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Clinicopathological response assessment to neoadjuvant chemotherapy in locally advanced breast cancer- A rural population-based case series

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Abstract

Introduction: Breast cancer is the commonest malignancy among women worldwide. Despite a multidisciplinary approach, locally advanced breast cancer remains a clinical challenge as most of the patients have a high rate of locoregional spread and develop distant metastases. Neoadjuvant chemotherapy not only paves the way for a more conservative surgical option but also decreases the incidence of positive nodes. This study was undertaken, to assess the effectiveness of neo-adjuvant chemotherapy and its impact on clinical and pathological response in locally advanced breast cancer. It also, compare patient characteristics, histological type, and hormonal receptor status with response to neo-adjuvant chemotherapy.

Materials and Methods: This is a prospective observational study over a one-year period on 30 locally advanced breast cancer patients from rural background who received neoadjuvant chemotherapy. All patients received a standard neoadjuvant treatment regimen and were evaluated clinically, radiologically, and pathologically pre- and post-chemotherapy. The clinical response was assessed by RECIST criteria, the pathological response was graded according to Chevalier classification, and the overall impact was assessed by AJCC response criteria.

Results: Most of the patients (46.7%) were in the age group of 35-48 years. The premenopausal and postmenopausal groups were 63% and 37%, respectively. In the present study, tumours expressing oestrogen, progesterone, and HER 2 were 73%, 66%, and 27%, respectively. Patients showing clinically complete responses post-neoadjuvant chemotherapy were 4, partial responses were 21, stable disease was 3, and progressive disease was 2. A pathological partial response was achieved in 93% of patients.

Conclusion: Neoadjuvant chemotherapy in locally advanced breast cancer not only downstages the disease but increases the scope of operability and thus makes it possible to resect the disease with a tumour-free margin in most cases.

Keywords: Locally advanced breast cancer (LABC), Neoadjuvant chemotherapy (NACT)

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Introduction

Breast cancer is among the most common cancers in women worldwide. In Globocan India 2020, breast cancer accounted for 13.5% of all new cancer cases in both sexes and 10.6% of all deaths, with a cumulative new case risk of 2.81 (1). The National Comprehensive Cancer Network describes locally advanced breast cancer (LABC) as American Joint Committee on Cancer (AJCC) (7th edition) stage III breast cancer in the absence of distant metastasis as tumours more than 5 cm in size with regional lymphadenopathy (N1–3) or of any size with direct extension to the chest wall (T4a) or skin (T4b) regardless of regional lymphadenopathy or presence of regional lymphadenopathy (clinically fixed or matted axillary lymph nodes, or any of ipsilateral infraclavicular, supraclavicular, or internal mammary lymphadenopathy) regardless of tumour stage. In the AJCC 7th edition, ipsilateral supraclavicular lymphadenopathy was reclassified as regional lymphadenopathy (N3), which was considered in the AJCC 6th edition as distant metastasis (2).

Despite widespread awareness of the benefits of screening and early detection, 10% to 20% of breast cancer patients are diagnosed with locally advanced disease in industrialized nations, compared to up to 50% of incidence cases in developing nations (3). The present study is based on a rural-based population who were diagnosed as LABC on initial presentation and is amenable to less attrition in our health care setup.

Studies show that with only treatment with radical mastectomy or roentgen, the five-year survival rate was 30% (4,5). Neoadjuvant chemotherapy became a part of standard treatment for LABC after the National Surgical Adjuvant Breast and Bowel Project B-18 trial, which found that it not only reduced tumour size but decreased the incidence of positive nodes and also showed benefit in assessing tumour response to it in vivo (6).

Histopathological response to primary chemotherapy was found to be the single most important prognostic factor for both disease-free and overall survival rates. Moreover, the extent of the remaining tumour determines the rate of local recurrence and dictates the necessity for additional loco-regional therapy (7).

Several studies have shown that oestrogen receptor-negative patients achieved a higher pathological complete response than positive patients (8). High tumour grade and tumour size were clinical determinants of pathological complete response (9).

