ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 05 | May - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

RESPONSE OUTCOME OF NEO ADJUVANT CHEMO THERAPY AND FEASIBILITY OF BREAST CONSERVATION SURGERY AMONG LOCALLY ADVANCED BREAST CANCER PATIENTS: A PROSPECTIVE EVALUATION

Breast Surgery

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ABSTRACT

Background: Locally advanced breast cancer (LABC) poses a substantial clinical challenge, particularly in regions like India where it accounts for a significant proportion of breast cancer cases. Neoadjuvant chemotherapy (NACT) has emerged as a promising strategy to downstage tumors and increase the feasibility of breast conservation surgery (BCS), thus improving patient outcomes. This prospective observational study aimed to comprehensively investigate the clinical characteristics of LABC patients and evaluate the impact of NACT on tumor downstaging and the feasibility of BCS. **Methods:** A total of 100 consecutive female LABC patients (Stage III) aged 25 to 70 years were enrolled in the study. Clinical and histopathological data were collected, including age, menstrual status, family history, symptom duration, tumor characteristics, and receptor status. NACT regimens were administered as per institutional protocols. Tumor and axillary lymph node size changes were measured, and clinical responses were evaluated using RECIST 1.1 criteria. Statistical analyses were conducted using SPSS software. **Results:** The study population exhibited a mean age of 49.43 years, with 61% of patients being premenopausal. The predominant histopathological subtype was invasive ductal carcinoma (91%), and common receptor statuses included ER+ PR+ HER2- (29%) and triple-negative (28%). Post-NACT, 82% of patients exhibited a partial response, while 10% achieved a complete response. Notably, BCS feasibility was observed in 60% of cases following NACT. Histological subtype and ER/PR status significantly influenced response rates ($p < 0.05$). **Conclusion:** Neoadjuvant chemotherapy demonstrated its efficacy in downstaging LABC tumors, resulting in a higher feasibility of breast conservation surgery. Receptor status emerged as an important predictor of chemotherapy response. The study underscores the potential of a multimodal approach involving NACT and BCS to optimize treatment outcomes for LABC patients, particularly in resource-constrained settings.

KEYWORDS

Locally Advanced Breast Cancer, Neoadjuvant Chemotherapy, Breast Conservation Surgery, Clinical Response, Receptor Status

The shifting epidemiological patterns have highlighted breast cancer as the most prevalent malignancy affecting women on a global scale (1). In India, it constitutes 13.5% of all cancer cases, as indicated by the 2020 Globocan data (2). Worldwide, the diagnosis of breast cancer surpasses a million cases. However, a striking difference is noted in the distribution, with only 10-20% of cases in Western countries being classified as Locally Advanced Breast Cancer (LABC), while in India, this category accounts for 40-50% of annual diagnoses (3, 4, 5).

The term LABC encompasses a heterogeneous spectrum of breast tumors characterized by extensive locoregional expansion. These tumors may range from being amenable to surgical intervention to cases considered inoperable. Despite the absence of clinical and radiological signs of distant metastasis, LABC presents a challenging scenario. According to the eighth edition of the American Joint Committee on Cancer (AJCC) cancer staging manual, LABC includes tumors classified as T3 (larger than 5 cm) that might involve the skin or chest wall. It also encompasses inflammatory breast cancers (IBCs), instances of clustered ipsilateral axillary lymph nodes, fixed axillary lymph nodes, as well as the presence of ipsilateral supraclavicular lymph nodes (SCLNs) and/or internal mammary lymph nodes. All of this occurs while ruling out the presence of distant metastases (6).

In the context of treatment advancements, a comprehensive analysis of clinical trials recently concluded that neoadjuvant chemotherapy demonstrates effectiveness in terms of both survival rates and the prevention of distant recurrence. This finding underscores the evolving landscape of breast cancer management and its potential positive impact on patient outcomes. (7)

The effective management of Locally Advanced Breast Cancer (LABC) presents a notable challenge for healthcare providers, necessitating a strategic approach that has evolved over time from a singular to a more multifaceted methodology. Neoadjuvant chemotherapy has emerged as a primary frontline intervention for patients diagnosed with LABC. This approach has garnered significant attention due to its potential to contribute to therapeutic decision-making processes through the assessment of pathological tumor response. Moreover, neoadjuvant systemic therapy has demonstrated benefits such as enhanced local tumor control and improved survival rates in numerous studies (8,9,10)

