Groups</b>		<b>Sonomammography</b>				<b>P-value</b>	<b>Pathology</b>				<b>P-value</b>
		<b>Complete response</b>	<b>Partial response</b>	<b>Stable disease</b>	<b>Progressive disease</b>		<b>Complete response</b>	<b>Partial response</b>	<b>Stable disease</b>	<b>Progressive disease</b>	
HR+ / HER2 -	N	0	18	8	4	0.046	2	14	10	4	0.098
	%	0.0%	60.0%	26.7%	13.3%		6.7%	46.7%	33.3%	13.3%	
HR+ / HER2 +	N	0	0	6	2		0	0	6	2	
	%	0.0%	0.0%	75.0%	25.0%		0.0%	0.0%	75.0%	25.0%	
HR- / HER2 +	N	0	4	2	2		0	4	2	2	
	%	0.0%	50.0%	25.0%	25.0%		0.0%	50.0%	25.0%	25.0%	
HR- / HER2 -	N	0	6	2	0		2	4	2	0	
	%	0.0%	75.0%	25.0%	0.0%		25.0%	50.0%	25.0%	0.0%	

\*Chi square.

**Table (4):** The mean diameters of pre and post chemotherapy tumor size of different breast subtypes in radiological assessment:

Size (cm)		Groups				ANOVA	
		HR+ / HER2-	HR+ / HER2+	HR- / HER2+	HR- / HER2-	F	P-value
Pre	Range	2.5-10	4.5-7.2	4-7.2	3.4-5.2	2.116	0.110
	Mean ±SD	5.955 ±2.082	5.850 ±1.021	5.750 ±1.362	4.250 ±0.687		
Post	Range	1.5-10	3-6.1	2.5-9.8	1.9-4.1	3.487	0.023*
	Mean ±SD	4.686 ±2.170	4.300 ±1.202	6.325 ±2.816	3.075 ±0.876		
Differences	Mean ±SD	1.269 ±2.057	1.550 ±0.307	-0.575 ±2.117	1.175 ±0.620		
Paired Test	P-value	0.002*	<0.001*	0.467	0.001*		

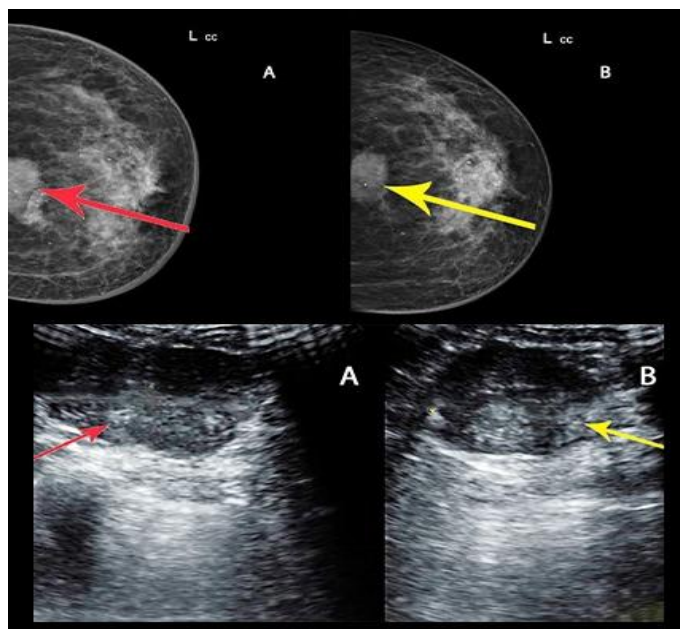
\*Anova test.