The present study was undertaken to assess the effectiveness of neo-adjuvant chemotherapy and its impact on clinical and pathological response in locally advanced breast cancer and to compare patient characteristics, histological type, and hormonal receptor status with response to neo-adjuvant chemotherapy (NACT).

Materials and Methods

After getting the ethical approval of the project, consent and agreement were obtained from all the patients. In this way, the study was conducted prospectively on 30 rural background-based patients attending the surgery outpatient department of Fakhruddin Ali Ahmed Medical Hospital, Barpeta, Assam, India, from September 2021 to August 2022.

All patients above 18 years of age diagnosed with locally advanced breast cancer who were willing to undergo follow-up were included in the study. Operable Locally advanced breast cancer (T3N1M0), history of prior radiotherapy to the breast, the presence of distant metastases, and patients in whom neoadjuvant chemotherapy is contraindicated were excluded from the study.

Patients presenting with breast lumps were evaluated clinically, radiologically, and pathologically by tru-cut biopsy to confirm the primary tumour as locally advanced breast cancer. The patient baseline and tumour characteristics, including age, menstrual status, tumour size, nodal status, tumour grade, hormonal receptor HER2 status, and histological type, were noted, and metastatic workup was done .

Patients were treated with a standard neoadjuvant chemotherapy regimen of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC). In triple negative cases, dose-dense AC followed by taxane drugs (Paclitaxel or docetaxel) was given. In HER2-positive cases, AC followed by taxane with trastuzumab and or pertuzumab was given.

After the completion of 3-4 cycles or additional neoadjuvant chemotherapy as needed, the tumour was assessed clinically, and radiologically for tumour size, nodal status, and clinical stage, after which all the patients underwent modified radical mastectomy with en bloc axillary dissection, and a specimen was sent for gross and histopathological examination. Clinical response was assessed by RECIST criteria (response evaluation criteria in solid tumours) (Table 1.)

Table 1. RECIST criteria for clinical response evaluation.

Complete Response (CR)	Clinical disappearance of primary tumour
Partial Response (PR)	>30% decrease in longest diameter
Stable Disease (SD)	<30% decrease or <20% increase
Progressive Disease (PD)	>20% increase in longest diameter

Histopathological response is graded according to Chevalier classification (9).

Table 2. Chevalier classification for grading histopathological response.

No cancer in breast and axillary nodes.	**Pathological complete response (pCR)**
Only in situ carcinoma remains, nodes negative	Pathological partial response (pPR)
Invasive carcinoma with stromal fibrosis.	
No or few modifications in stromal fibrosis.	Pathological no response (pNR)

The overall impact will be assessed by AJCC response criteria (8th edition) (10).

Table 3. AJCC response criteria for overall impact evaluation.

Complete response (CR)	Absence of invasive carcinoma in breast and nodes.
Partial response (PR)	Decrease of either or both T & N stage.
No response (NR)	No apparent change in either T or N stage

Results

The mean age of LABC patients ranged from 35 to 48 years (Figure 1). 57% of patients had right-sided breast disease. 37 % of patients were postmenopausal women, and 63% were premenopausal (Figure 2). A positive family history was found only in one patient, with her mother being affected by the disease.

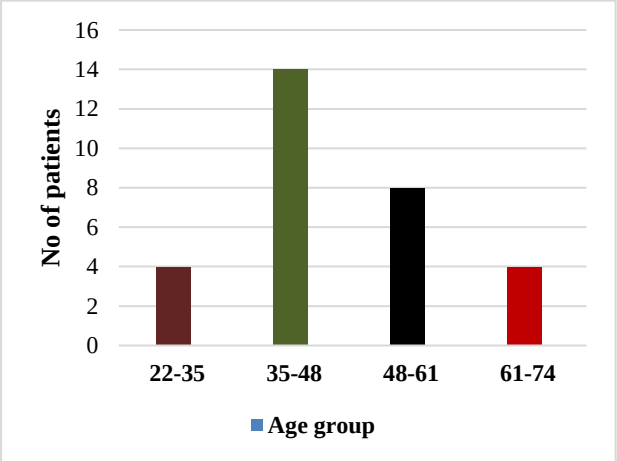

Figure 1. Graph showing age distribution of LABC patients.

