

## ROLE OF ULTRASONOGRAPHY IN RESPONSE ASSESSMENT FOLLOWING NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CARCINOMA: EXPERIENCE FROM A TERTIARY CARE CENTER

BIDYUT BISWAS<sup>1</sup>, MD ASIF ALI<sup>2</sup>, ARABINDA ROY<sup>3</sup>, LINKON BISWAS<sup>4\*</sup>

<sup>1</sup>Department of Surgery, Raiganj Government Medical College and Hospital, Raiganj, West Bengal, India. <sup>2</sup>Department of Radiology, Raiganj Government Medical College and Hospital, Raiganj, West Bengal, India. <sup>3</sup>Department of Radiotherapy, Raiganj Government Medical College and Hospital, Raiganj, West Bengal, India. <sup>4</sup>Department of Radiotherapy, Nilratan Sircar Medical College and Hospital, Kolkata, West Bengal, India.

\*Corresponding author: Linkon Biswas; Email: linkonbiswas30891@gmail.com

Received: 28 January 2024, Revised and Accepted: 13 March 2024

### ABSTRACT

**Objective:** Neo-adjuvant chemotherapy (NACT) has a pivotal role in the treatment of locally advanced breast carcinoma (LABC). In this study, we assess the efficiency of ultrasound in the response assessment of NACT in patients with LABC using RECIST criteria and its correlation to the final histopathological report.

**Methods:** 40 patients with LABC underwent clinical examination and ultrasonography (USG) of the bilateral breast and axilla before starting NACT. After receiving three cycles of NACT, a repeat USG and clinical examination were done to assess the response to chemotherapy. Patients with responsive disease underwent radical surgery, and we correlate the findings of histopathological examination (HPE) with those of post-NACT USG findings.

**Results:** After three cycles of NACT, clinical examination showed a complete response in 15 (37.5%) patients and a partial response in 21 (52.5%) patients. While USG detected a complete response in 8 (20%) patients and a partial response in 28 (70%) patients, seven patients, in whom clinical examination did not find any disease, were detected by USG. HPE showed a complete pathological response in 5 specimens, and in the rest of 31 cases, HPE revealed a residual tumor. USG did not miss any of the pCR cases but overestimated CR cases by 9% (3 patients). On the other hand, all partial response diagnoses by USG were acknowledged by HPE.

**Conclusion:** To conclude, it can be said that USG can be used as an effective radiological tool for response assessment and subsequent treatment decisions, especially in places where there is a lack of infrastructure and affordability.

**Keywords:** Locally advanced breast cancer, Ultrasonography, Neoadjuvant chemotherapy, Response assessment.

© 2024 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2024v17i6.50477>. Journal homepage: <https://innovareacademics.in/journals/index.php/ajpcr>

### INTRODUCTION

As per GLOBOCAN 2020 data, breast cancer is the most common malignancy worldwide. In India, it constituted 13.5% of all cancer cases in 2020 [1]. Due to urbanization with changing lifestyle and dietary habits, there is an increase in the incidence of breast cancer in urban areas than in rural regions [2]. In our country, most patients present at an advanced stage due to ignorance, lack of awareness, and limited access to health-care facilities.

Previously, radical surgery with or without radiotherapy was the standard treatment for breast carcinoma. However, over the time, neoadjuvant chemotherapy (NACT) has become a key component of the management of locally advanced breast carcinoma (LABC) [3]. NACT downsizes the tumor, treats the micro-metastasis, and thus improves the surgical as well as survival outcomes. Attainment of pathological complete response (pCR) is directly proportional to improved disease-free survival and overall survival; thus, it is a surrogate indicator for long-term outcome. However, the pre-operative response assessment of NACT is important to take decision regarding surgery. In the present day, clinical as well as many other radiological imaging modalities such as mammography, ultrasonography (USG/US), computed tomography (CT), and magnetic resonance imaging (MRI) (based on the age and density of the breast of the patient) are available for response assessment [4,5]. Hence, there is a need to choose a specific modality to predict the tumor response which will be in correlation with the final pathologic report.

