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**Original research article**

# Evaluation of Response Outcomes of Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer

**Dr. Rakesh Kumar Thakur,[1] Dr. Vijay Shankar Prasad[2]**
**[1]MBBS, M.S. (Gen. Surgery), Specialist Medical Officer (Surgery), Andhratharhi, Madhubani, Bihar, India**
**[2]MBBS, M.S. (Gen. Surgery), Ph.D., FICS, Associate Professor and Head of Department, Upgraded Department of Surgery, Darbhanga Medical College and Hospital, Laheriasarai, Bihar**

**Corresponding Author: Dr. Vijay Shankar Prasad**

## ABSTRACT

**Background :** Introduction of neo adjuvant chemotherapy (NACT) has dramatically changed the management of locally advanced breast cancer (LABC). However, very few randomized trials of NACT have been carried out specifically in LABC patients in our country. In this retrospective analysis, we presented our experience with NACT in LABC patients.

**Materials and Methods :** Seventy patients diagnosed with locally advanced breast cancer were enrolled in this prospective study. After thorough preoperative workup, patients were either taken up for upfront surgery or neo adjuvant chemotherapy followed by surgery. Post chemotherapy clinical response of the tumor and post operative histo pathological evaluation of the specimen was performed.

**Results :** The mean age of the patients in our study was 45 years. Out of 70 patients, 18 underwent upfront surgery and 52 received neo adjuvant chemotherapy followed by surgery. A total of 44 cases had a clinical response to chemotherapy with 9% having a complete response. The incidence of margin positivity in the postoperative specimen was significantly lower in patients who received neo adjuvant chemotherapy.

**Conclusion:** Locally advanced breast cancer accounted for the predominant number of breast cancer patients mostly females in their middle age. Neo adjuvant chemotherapy was effective in down staging the tumor in the majority of cases, although complete clinical response was lower in our study. The rate of margin positivity in mastectomy specimens can also be reduced if chemotherapy is considered prior to mastectomy.

**Keywords:** margin positivity, complete clinical response, neo-adjuvant chemotherapy, breast cancer, locally advanced breast-cancer

## INTRODUCTION

Locally advanced breast cancer (LABC) is defined by presence of a large primary tumor (>5 cm or T3), associated with or without skin or chest-wall involvement (T4) or with fixed (matted) axillary lymph nodes or with disease spread to ipsi lateral internal mammary or supraclavicular nodes in the absence of any evidence of distant metastases.[1] LABC accounts for 10-20% in the West,[1] while in India, it accounts for 30-35% of all cases. LABC encompasses a wide spectrum

of malignant breast tumors with varying presentation and poses a significant therapeutic challenge. The treatment of LABC has changed dramatically over last few decades. The introduction of neo adjuvant chemotherapy (NACT) in LABC offered us advantages like initiation of early systemic therapy, delivery of drugs through intact vasculature, down-staging of tumors, which makes inoperable tumors operable and renders tumors suitable for breast conserving surgery (BCS).[2,3] It also helps *in vivo* assessment of response. National Surgical Adjuvant Breast and Bowel Project (NSABP)-18 and Milan trials have shown that there were no difference in disease free survival (DFS) and overall survival between the patients who had received NACT when compared to the patients who had received postoperative adjuvant chemotherapy.[3] This has led NACT to gain a major foothold in the management of LABC. There are very few Indian studies of NACT in LABC published until date.

## AIMS OF STUDY

- To prospectively study the clinical profile of the LABC patients
- To evaluate the role of neo-adjuvant chemotherapy in down staging the tumor.

## MATERIALS AND METHODS

Present prospective observational study conducted at Darbhanga Medical College and Hospital, Laheriasarai, Bihar from 2009-2012. Patients with locally advanced breast cancer belonging to Stage IIB(T3N0), IIIA, IIIB, and IIIC were included in this study. Exclusion criteria were male breast cancer, pregnant women, all cases with distant metastasis. Seventy consecutive patients who were admitted to our department with breast cancer and satisfying inclusion and exclusion criteria were recruited in the study. Informed consent was obtained from all the patients.

Patients who presented to our department and satisfying criteria were evaluated as per National Comprehensive Cancer Network (NCCN) guidelines which included: history and physical examination, diagnostic mammogram and ultrasound as necessary, trucut biopsy for diagnosis and estrogen receptor (ER) status, progesterone receptor (PR) status, and HER2/neu (human epidermal growth factor receptor 2)receptor status, genetic and fertility counseling for hereditary cancers and premenopausal women.

