Assessment of response of neoadjuvant chemotherapy in carcinoma breast patients by high-frequency ultrasound

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Abstract

Aim: To assess the response of neoadjuvant chemotherapy in carcinoma breast patients by high-frequency ultrasound. **Material and Method:** The current single blind, observational study was conducted at rural tertiary healthcare center of Acharya Vinoba Bhave Rural Hospital from October 2018 to Sept 2020. We incorporated breast cancer patients with TNM stages IIIA and IIIB who received neoadjuvant chemotherapy with Cyclophosphamide/Adriamycin/5 FU and Paclitaxel respectively followed by standard surgical procedure modified radical mastectomy. Successive ultrasound examination of the breast malignancy and the axilla was done after 21 days of either of any neoadjuvant chemotherapy for 3 cycles. Assessment of response to neoadjuvant chemotherapy was applied in terms of reduction in the breast tumour volume on ultrasound and percentage of tumour response calculated by Response Evaluation Criteria for Solid Tumours (RECIST). Data were analysed using SPSS version 24.0. **Results:** Higher frequency of patients was invasive ductal breast cancer. In our study, Paclitaxel group showed better response in terms of CR and PR than CAF group. Our study noticed a consistent decrement in tumour volume after every cycle of either CAF or Paclitaxel NACT. Axillary ultrasound was able to predict the response of axillary lymph nodes in terms of increase or decrease in number and morphological changes after 3 cycles of NACT with similarity on final histopathology. **Conclusion:** It can be concluded from the results of the present study that high-frequency ultrasound is appropriate tool for assessment of response of primary breast malignancy and lymphnode metastasis in the axilla after neoadjuvant chemotherapy.

Keywords: Breast, carcinoma, NACT, ultrasound

Introduction

Breast cancer is the most commonly occurring cancer in female gender everywhere around the world with an approximated 1.67 million novel cases of cancer diagnosed in 2012 and around 5,70,000 deaths in 2015.[1] It is the most commonly arising cancer amongst women in urban cities like Delhi, Mumbai, Kolkata, Ahmedabad and Trivandrum where it accounts for more than 30% of cancer cases in women as per Indian council of medical research (ICMR) cancer registry data. In rural areas of India, breast cancer is the second prime cause of cancer only after cervical cancer.[2] The increase in incidence of breast cancer is probably higher amongst urban cities than in rural villages as there is increase in urbanization and westernization with changing lifestyle trends and dietary-habits.[3] Historically, Radical surgery with/or Radiation therapy were significant in management of locally advanced breast cancer (LABC) patients. Over the time, management of LABC has been outstandingly revised. Primary anterior neoadjuvant chemotherapy (NACT) has now become an inherent part of management of LABC.[4] NACT escalates the rate of breast conserving surgery as well improves disease free survival (DFS) and overall survival (OS). Overall, attainment of pathological complete response (pCR) is directly proportional to improved DFS and OS, thus making it a surrogate end-point prognostic indicator for long term outcome of the patient. Although measurement of response to NACT in pre-operative setting is useful for surgical

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decision, any type of breast surgery still is considered essential for definitive assessment of presence or absence of residual tumour.

In the present day, clinical as well as pathological tumour response to NACT can be predicted on the basis of molecular subtypes of breast cancer by clinical examination (including clinical breast examination as well as radiological imaging – mammography (MMG), ultrasonography (USG/US), computed tomography (CT) and magnetic resonance imaging (MRI) based on the age and density of the breast of the patient). Here, a lot of confusion arises on choosing a specific modality out of the above mentioned modalities in assessment of response of NACT in order to predict the tumour response which is in correlation to the final pathologic complete response (pCR).[5] Even though a lot of studies have been previously published on assessment of tumour response as well as the World Health Organization (WHO) guidelines or the Response evaluation criteria in solid tumours (RECIST) criteria, none of the above mentioned could actually address the breast imaging aspect in prediction of response in detail.[6]

Out of the modalities put forward by NCCN board, we have utilized USG as the modality to assess the response of NACT as it is widely available, cost-effective than other radiological examinations and is indifferently used by primary, secondary and tertiary healthcare centres in India. As there is a gap between the assessments of clinical response of tumour to predict the final pCR after NACT, we have undertaken this study in order to assess the efficiency of ultrasound in assessment of response of two different types of NACT regimens commonly administered in patients of LABC using RECIST criteria. Here, we have used USG as a diagnostic tool in evaluation of response of NACT and its correlation to final histopathological response.