At our center, most of the patients are from lower socioeconomic class who cannot afford an MRI, CT scan, or other advanced imaging modalities. Hence, we chose USG as the modality of response assessment for NACT because of its wide availability, cost-effectiveness, and simple procedure. At present, there is a gap between the assessments of the clinical response of the tumor to predict the final pCR after NACT. In this study, we assess the efficiency of ultrasound in the response assessment of NACT in patients with LABC using RECIST criteria and its correlation to the final histopathological report.

### METHODS

It was a prospective study done at our institute among LABC patients who received NACT before radical surgery. The study was conducted between June 2022 and November 2023. The study was initiated after getting ethical clearance from the institutional ethics committee.

#### Inclusion criteria

1. LABC (T3 with any N, any T1T3 with N2, T4 with any N, and any T with N3)
2. Age 20–60 years
3. ECOG 0–2.

#### Exclusion criteria

1. Bilateral breast carcinoma
2. Recurrent breast carcinoma
3. Metastatic breast carcinoma

4. Multiple synchronous malignancies
5. Medically unfit for chemotherapy, doing radical surgery, or both
6. Previous history of treatment with chemotherapy or radiotherapy.

#### Study technique

We enrolled 40 patients with LABC using the above-mentioned inclusion and exclusion criteria. All the patients underwent clinical examination and USG of the breast and axilla before starting NACT.

The USG machine used was a Philips Affiniti 70G (Ultrasound/Color Doppler) with a linear probe with a high frequency of 5–12 Hz.

Then patients were given 3 cycles of NACT with a docetaxel, doxorubicin, and cyclophosphamide (TAC) regimen. Following 3 cycles of NACT, USG, and clinical examination, it was done again to note the size of the existing lesion and for response assessment according to RECIST 1.1 criteria.

Patients with responsive disease underwent radical surgery. The residual tumor detected (if any) in histopathological examination (HPE) was correlated with that of response assessment by clinical examination and USG.

#### Statistical analysis

All the data were analyzed by the Statistical Package for Social Sciences Software (version 20) using appropriate statistical tests. Data related to numerical variables were summarized as mean and standard deviation and data for categorical variables as percentages and counts.

#### RESULTS

The mean age of the study population was  $46.5 \pm 10.8$  years. Most of the patients were in the age group of 41–50 years. Most patients had a tumor size of 5–6 cm with a mean tumor size of  $5.2 \pm 1.2$  cm, and among them, 57% patients had a clinically palpable axillary lymph-node. Most lymph node-positive patients had N1 disease (as per the American Joint Committee on Cancer staging). 52.5% of patients had stage IIIB disease; the rest had stage IIIA disease (Table 1).

#### Post-chemotherapy evaluation of clinical response

The following NACT response assessment was done by clinical examination as well as by USG of the breast and bilateral axilla. As per clinical examination, 37.5% of patients had a complete response and 52.5% had a partial response. USG revealed 20% of patients had a complete response, but 70% had a partial response 17% higher than the clinical examination. Three people had progressive disease, and one had stable disease on USG. These patients did not undergo radical surgery. Hence, for the final treatment, 36 patients became eligible (Table 2).

After NACT, 36 patients underwent radical surgery. Among them, five patients had pCR, in contrast to eight in the USG. 31 patients had residual disease in the operative specimen (Table 3).

#### DISCUSSION

Initially, 40 patients were included in this study. However, after giving three cycles of chemotherapy, 36 patients who had a response in the form of either a complete or partial response after NACT underwent surgery. The mean age of the study population was  $46.5 \pm 10.8$  years. The study by Dighe *et al.* also showed a similar mean age ( $47.68 \pm 11.6$ ). Most of the patients (52.5%) in our study had stage IIIB disease, similar to the findings by Alassas *et al.* where out of 34 patients assigned NACT, 23 (68%) patients had stage IIIB disease. Dighe *et al.* also had similar results [6,7].