Metastatic workup (if signs and symptoms are present) included chest and abdomen CT, bone scan, PET CT(optional). An index core biopsy was performed in all patients to record the following histo pathological features of the tumor type, estrogen receptor (ER) status, progesterone receptor (PR) status, and HER2/neureceptor status.

Out of 70 patients, 18 (stage IIB, IIIA) were considered for upfront surgery (modified radical mastectomy) followed by chemotherapy and radiotherapy depending on pathological staging based on the operability of the disease and patients' preference after obtaining consent. Histopathology of the specimen was recorded with emphasis on margin positivity, histopathology staging, and immune histochemistry (IHC). There maining 52 patients received an anthracycline-based chemotherapy regimen with 5-fluorouracil,adriamycin or epirubicin, and cyclophosphamide (FAC/FEC) every 3 weeks during -6 cycles before surgery.

Tumor measurements at the baseline and after the final cycle of neo adjuvant therapy were recorded byphysical examination. Although CT and MRI are best in evaluating the response, due to cost considerations and patient willingness, the response was measured clinically using caliper and tape and radiologically by USG following each cycle of chemotherapy Clinical response was assessed using RECIST criteria by measuring tumor size and node size after neoadjuvant chemotherapy. RECIST 1.16[4] utilized the following classifications for therapeutic response:

complete response (CR), primary tumor disappearance; partial response (PR), 30% or greater decrease in the longest diameter of the primary tumor; progressive disease (PD), 20% or greater increase in longest diameter of the primary tumor; stable disease (SD), tumors that did not show either sufficient shrinkage to be classified as PR or sufficient increase to be classified as PD.
Post chemotherapy, all the patients underwent modified radical mastectomy with axillary lymph node dissection (level I, II). Histopathology of the specimen was recorded with emphasis on margin positivity, histopathology staging, and IHC. We evaluated the role of neo adjuvant chemotherapy in down staging the tumor and achieving negative margin status. Response to chemotherapy was further evaluated based on IHC, stage nodal status.

**Statistical analysis**

The data were entered and analyzed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). The frequencies and percentages of all variables were computed. A Chi-square ($\chi^2$) test was used to analyze the statistical association of various variables in the study. P-value less than 0.05 was considered as statistically significant for comparative analysis.

## RESULTS

A total of 70 patients were recruited in this study. In this study, the median age of the patients was 45 years (range 25 to 68 years), the median size of the initial tumor was 6 cm (range 2 to 9 cm). Out of 70 patients, 36(51%) were postmenopausal women. As per the tumor, node, metastasis (TNM) staging, 66% belonged to Stage IIIA and IIIB. Predominant histopathology observed was infiltrative ductal carcinoma (81%). Receptor study helped to gain an insight into the behavior of tumor with 63% of cases having PR negative status, ER and HER2/neu had almost equal distribution. Triple-negative cancers constituted 31% of cases. The distribution of various general characteristics among the study population is presented in Table 1.

**Table 1 : Distribution of various clinic pathological characteristics of study population**

| Characteristics | No. of cases (n) | Percentage (%) |
|---|---|---|
| **Age (yrs.)** | | |
| • <50 | 49 | 70% |
| • ≥50 | 21 | 30% |
| **Menopausal status** | | |
| • Premenopausal | 34 | 49% |
| • Postmenopausal | 36 | 51% |
| **Stage** | | |
| • Stage IIB | 14 | 20% |
| • Stage IIIA | 23 | 33% |
| • Stage IIIB | 23 | 33% |
| • Stage IIIC | 10 | 14% |
| **History** | | |
| • IDC | 57 | 81% |
| • ILC | 11 | 16% |
| • Others (papillary, medullary) | 2 | 3% |
| **ER** | | |
| | 32 | 46% |

| | | |
|---|---|---|
| • Positive<br>• Negative | 38 | 54% |
| **PR** | | |
| • Positive<br>• Negative | 26<br>44 | 37%<br>63% |
| **HER2** | | |
| • Positive<br>• Negative | 35<br>35 | 50%<br>50% |