Material and Method

The current single-blind, observational study was conducted at rural tertiary health care center of AVBRH from October 2018 to Sept 2020. We incorporated breast cancer patients with TNM stage IIIA and IIIB who received NACT with Cyclophosphamide/Adriamycin/5 FU and Paclitaxel, respectively, followed by standard surgical procedure modified radical mastectomy. Data were accumulated through pre-formed proformas and after obtaining an appropriate informed consent from the patient. Our study was permitted by the Institutional Ethics committee of DMIMS (DU) (IEC no-2018-19/7407) and was funded by the Intramural Grant Program of DMIMS (Ref no - DMIMSU (DU) R&D/2019/71). All the patients were explained the nature of the study and ill-effects of NACT and those who gave informed consent were included in the study.

A total of 46 patients were recruited based on the sample size calculation. Patients with LABC, T3 with any N, any T1-T3 with N2, T4 with any N and any T with N3 characteristics were included in the study. Patients with characteristics like early breast cancer, breast cancer with metastasis, unfit for

chemotherapy, that is, cardiac dysfunction, hepatic or renal derangements, delay in administration of chemotherapy due to toxic effects more than 15 days, pregnancy/lactation, recurrent breast cancer, bilateral breast cancer, concomitant radiotherapy, and received prior chemotherapy were excluded from the study. Registered patients were allocated to obtain either Paclitaxel or Cyclophosphamide/Adriamycin/5Flurouracil regimen as NACT as advised by the tumour board panel at AVBRH comprising of a multi-disciplinary team composed of oncologist, onco-surgeon, radiologist and radio-therapist. Dose of Paclitaxel group was 175 mg/m2 as a 3 hour IV infusion and for CAF group was Cyclophosphamide – 500 mg/m2 as IV infusion, Adriamycin 50 mg/m2 as IV infusion and 5 Fluorouracil – 500 mg/m2 as IV infusion. NACT was administered to the patient after calculation of the body surface area. Fine Needle Aspiration Cytology was accomplished for primary diagnosis of all the patients. Routine investigation like complete hemogram, renal, and hepatic function tests were mandatorily done. Metastatic assessment was conducted using chest X-ray and abdominal ultrasound. Ultrasound Breast and Axilla with assessment of supraclavicular space was conducted as a baseline. USG machine used was of Hitachi Aloka brand Arietta 70 (Ultrasound/Color Doppler) with 6 probes and high frequency of 8 to 12 Hz. Malignant breast tumour and axillary lymph nodes were segregated on the foundation of following characteristics on USG[7]:

1. Breast Lump – Number of the breast lump, size of the breast lump, hypo-echogenicity of the breast lump, length and width of the tumour (Taller than broader)
2. Axilla – Number of axillary lymph nodes, type – Benign/Intermediate/Suspicious, Eccentric cortical thickness of LN >3 mm (irregular/even), Absent fatty hilum, Rounded morphology
3. Color Doppler – Hyper-vascularity, Irregular course and caliber, AV shunts

Baseline ultrasound was followed by Trucut biopsy of the tumor which was done with 18 G Bard Trucut biopsy needle under local anaesthesia in all aseptic condition. The specimens were collected and preserved in formalin and were sent for assessment of tumour histological examination, Scarff-Bloom-Richardson grade and Immunohistochemistry evaluation[8] (Estrogen and progesterone receptor status, Her2/neu receptor status and Ki67 proliferative index). Successive ultrasound examination of the breast malignancy and the axilla was done after 21 days of either of any NACT for three cycles. Assessment of response to NACT was applied in terms of reduction in the breast tumour volume on ultrasound and percentage of tumour response calculated by Response Evaluation Criteria for Solid Tumours (RECIST).[9]

Tumour response for all 3 cycles of NACT was calculated according the following formula:[10]