**Table (5):** Comparison of the accuracy of different diagnostic methods for different disease groups (Fleiss' kappa) using pathology as reference:

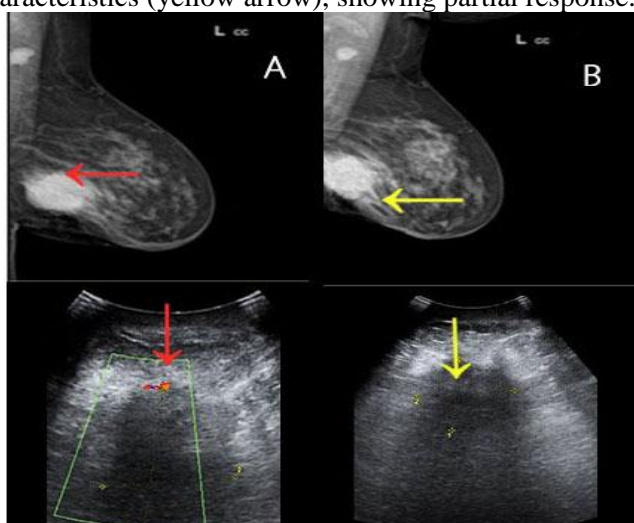
	US	Mammography	Sono-mammography
<b>Total</b>			
Complete response	-0.038	-0.038	-0.038
Partial response	0.621	0.682	0.777
Stable disease	0.841	0.628	0.919
Progressive disease	0.867	0.836	1
Overall Fleiss Kappa	0.716	0.647	0.826
<b>HR+ / HER2+</b>			
Complete response			
Partial response			
Stable disease	0.750	0.875	0.750
Progressive disease	0.250	0.125	0.250
Overall Fleiss Kappa	1.000	-0.143	1.000
<b>HR+ / HER2-</b>			
Complete response	0.033	0.033	0.033
Partial response	0.467	0.433	0.533
Stable disease	0.333	0.400	0.300
Progressive disease	0.167	0.133	0.133
Overall Fleiss Kappa	0.585	0.684	0.780
<b>HR- / HER2+</b>			
Complete response			
Partial response	0.500	0.500	0.500
Stable disease	0.250	0.250	0.250
Progressive disease	0.250	0.250	0.250
Overall Fleiss Kappa	1.000	1.000	1.000
<b>HR- / HER2-</b>			
Complete response	0.125	0.125	0.125

Partial response	0.625	0.375	0.625
Stable disease	0.250	0.500	0.250
Progressive disease			
Overall Fleiss Kappa	0.529	0.158	0.529

\* Fleiss' kappa.

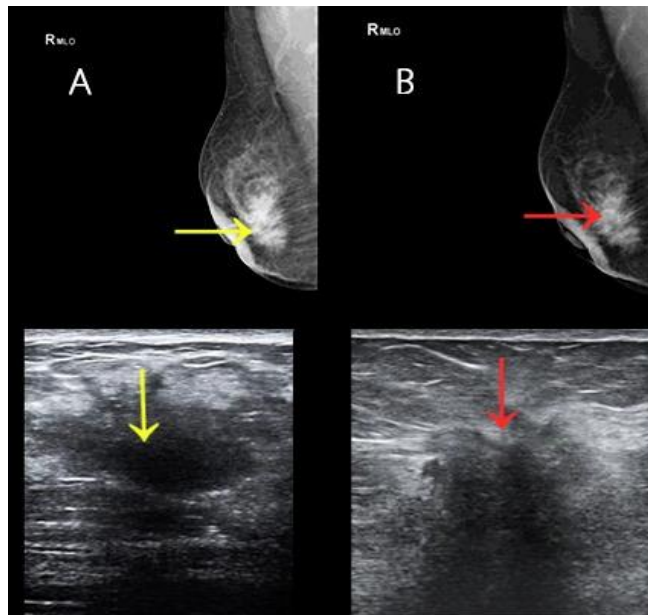


**Figure (1):** 40 years old patient with combined sonomammography showing **A. Pretreatment:** Mammography CC view: fairly defined irregular radiopaque lesion abutting the chest wall showing internal calcification associated with diffuse skin thickening (red arrow). Breast ultrasound: fairly defined irregular hypoechoic mass showing internal microcalcification (red arrow). **B. Post-treatment:** mammography CC views: Lesion with the same characteristics showing reduction of dimensions, with partial response (yellow arrow). Breast ultrasound: lesion with the same characteristics (yellow arrow), showing partial response.



**Figure (2):** 48 years old patient with combined sonomammography showing **A. Pretreatment.** mammography CC view: irregular radiopaque lesion seen at the LIQ with skin dimpling and mild skin thickening (red arrow). Breast ultrasound: irregular deep seated hypoechoic soft tissue lesion (red arrow). **B. Post-treatment:** mammography CC views: Lesion with the same characteristics showing no change of dimensions, with partial

response (yellow arrow). Breast ultrasound: lesion with the same characteristics (yellow arrow), showing stable disease.