ER : estrogen receptor, PR : progesterone receptor, IDC : Infiltrative ductal carcinoma, ILC : Infiltrative lobular carcinoma, HER2 : human epidermal growth factor receptor 2

Of the 70 patients in our study, 18 (26%) patients underwent upfront surgery, and the remaining 52 (74%) patients received neo adjuvant chemotherapy followed by surgery. All patients received neo adjuvant chemotherapy with anthracyclines: FEC100 (doxorubicin, 5 Fluorouracil, cyclophosphamide), the median number of cycles was three (extremes 2 to 6), median delay from the last cycle of chemotherapy and surgery was 36 days. Out of 52 patients, clinical response was observed in 44 patients. Complete clinical response was observed in five (9%) patients. Eight (17%) patients were non-responders (stable and progressive disease). The post-neo adjuvant chemotherapy (NACT) clinical response in breast tumor according to RECIST criteria is depicted in Table 2.

**Table 2 : Post-Neoadjuvant chemotherapy clinical response rate**

| Clinical response | No. of cases (n) | Percentage (%) |
|---|---|---|
| Complete response | 5 | 9% |
| Partial response | 39 | 74% |
| Stable disease | 7 | 15% |
| Progressive disease | 1 | 2% |
| Total | 52 | 100% |

Clinical response rate with respect to age, stage of presentation, histopathology, and receptor status and their statistical association is depicted in Table 3. In comparison to the response rate with respect to tumor histology, invasive ductal carcinoma has a significantly better response over other types ($p<0.05$).

No statistically significant response was observed when comparing the response rates with respect to other factors. Response with respect to receptor status was not statistically significant individually but 98% of triple-negative cancers responded well to chemotherapy.

**Table 3 : Post-Neo adjuvant chemotherapy clinical response rate compared with various variables**

| | | Complete response | Partial response | Stable disease | Progressive disease | Total |
|---|---|---|---|---|---|---|
| Age (p=0.87) | <50 years | 3 | 23 | 4 | 1 | 31 |
| | >50 years | 2 | 16 | 3 | 0 | 21 |
| ER status (p=0.68) | Positive | 2 | 18 | 4 | 1 | 25 |
| | Negative | 3 | 21 | 3 | 0 | 27 |
| PR status | Positive | 1 | 13 | 4 | 1 | 19 |

| | | | | | | |
|---|---|---|---|---|---|---|
| (p=0.28) | Negative | 4 | 26 | 3 | 0 | 33 |
| HER2/neu | Positive | 3 | 16 | 5 | 1 | 25 |
| (p=0.29) | Negative | 2 | 23 | 2 | 0 | 27 |
| History (p<0.05) | IDC | 4 | 32 | 6 | 0 | 42 |
| | ILC | 1 | 7 | 0 | 1 | 9 |
| | Others | 0 | 0 | 1 | 0 | 1 |
| Stage (p=0.09) | IIB | 2 | 4 | 1 | 0 | 7 |
| | IIIA | 3 | 12 | 0 | 1 | 16 |
| | IIIB | 0 | 13 | 5 | 0 | 18 |
| | IIIC | 0 | 10 | 1 | 0 | 11 |

ER : estrogen receptor, PR : progesterone receptor, IDC : Infiltrative ductal carcinoma, ILC : Infiltrative lobular carcinoma, HER2 : human epidermal growth factor receptor 2

Pre-NACT and post-NACT nodal status is depicted in Table 4. Out of 52 patients who received NACT, 20 had N0 nodal status. Out of 32 patients with the nodal disease who received chemotherapy 21 cases showed a response; CR in 53% of cases, PR in 13% of cases, and 34% cases were non-responders. Nodal clinical response to NACT was not statistically significant.

**Table 4 : Comparison of Pre-Neo adjuvant chemotherapy vs Post-Neo adjuvant chemotherapy Nodal status**

| | | **Post-Neo adjuvant chemotherapy Nodal status** | | | | |
|---|---|---|---|---|---|---|
| | | **N0** | **N1** | **N2** | **N3** | **Total** |
| **Pre-NACT nodal stage** | **N0** | 20 | 0 | 0 | 0 | 20(38.4%) |
| | **N1** | 14 | 0 | 0 | 0 | 14(27.0%) |
| | **N2** | 3 | 3 | 2 | 0 | 8(15.4%) |
| | **N3** | 0 | 1 | 0 | 0 | 10(19.2%) |
| **Total** | | 37(71.1%) | 4(7.7%) | 2(3.8%) | 9(17.4%) | 62(100%) |

Out of 18 cases that underwent upfront surgery, four cases had margin positivity compared to one case in the group receiving neo-adjuvant chemotherapy. A high rate of margin positivity was seen in cases undergoing upfront surgery compared to cases receiving NACT (p<0.04) (Table 5). However, in this study, no complete pathologic response in the surgical excision specimen was seen as compared to complete clinical response.