Tumour Response = 100 X (Before T - After T)/Before T

Measurements were obtained by ultrasound following which on the basis of measurements of the final ultrasound after

the 3rd NACT, the patients were bifurcated into two major categories:[9]

Responders

a. Complete Response (CR) – No radiological evidence of residual tumour, Disappearance of all target lesions, Reduction in short axis (<10 mm) in any suspicious lymph node.
b. Partial Response (PR) – Reduction in size of the tumour more than 30%. [Figure 1]

Non-Responders

a. Stable Disease (SD) – reduction in size of tumour inferior than 30%.
b. Progressive Disease (PD) – 20% increase in size of tumour dimensions or appearance of new lesions.

Pathologic Complete Response (pCR) was defined as no residual malignant cells on microscopy and Pathologic Incomplete Response (pIR) showed residual malignant cells on microscopy. Clinical response (cCR) of primary tumour and axillary lymph nodes after 3rd cycle of chemotherapy on ultrasound was correlated to final pCR.

Statistical analysis was performed utilizing descriptive as well as inferential statistics, Chi-square test, student's unpaired t-test and one-way ANOVA. SPSS 24.0 version was employed as software in analyzing the statistics. $P < 0.05$ is considered as level of significance.

Results

Mean age in CAF group was 47.68 ± 11.68 and in Paclitaxel group was 54.47 ± 11.86 which was statistically non-significant on comparison (p value = 0.25). 14 (56%) patients had carcinoma on left side and 11 (44%) patients had carcinoma on right side in CAF group. In Paclitaxel group, 15 (71.43%) patients had carcinoma on right side and 6 patients (28.57%) had carcinoma on left side. This relation was statistically non-significant (p value-0.06).

In CAF group, 22 (88%) patients were Invasive ductal (No specific type), followed by 2 (8%) patients of medullary carcinoma type and 1 (4%) patient in mucinous colloid type, there was no patient in invasive lobular group. In PACLITAXEL group, 18 (85.71%) patients were of Invasive ductal (No specific type), followed by 2 patients in mucinous colloid type and 1 patient in medullary carcinoma type.
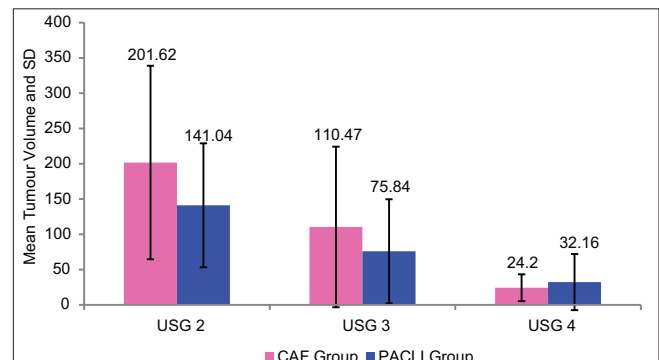
In CAF group and Paclitaxel group, it was found that there was a statistically significant relation in tumour response on USG 2. On USG 3, there was no significant statistical relation in tumour response of each respective chemotherapy regimen but on USG 4 there was a statistical significant relation between both the NACT regimens (p-0.042). [Figure 2]
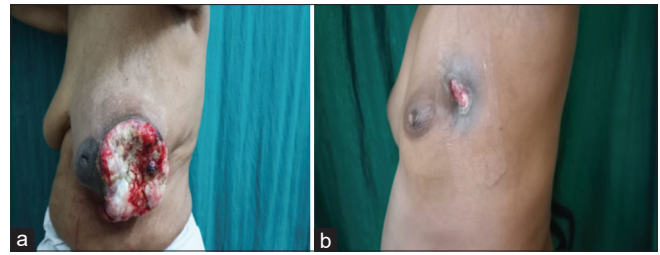
Figure 1: (a) Fungating malignant mass on left breast, patient underwent 3 cycles of paclitaxel. (b) After completion of 3 cycles of paclitaxel
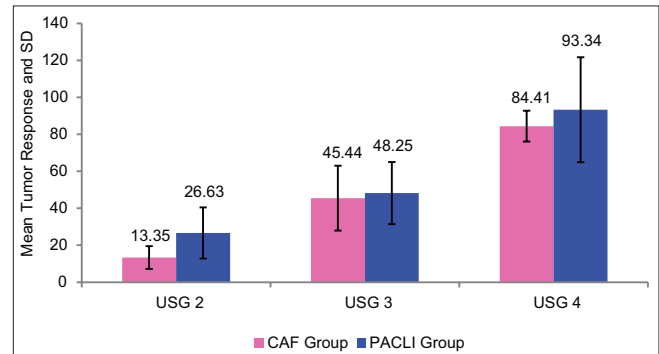
Figure 2: Comparison of tumour response in both groups by USG by value calculated from RECIST criteria