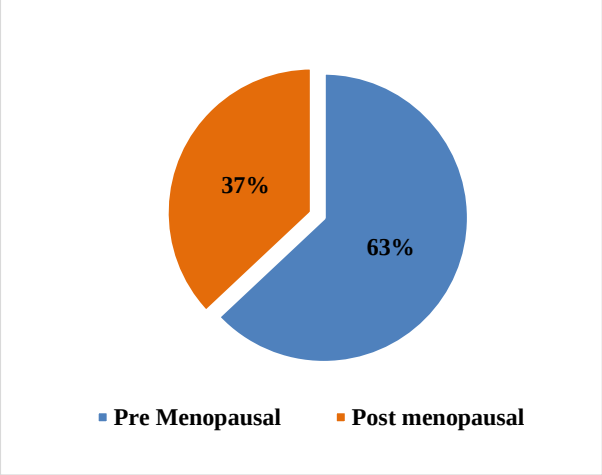

Figure 2. Pie diagram showing menstrual status of LABC patients.

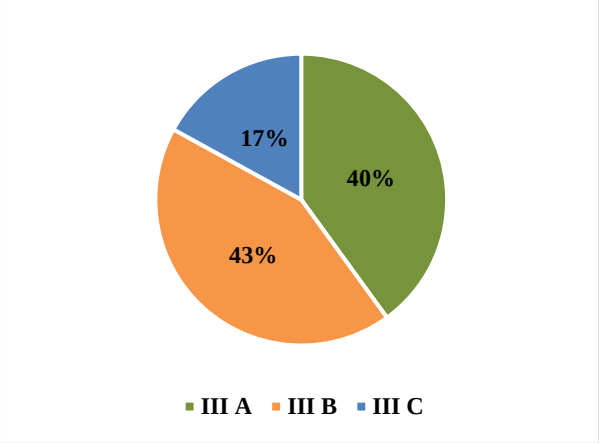

Figure 3. Pie diagram showing tumour stage.

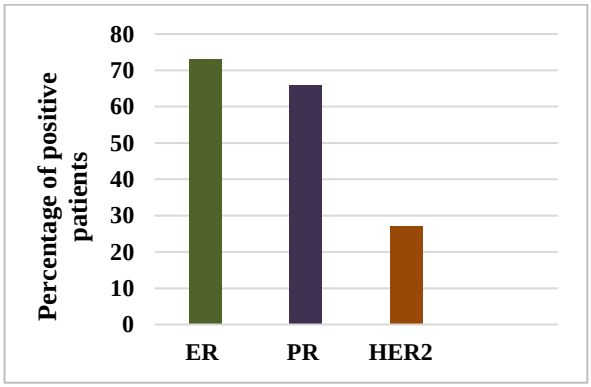

Figure 4. Graph showing tumour ER, PR, HER2 receptor status.

Out of 30 LABC patients, 40% belonged to stage IIIA, 43% were stage IIIB, and 17% had stage IIIC disease (Figure 3). The percentages of oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)-positive tumours were 73%, 66%, and 27% respectively (Figure 4). Most of the patients had invasive ductal carcinoma.

Table 4. Pre-NACT T-Stage vs Post-NACT T-Stage.

		Post chemotherapy tumour stage				
		T0	T1	T2	T3	T4
Pre chemotherapy tumour(T) stage	T2	0	4	0	0	0
	T3	1	1	5	2	0
	T4	3	0	11	1	2

In our study, most patients belonged to T4b 17 before receiving neoadjuvant chemotherapy, but post-therapy, the tumour size reduced, and the majority belonged to T2 17 patients (Table 4). Pre chemotherapy maximum patients belong to N2 18, but post-therapy maximum patients belong to N1 17 patients (Figure 5).