After three cycles of chemotherapy, patients underwent response assessment with USG of the breast and bilateral axilla. In their study, Boughey *et al.* concluded that axillary ultrasound is recommended after NACT to guide axillary surgery [8]. Results from the study by Yeh *et al.*

**Table 1: General clinical characteristics of patients**

Parameter	Number (%)
Age group (in years)	
20–30	04 (10)
31–40	10 (25)
41–50	18 (45)
51–60	08 (20)
Total	40 (100)
Size of tumor (in cm)	
5–6	22 (55)
6–7	06 (15)
7–8	04 (10)
8–9	08 (20)
Total	40 (100)
Lymph node status	
Node negative	17 (42.5)
Node positive	23 (57.5)
Total	40 (100)
Clinical staging	
IIIA	19 (47.5)
IIIB	21 (52.5)
Total	40 (100)

**Table 2: Response assessment by clinical examination and USG**

Response	Modality of assessment	
	USG (%)	Clinical examination (%)
Complete response	08 (20)	15 (37.5)
Partial response	28 (70)	21 (52.5)
No response or stable	01 (2.5)	03 (7.5)
Progressive	03 (7.5)	01 (2.5)
Total	40 (100)	40 (100)

USG: Ultrasonography

**Table 3: Response assessment by histopathology and ultrasonography**

Response	Modality of assessment	
	Ultrasonography (%)	Histopathological examination (%)
Complete response	08 (22.2)	05 (13.8)
Partial response	28 (77.7)	31 (86.1)
Total	36 (100)	36 (100)

suggested that the use of axillary ultrasound is an effective imaging technique to assess the response of axillary lymph nodes after NACT.

After three cycles of NACT with the TAC regimen, clinical examination showed a complete response in 15 (37.5%) patients and a partial response in 21 (52.5%) patients. While USG detected a complete response in 8 (20%) patients and a partial response in 28 (70%) patients, seven patients, in whom clinical examination did not find any disease, were detected by USG.

A real picture came out after the HPE of the operative specimen. HPE showed a complete pathological response in 5 specimens and in the rest of 31 cases, HPE revealed a residual tumor. USG did not miss any of the pCR cases but overestimated CR cases by 9% (3 patients). On the other hand, all partial response diagnosis by USG was acknowledged by HPE. USG correlates well with HPE but with some overestimation for CR and underestimation for PR cases.

Mohamed *et al.* in their study observed that post-NACT USG revealed CR in 30 (20.4%) patients and PR in 92 (62.6%) patients. When they correlated the findings with the histopathology report, it was seen that pCR was achieved in 25 (17%) patients and residual disease was there

in 102 (74.1%) patients [9]. Hamisa *et al.* observed that at the end of 3 cycles of NACT, USG detected CR in 1 (3%) patient, PR in 16 (49%) patients, SD in 9 (27%) patients, and PD in 5 (15%) patients [10]. Yeh *et al.* in their study showed that among 31 patients, USG detected CR in 9 patients, PR in 12 patients, 8 patients with SD, and 2 patients with immeasurable lesions on USG. In a study with 120 patients by Soyemi *et al.*, USG was able to detect PR in 100 patients and CR, PD, and SD in 6 patients each [11]. All these studies reflected the fact that USG is a useful modality for response assessment of NACT in LABC, and the same finding was also there in our study also.

We included the color Doppler study in the USG assessment of tumor response as it is more effective in predicting tumor response and correlation with HPE. Kumar *et al.* also observed that Doppler-based findings were well correlated with histopathological responses [12]. Several review articles on this topic are in concordance with our study in view of the fact that ultrasound is better for assessment as it is cost-effective and available all over [13].

But this study has certain limitations as well. First, the sample size was relatively small. Second, a comparison of tumor volume in USG and operative specimens was not done, which, if it had been done, may better reflect the correlation between USG and histopathology.

### CONCLUSION

In conclusion, it can be said that USG is an effective radiological tool for the response assessment of NACT in locally advanced breast cancer. In resource-limited centers with a huge patient load, USG is an effective tool for assessment due to its easy availability, cost-effectiveness, and simple procedure.

### ACKNOWLEDGMENT

We acknowledge the help of the Department of Radiology, Radiotherapy, and General Surgery at Raiganj Medical College and Hospital in completing this research work.

### AUTHORS' CONTRIBUTION

Dr. Bidyut Biswas and Dr. Md Asif Ali: designed, conducted the research, and finalized the manuscript. Dr. Arabinda Roy: did the statistical analysis, data interpretation, and editing of the manuscript. Dr. Linkon Biswas: did the literature review, reviewing, and final editing of the manuscript.