Figure 3: Comparison of tumour volume in both groups by high-frequency ultrasonography after every NACT

Tumour volume in USG 2 in CAF group and Paclitaxel group was (201.62 ± 137.16) and (141.04 ± 87.73), respectively, with statistically non-significant relation (p-0.10)). In USG 3, Tumour volume in CAF group and Paclitaxel group was (110.47 ± 113.79) and (75.84 ± 73.85) with statistically non-significant relation (p value-0.25). In final USG 4, in CAF group and Paclitaxel group, tumour volume was (24.20 ± 19.11) and (32.16 ± 39.69) with statistically non-significant relation (p value-0.39).

In CAF group, tumour volume on USG was (20.90 ± 10.46) and on Histopathology was (19.46 ± 11.09) with a statistically non-significant relation (p value-0.65). In Paclitaxel group, tumour volume was (18.93 ± 25.54) and on Histopathology was (13.06 ± 15.82) with a statistically non-significant relation [|Figure 3].

In final USG 4, in CAF group and Paclitaxel group, axillary lymph nodes were (1.68 ± 0.94) and (1.30 ± 0.67) with statistically non-significant relation (p value-0.26). In CAF group, Axillary lymphnodes on USG were (1.33 ± 1.09) and on Histopathology were (2.20 ± 1.22) with a statistically significant relation (p value-0.012). In Paclitaxel group, Axillary lymphnodes on USG was (0.68 ± 0.82) and on Histopathology were (1.11 ± 1.32) with a statistically non-significant relation.

Discussion

We encompassed a total of 46 female patients fulfilling the inclusion criteria in which 25 patients were given Anthracycline-based (CAF) NACT and 21 patients were given Taxane-based (Paclitaxel) NACT.

We had more patients in Stage IIIB group as NACT is mostly preferred modality of treatment to downstage the size of the tumour converting an inoperable tumour into an operable one.[11] In a study by Alassas *et al.*,[12] out of 34 patients assigned NACT, 11 (32%) patients exhibited stage IIIA, and 23 (68%) patients exhibited stage IIIB. Soyemi *et al.*[11] observed that out of 120 patients, 62 (51.7%) patients were in stage IIIB followed by 28 (20%) patients in stage IIIC and 24 (23.3%) patients in stage IIIA and 6 (5%) patients in stage IIB.

Of all 46 patients in our study, 40 patients were of Invasive ductal (no significant) type, followed by 3 patients in Mucinous Colloid type and Medullary carcinoma each. All the studies conducted by Romero *et al.*,[13] Del Prete *et al.*[14] and Sivasanker *et al.*[15] are in congruence with our study thus supporting the higher frequency of invasive ductal breast cancer.

Our study had 1 patient out of 24 in CAF regimen who attained complete response (CR) on final USG, rest 23 patients attained partial response (PR). In PACLITAXEL group, out of 19 patients, 4 patients obtained complete response (CR) whilst remaining 15 patients obtained partial response. Our study did not have any patient in non-responder group. In our study, Paclitaxel group showed better response in terms of CR and PR than CAF group. Hamisa *et al.*[16] observed that at the end of 3 cycles of NACT, USG detected only 30 lesions in 33 patients and displayed CR in 1 (3%) patient, PR in 16 (49%) patients, SD in 9 (27%) patients, PD in 5 (15%) patients and in 2 (6%) patients, the lesion was immeasurable by USG either due to ill-defined outline or by was obscured by remarkable breast edema post NACT effect. In the study by Yeh *et al.*[17], out of 31 patients USG was able to detect 9 patients with CR, 12 patients with PR, 8 patients with SD, and 2 patients had immeasurable lesion on USG.