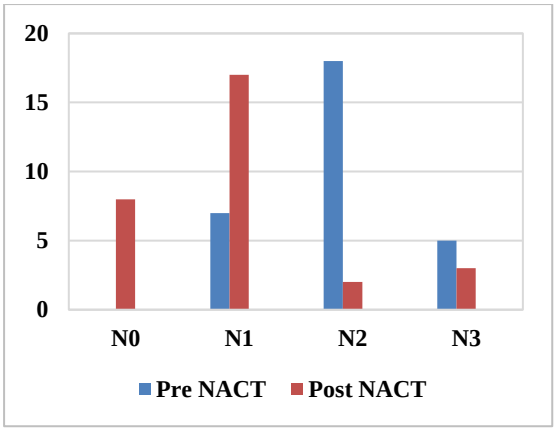

Figure 5. Graph showing pre NACT vs Post NACT N stage.

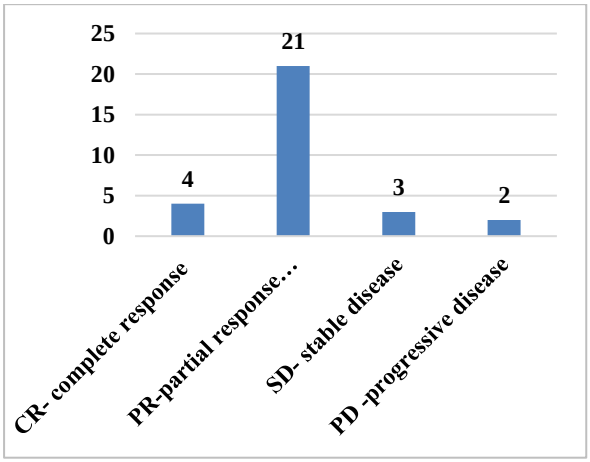

Figure 6. Graph showing clinical response to NACT.

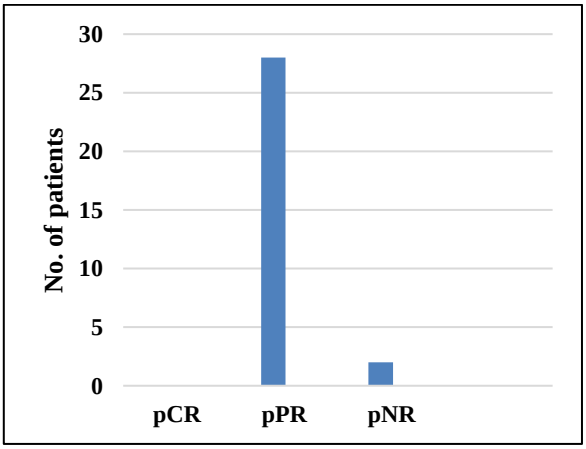

Figure 7. Graph showing pathological response to NACT.