### CONFLICT OF INTEREST

None of them to declare.

### AUTHORS' FUNDING

None.

### REFERENCES

- Sung H, Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2020;68:394-424.
- Sharp L, Donnelly D, Hegarty A, Carsin AE, Deady S, McCluskey N, *et al.* Risk of several cancers is higher in urban areas after adjusting for socioeconomic status. Results from a two-country population-based study of 18 common cancers. *J Urban Health.* 2014;91(3):510-25. doi: 10.1007/s11524-013-9846-3, PMID 24474611.
- Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, *et al.* Preoperative chemotherapy: Updates of National Surgical Adjuvant Breast And Bowel Project Protocols B-18 and B-27. *J Clin Oncol.* 2008;26(5):778-85. doi: 10.1200/JCO.2007.15.0235, PMID 18258986.
- Vriens BE, de Vries B, Lobbes MB, van Gastel SM, van den Berkortel FW, Smilde TJ, *et al.* Ultrasound is at least as good as MRI in predicting tumour size post-NACT in breast cancer. *Eur J Cancer.* 2016 Jan;52:67-76. doi: 10.1016/j.ejca.2015.10.010, PMID 26650831.
- Zhi W, Liu G, Chang C, Miao A, Zhu X, Xie L, *et al.* Predicting treatment response of breast cancer to neoadjuvant chemotherapy using ultrasound-guided diffuse optical tomography. *Transl Oncol.* 2018;11(1):56-64. doi: 10.1016/j.tranon.2017.10.011, PMID 29175630.
- Alassas M, Chu Q, Burton G, Ampil F, Mizell J, Li BD. Neoadjuvant chemotherapy in stage III breast cancer. *Am Surg.* 2005;71(6):487-492. doi: 10.1177/000313480507100607, PMID 16044927.
- Dighe S, Shinde R, Shinde S, Verma P. Assessment of response of neoadjuvant chemotherapy in carcinoma breast patients by high-frequency USG. *J Family Med Prim Care.* 2022;11(8):4717-22. doi: 10.4103/jfmpe.jfmpe\_2186\_21, PMID 36353032.
- Boughey JC, Ballman KV, Hunt KK, McCall LM, Mittendorf EA, Ahrendt GM, *et al.* Axillary ultrasound after neoadjuvant chemotherapy and its impact on sentinel lymph node surgery: Results from the American College of Surgeons Oncology Group Z1071 Trial (Alliance). *J Clin Oncol.* 2015;33(30):3386-93. doi: 10.1200/JCO.2014.57.8401, PMID 25646192.
- Mohamed AA, Mohamed KE, Saad EA, Mahmoud SM. The response, operability, and type of surgery following neoadjuvant chemotherapy in Sudanese patients with locally advanced breast cancer. *Sudan J Med Sci.* 2018;13(3):219-29. doi: 10.18502/sjms.v13i3.2961.
- Hamisa M, Dabess N, Yosef R, Zakeria F, Hamed Q. Role of breast ultrasound, mammography, MRI and DWI in predicting pathologic response of breast cancer after neoadjuvant chemotherapy. *Egypt J Radiol Nucl Med.* 2015;46:245-57.
- Soyemi TO, Ayandipo OO, Ademola AF, Obajimi GO, Obajimi MO, Ogundiran TO. Role of breast ultrasound in evaluating the response of locally advanced breast cancer to neoadjuvant anthracycline chemotherapy in Ibadan. *Age.* 2018;26:5-6.
- Kumar A, Singh S, Pradhan S, Shukla RC, Ansari MA, Singh TB, *et al.* Doppler ultrasound scoring to predict chemotherapeutic response in advanced breast cancer. *World J Surg Oncol.* 2007;5:99. doi: 10.1186/1477-7819-5-99, PMID 17725837.
- Dighe SP, Shinde RK, Shinde SJ, Anand A. Review on assessment of response of neo-adjuvant chemotherapy in patients of carcinoma breast by high frequency ultrasound. *J Evol Med Dent Sci.* 2020;9(51):3873-81. doi: 10.14260/jemds/2020/849.