**Figure (3):** 53 years old patient with combined sonomammography showing **A. Pretreatment.** mammography CC view: speculated dense lesion seen at the retroareolar region with retracted nipple (yellow arrow). Breast ultrasound: ill-defined irregular hypoechoic soft tissue lesion (yellow arrow). **B. Post-treatment:** mammography CC views: Lesion with the same characteristics showing no change of dimensions, (red arrow). Breast ultrasound: lesion with the same characteristics (red arrow), showing partial response.

### DISCUSSION

The rationale for NACT in LABC management is established on its efficacy in early evaluating of the response, as well as possibly preferable outcomes for certain subtypes of high-risk patients [16].

Concerning the breast cancer subtypes of the included patients in our study, HR+ / HER2-subtype is the highest percentage of 55.6%. Herein, we evaluated the response of the different intrinsic subtypes of breast cancer to NACT and we made the following observations. First, we have found that patients with the triple negative and luminal subtype of breast cancer have a higher rate of response to NCT than the HER2 overexpressing and luminal B subtype. This shows disagreement with previous studies, Krijgsman et al. [17], who tested neoadjuvant chemotherapy response in 1212 breast cancer patients, treated with neoadjuvant chemotherapy, they found that response to NACT is higher in TNBC followed by HER2-type followed by luminal- B type subgroup then luminal-A type subgroup. This could be explained by not using anti HER2 therapy. This denotes the importance of

using anti HER2 therapy in all HER2 overexpressing molecular subtypes of breast cancer and its major difference in pathologic complete response [18].

Second, In our analyzed group only 25% patients with TNBC subtype and only 6.7% of luminal A subtype achieved pCR while none of luminal A or HER2 overexpressing subtypes achieved pCR with overall 7.4% of patients achieved pCR, which is less than expected and could be explained by low number of patients examined and some studies indicate that LABC in Egypt shows a more aggressive biology [19]. Clinical studies reported pCR rate of 16-20% pCR with sequential use of antracycline-taxane regimens [20].

Studies of neoadjuvant chemotherapy have used a variety of approaches for detect tumor response. Recently, there are no known clinical practice guidelines for how best to detect tumor response to neoadjuvant chemotherapy. Usually, patients undergo conventional breast imaging (mammography and ultrasonography [US]) and physical examination although the predictive power

of both mammography and ultrasound for measuring response to NAC is varied. Mammography has also been proven to be less precise and may overestimate therapy response [21]. After neoadjuvant therapy, ultrasound had been demonstrated to be a better predictor of pathologic tumor size than mammography [22]. The combination of mammography and ultrasound appears to be the best approach for monitoring tumor response [23].

Our results revealed that there was no significant difference between combined sonomammography or pathology and the response rate. There was also no significant difference between post chemotherapy diameters assisted sonomammographically or pathologically.

In line with our results, in a retrospective analysis of 93 patients undergoing neoadjuvant chemotherapy for breast cancer and had presurgical radiological assessment, Mankanjuola et al. [24] found that a radiologic response correlated highly (93%) with pathological response in both ultrasound and mammographic evaluations.

Our study revealed that the agreement for all patients was observed higher in the ultrasound ( $\kappa=0.716$ ) than the Mammography ( $\kappa=0.647$ ) which with a line with study conducted by Keune et al. [25] of retrospective analysis to detect the ability of mammography and breast ultrasound to accurately measure residual tumor size following neoadjuvant chemotherapy compared with surgical pathology measurement of the residual tumor demonstrated that residual tumors were sized accurately using breast ultrasound compared with using mammography.

The Limitations of this review are rather small sample size and the retrospective study design.

## CONCLUSION

In patients with LABC, mammography and breast ultrasonography are regarded more reliable techniques for assessing tumor size and nodal staging of breast cancer subtypes prior to or after treatment. When used together, they have a high degree of accuracy in terms of evaluation of tumor response following neoadjuvant chemotherapy.

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