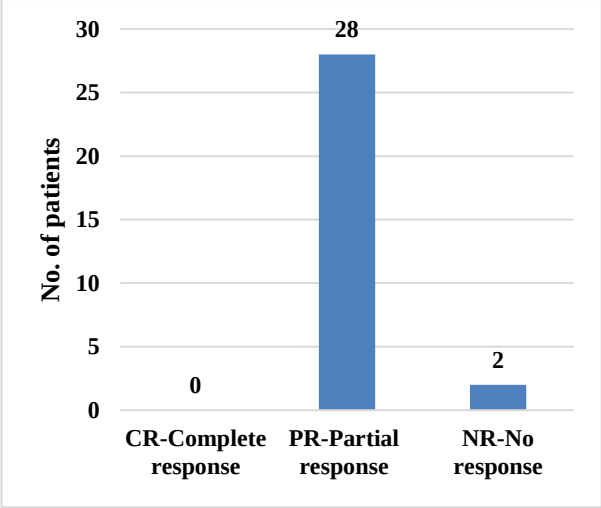

Figure 8. Graph showing overall response to NACT**.**

Among 30 LABC patients, according to RECIST criteria (Table1), clinical complete response post NACT was 13%, partial response 70%, stable disease 10%, and progressive disease 7% (Figure 6). 28 patients showed a pathological partial response according to Chevalier classification (Table 2) (Figure 7), which also corresponds to overall response (Table 3) (Figure 8). The comparison of patient and tumour characteristics with clinical, pathological, and overall response showed the maximum partial clinical response in premenopausal women of less than 50 years having invasive ductal carcinoma and oestrogen progesterone receptor positive, which also corresponds to the partial pathological and overall response (Table 5)**.**

Table 5. Comparison of patient and tumour characteristics with the clinical, pathological and overall response**.**

Characteristics		RECIST				Chevililier classification			Overall response		
		CR	PR	SD	PD	pCR	pPR	pNR	CR	PR	NR
Age	<50 years	2	15	3	2	0	20	2	0	20	2
	51 & above	2	6	0	0	0	8	0	0	8	0
Menopausal	Pre	1	14	3	1	0	18	1	0	18	1
	Post	3	7	0	1	0	10	1	0	10	1
ER status	Positive	3	17	0	2	0	20	2	0	20	2
	Negative	1	4	3	0	0	8	0	0	8	0
PR status	Positive	1	17	0	2	0	18	2	0	18	2
	Negative	3	4	3	0	0	10	0	0	10	0
Histology	Invasive ductal	4	20	3	2	0	27	2	0	27	2
	Invasive lobular	0	1	0	0	0	1	0	0	1	0

Discussion

In the present study, we found that most of the patients 63% were premenopausal and 37% were postmenopausal which was similar to a study by Mishra et al. (12) with 70% cases of premenopausal and 30% cases of postmenopausal.

In our study, post chemotherapy 4 (13.3%) patients had complete clinical remission (cT0). Amongst the 17 (56.6%) patients with pre-chemotherapy T4 disease, only 2 (6.6%) patients remained in T4 stage after chemotherapy, which was comparable to Kunnuru et al. (11) with 32 (53.3%) patients with pre-NACT T4 disease to only eight (13.3%) patients in T4 stage after NACT .

Post chemotherapy, 26.6% of patients had a complete nodal response. In addition to this, N2 stage disease was present in 18 (60%) patients (pre-chemotherapy), which reduced to four (13.3%) patients after chemotherapy.

The usage of NACT in LABC is very effective. In our study, the overall response rate was 93.3% (complete and partial). In patients who achieved a complete clinical response, residual tumours might persist histologically. In our study, 4 patients (13.3%) had a complete clinical response, but all had residual disease histologically. While comparing with another study, the complete clinical response in our study (13.3%) was comparable with Alvarado et al. (12) and Garbhi Olfa et al, (13) which showed a complete clinical response of 12% and 14%, respectively.

In our study group, the relative overall response rates by total number of patients for each factor were as follows: 90.9% in ER-positive tumours, 90% in PR-

positive tumours, and 25% in HER2-positive tumours after three cycles of chemotherapy. A good pathological response of 16.6% was found in triple-negative patients, followed by 90% of 20 luminal A patients.

In the current study, 80% of patients had negative margins post-modified radical mastectomy, probably due to tumour shrinkage following NACT. Very few comparison studies exist stating the same.

Despite being a prospective study due to the short follow-up period of one year, the study faced the challenge of assessing NACT's impact on disease free and overall survival. Due to the small sample size and lack of comparative grouping, generalizing of results became difficult.

Conclusions

In locally advanced breast cancer, NACT not only downstages the disease but also increases the scope of operability for tumours responding to it, and thus making it possible to resect the disease with a tumour free margin in most cases. Including NACT in a protocol-based multimodal approach helps yield better results in locally advanced breast cancer patients.

Author contribution

All authors have equal contribution.

Conflict of interest

The authors have no conflict of interest to declare.

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