**Table 5 : Comparison of margin status between upfront surgery and Neo-adjuvant chemotherapy groups**

| | **Margin positive** | **Margin negative** | **Total** |
|---|---|---|---|
| Upfront surgery group | 4 | 14 | 18 |
| NACT group | 1 | 51 | 52 |
| P<0.04 | | | |

## DISCUSSION

In our study, 45 years was the median age of the patient cohort. This finding is consistent with other studies like Raina et al.[5] with the reported median age of 47 years and Min et al. [6] with 49 years as the median age of presentation. Chin et al. [7] study shows a median age of 52 years in the Jamaican population. 51% of our patients were postmenopausal, which is similar to studies

by Yadav et al. [8], Chen et al. [9]. In this study, predominantly cases belonged to stage IIIA, IIIB, 33% each which is comparable to other studies -stage IIB (T3 N0) was included in the study as the tumor size was more than 8 cm in the majority of the cases. Invasive ductal carcinoma was noted in 81% of the patients which is slightly lower when compared to other studies [10-12]. 11% of cases had invasive lobular carcinoma which is higher than other studies in locally advanced breast cancer. Histopathology and grade of the tumor may be associated with the aggressiveness of the cancer. Estrogen positivity was seen in 46% of cases which is lower than the Western literature which reported ER positivity of around 60%. PR negativity in 63% of cases is comparable to data from Taucher S et al. [13] which showed PR negativity of 70%. HER2 receptors were found to be positive in50% of the cases. Triple-negative cancers constituted 31% of cases, which is consistent with many studies showing a higher prevalence of triple-negative breast cancers in the Indian population compared to the Western population [14-16].

In our study, 18 (22%) patients belonging to stage IIB, IIIA on clinical assessment were operable and underwent upfront modified radical mastectomy. Primary surgery was considered in this subset according to the patient's preferences and operable tumors at the initial presentation. The remaining 52 cases (74%) received neo adjuvant chemotherapy followed by modified radical mastectomy based on the down staging of the tumor. This modality of management has been accepted as a standard procedure for locally advanced inoperable breast cancer as shown by Shenkier et al. [17]. As per the institutional protocol, the majority of the patients received anthracycline-based chemotherapy. In accordance with prevailing NCCN guidelines,94% of the cases received FEC regimen and the remaining cases received AC and FAC regimens.

Buccholz etal. [18] study showed improved outcomes with neoadjuvant chemotherapy followed by surgery. The response was evaluated according to RECIST criteria. Prasad et al. [19] demonstrated that RECIST criteria is more specific than WHO criteria in assessing response to chemotherapy. Although CT and MRI are best in evaluating the response, due to cost considerations and patient willingness, the response was measured clinically using calipers and tape and radiologically by ultrasonography (USG) following each cycle of chemotherapy. Herrada et al.[20] demonstrated that physical examination correlated best with pathological findings in the measurement of the primary tumor. In our study, the median number of cycles was three. In the existing literature, a lot of variation exists in the number of cycles of chemotherapy given in neoadjuvant settings[21]. Investigators have administered either 3-4 cycles of chemotherapy or chemotherapy was continued up to maximal response.

## CONCLUSIONS

Locally advanced breast cancer accounted for the predominant number of breast cancer patients, mostly females in their middle age. Neoadjuvant chemotherapy was effective in down staging the tumor in majority of cases, although complete clinical response was lower in our study. Rate of margin positivity in mastectomy specimen can also be reduced if chemotherapy is considered prior to mastectomy.

## REFERENCES

1. Valero VV, Buzdar AU, Hortobagyi GN. Locally Advanced Breast Cancer. *Oncologist.* 1996;1:8–17.
2. Fisher B, Brown A, Mamounas EL. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: Findings from national surgical adjuvant breast and bowel project B-18. *J ClinOncol.* 1997;15:2483–93.