Baumgartner *et al.*[18] in his study observed that USG was able to depict CR in 68 (54.8%) patients and PR in 56 (45.2%) patients out of 124 patients. In a study by Soyemi *et al.*[11] concluded that among 120 patients, USG was able to depict PR in 100 patients and CR, PD, SD in 6 patients, respectively. Del Prete *et al.*[14] in his observed that out of 117 patients from his study, USG revealed

46 patients with CR, 43 patients with PR, 23 patients with SD and 5 patients with PD. Mohammed *et al.*[19] in this randomized study observed that following NACT, CR was seen in 30 (20.4%) patients, PR in 92 (62.6%) patients, SD in 20 (13.6%) patients and 5 (3.4%) patients had PD. Out of these pCR was achieved in 25 (17%) patients, pPR in 102 (74.1%) patients and pSD in 13 (8.8%) patients. All the mentioned studies suggest that USG is a valuable tool in assessment of response of any type of NACT which reinforce our study.

We assessed the progression or regression of tumour volume after every cycle of both regimens of NACT. Our study noticed a consistent decrement in tumour volume after every cycle of either CAF or Paclitaxel NACT. In present literature, there is no study available which is depicting the increase or decrease in tumour volume after NACT by ultrasound.

In both groups, after the end of 3rd cycle of NACT regimens, there was a gradual decrease in the tumour vascularity which suggested CR/PR of both the NACT regimens. Kedar *et al.*,[20] in a study showed that out of 126 treatment cycles given to 34 patients, in 97 treatment cycles (77%) there were changes seen in the vasculature which were in concordance with changes in the size of the tumours. The study concluded that use of Color Doppler can assess and predict the response of breast cancer to conservative management of LABC. Kuo *et al.*[21] and Kumar *et al.*,[22] in their studies observed that Doppler CR was well correlated with histopathological response. All the above introduced studies report that color Doppler is a useful assessment aid in evaluation of response of NACT which is similar to our current study.

In 3 consecutive axillary ultrasounds, after each cycle in both groups of NACT, all 43 patients either showed CR/PR in the axilla. There was a gradual decrease in the number of suspicious lymphnode in both the groups. Overall axillary ultrasound was able to predict the response of axillary lymphnodes in terms of increase or decrease in number and morphological changes after 3 cycles of NACT with similarity on final histopathology. Boughey *et al.*[23] in his study concluded that axillary ultrasound is recommended after NACT to guide axillary surgery. In a study by Ye *et al.*,[24] the result suggested that use of axillary ultrasound is a useful imaging technique to assess the response of axillary lymphnodes to NACT and is best depicted in patients who have finished 4 cycles of NACT, and as the number of NACT cycles increases to 6, the false negative rate increases. All these studies are in concordance with our studies, suggesting that axillary ultrasound can predict the response to NACT when compared to final histopathology. Several review studies performed on this are in concordance with our study in view that ultrasound is better in assessment as it is cost-effective and available allover.[25,26]

Conclusion

Results of the present study suggests that ultrasound can be used as an assessment tool for measuring response to

Anthracycline-based and Taxane-based NACT at even primary care level by primary care physicians and there is no need of high center referrals for assessing the response as ultrasound is available at all levels of healthcare set-up. Our study also concludes that ultrasound is more effective in assessing the number of axillary nodes mainly in patients administered with Paclitaxel regimen and tumour volume assessed on USG is comparable to tumour volume on Histopathologic evaluation. Also Paclitaxel group has shown better tumour response when compared to CAF group. There are few limitations of this present study like its small sample size, poor compliance of patient to the treatment either due to lack of education or due to monetary issues and also that ultrasound is operator dependent needs specialized training and interest.

To conclude, we have assessed the response of NACT regimens by high frequency ultrasound and thereby recommend that high frequency ultrasound is appropriate tool for assessment of response of NACT in breast cancer and lymphnode metastasis in the axilla irrespective of any healthcare setups.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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