3. Fisher ER, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N. Pathobiology of preoperative chemotherapy: Findings from the national surgical adjuvant breast and bowel (NSABP) protocol B-18. *Cancer.* 2002;95:681–95.
4. Eisenhauer EA, Therasse P, Bogaerts J, et al.: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009, 45:228-47.
5. Raina V, Bhutani M, Bedi R, et al.: Clinical features and prognostic factors of early breast cancer at a major cancer center in North India. Indian J Cancer. 2005, 42:40-5.
6. Min SY, Lee SJ, Shin KH, et al.: Locoregional recurrence of breast cancer in patients treated with breast conservation surgery and radiotherapy following neoadjuvant chemotherapy. Int J RadiatOncolBiol Phys. 2011, 81:e697-705.
7. Chin SN, Green CM, Gordon-Strachan GM, Wharfe GH: Locally advanced breast cancer in Jamaica: prevalence, disease characteristics and response to preoperative therapy. Asian Pac J Cancer Prev. 2014,
8. Yadav BS, Sharma SC, Singh R, Singh G: Patterns of relapse in locally advanced breast cancer treated with neoadjuvant chemotherapy followed by surgery and radiotherapy. J Cancer Res Ther. 2007, 3:75-80.
9. Chen AM, Meric-Bernstam F, Hunt KK, et al.: Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience. J ClinOncol. 2004, 22:2303-12.
10. Goel A, Bhan CM, Srivastava KN: Five year clinico pathological study of breast cancer . Indian J Med Sci. 2003, 57:347-9.
11. Sandhu DS, Sandhu S, Karwasra RK, Marwah S: Profile of breast cancer patients at a tertiary care hospital in north India. Indian J Cancer. 2010, 47:16-22.
12. Viswambharan JL, Kadambari D, Iyengar KR, et al.: Feasibility of breast conservation surgery in locally advanced breast cancer downstaged by neoadjuvant chemotherapy: a study in mastectomy specimens using simulation lumpectomy. Indian J Cancer. 2005, 42:30-4.
13. Taucher S, Steger GG, Jakesz R, et al.: The potential risk of neoadjuvant chemotherapy in breast cancer patients--results from a prospective randomized trial of the Austrian Breast and Colorectal Cancer Study Group (ABCSG-07). Breast Cancer Res Treat. 2008, 112:309-16.
14. Saha A, Chattopadhyay S, Azam M, et al.: Clinical outcome and pattern of recurrence in patients with triple negative breast cancer as compared with non-triple negative breast cancer group. Clin Cancer Investig J. 2012, 1:201-5.
15. Rao C, Shetty J, Kishan Prasad HL: Morphological profile and receptor status in breast carcinoma: an institutional study. J Cancer Res Ther. 2013, 9:44-9.
16. 26. Zubeda S, Kaipa PR, Shaik NA, et al.: Her-2/neu status: a neglected marker of prognostication andmanagement of breast cancer patients in India. Asian Pac J Cancer Prev. 2013, 14:2231-5.
17. Shenkier T, Weir L, Levine M, Olivotto I, Whelan T, Reyno L: Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer. CMAJ. 2004, 170:983-94.
18. Buchholz TA, Lehman CD, Harris JR, et al.: Statement of the science concerning locoregional treatments after preoperative chemotherapy for breast cancer: a National Cancer Institute conference. J ClinOncol. 2008, 26:791-7.

19. Prasad SR, Jhaveri KS, Saini S, Hahn PF, Halpern EF, Sumner JE: CT tumor measurement for therapeutic response assessment: comparison of unidimensional, bidimensional, and volumetric techniques initial observations. Radiology. 2002, 225:416-9.
20. Herrada J, Iyer RB, Atkinson EN, Sneige N, Buzdar AU, Hortobagyi GN: Relative value of physical examination, mammography, and breast sonography in evaluating the size of the primary tumor and regional lymph node metastases in women receiving neoadjuvant chemotherapy for locally advanced breast carcinoma. Clin Cancer Res. 1997, 3:1565-9.
21. Hortobagyi GN, Ames FC, Buzdar AU, et al.: Management of stage III primary breast cancer with primarychemotherapy, surgery, and radiation therapy. Cancer. 1988, 62:2507-16.

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