Neoadjuvant chemotherapy (NACT) stands as the established norm for treating locally advanced breast cancer (LABC) that has not yet metastasized. This approach yields the distinct advantage of reducing the size of inoperable tumors, thereby enhancing the potential for breast conservation surgery (BCS) in cases where mastectomy might have been the sole option (11,12,13). NACT introduces the ability to gauge the tumor's sensitivity to chemotherapy in vivo, potentially guiding the selection of subsequent treatment agents (14). Furthermore, NACT has contributed to a reduction in the invasiveness of axillary surgery, with sentinel lymph node biopsy (SLNB) becoming the standard practice for patients who initially present without clinically evident lymph node involvement. The evaluation of SLNB's role in patients initially presenting with positive lymph nodes is also an ongoing consideration in the post-NACT phase (15). Those undergoing NACT have demonstrated comparable outcomes in terms of recurrence-free survival (RFS) and overall survival (OS) to those who initially undergo surgery followed by adjuvant therapy. This advantage extends to preserving the breast and axillary regions, as noted earlier (16,17,18).

The safety and feasibility of BCS in early breast cancer (EBC) have been well-documented (19). While mounting evidence suggests that BCS is viable in LABC, reservations linger concerning an elevated risk of locoregional recurrence (LRR) or recurrence within the same breast, particularly in patients who opt for BCS following NACT for LABC (20,21,22). The success of BCS hinges significantly on achieving tumor-free surgical margins, a task that might be challenging for certain LABC cases post-NACT due to the intricacies

of tumor response (23).

Notably, unlike EBC, no randomized trial has been conducted to definitively establish the effectiveness of BCS in LABC. Existing data is primarily derived from small observational studies and case series. In India, a substantial proportion of women (29%–52%) are diagnosed at stage III, typically between the ages of 40 and 50 (24,25). Thus far, a single comprehensive study from India addressing the safety of BCS in LABC has been published, a significant contribution given that LABC is the prevalent presentation in many lower-middle-income countries.

Our objective encompassed a prospective investigation into the clinical characteristics of LABC patients seeking treatment at our institution. Additionally, we aimed to assess the impact of neoadjuvant chemotherapy on the process of downstaging the tumor. This study holds promise in shedding light on the clinical profile of LABC patients and the feasibility of BCS, while further elucidating the pivotal role that neoadjuvant chemotherapy plays in mitigating tumor progression and optimizing treatment outcomes.

MATERIALS AND METHOD:

This prospective observational study was conducted at Department of General Surgery of IPGMER and SSKM Hospital between January 2021 and July2022. The Ethics Committee approval for the same was received from the Institutional Ethics committee.

This study's inclusion criteria encompass female individuals who have been diagnosed with locally advanced breast cancer (Stage III) as per the AJCC classification (26). The age range for eligible participants is set between 25 to 70 years. Moreover, prospective participants must express their willingness to partake in the study and provide informed consent through a signature. On the other hand, the exclusion criteria involve cases of male breast cancer and patients displaying distant metastasis. Additionally, pregnant individuals are excluded from participation. Those with significant medical comorbidities are also excluded, along with individuals who have previously received a diagnosis of any other form of cancer. 100 consecutive cases of LABC were included in the study upon fulfilling the inclusion-exclusion criteria.

Statistical Analysis:

Continuous variables in the study were analyzed using the Z-test and Welch's t-test to assess extreme reactions. The results were reported as the mean, wherever applicable. Categorical variables were evaluated using Pearson's Chi-square test. A confidence interval of 95% was used for calculations, and a p-value ≤ 0.05 was considered statistically significant. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software, version 28.0.

RESULTS:

The mean age of the study population was 49.43 years, with a distribution as follows: 25 patients (≤ 40 years), 36 patients (41-50 years), 22 patients (51-60 years), and 17 patients (≥ 61 years). Among the total of 100 patients, 61% were identified as premenopausal. The average duration of disease among the patients was 2.87 months. The predominant histopathological subtype observed among the study patients was invasive ductal carcinoma (91%).

Regarding receptor status, the most prevalent cases were ER+ PR+ HER2- (29%) and triple-negative (28%). For a comprehensive overview of the various clinico-pathological characteristics of the study population, please refer to Table 1.

Table 1: Baseline distribution of Clinico- pathological characteristics of study population

Clinicopathological Characteristics		Frequency	Percentage (%)
Age (Years)	≤40	25	25
	41-50	36	36
	51-60	22	22
	≥61	17	17
Menopause Status	Pre-menopausal	61	61
	Post-menopausal	39	39
Parity	Nulliporous	11	11
	Multiporous	88	88
	Grandmultiporous	1	1
Hormone Pills	Yes	57	57
	No	43	43
Lump position	Upper outer	38	38
	Upper inner	25	25
	Lower outer	15	15
	Lower inner	6	6
	Central	5	5
	All 4 quadrants	3	3
	Upper outer and lower quadrant	3	3
	Upper inner and outer quadrants or upper half	2	2
	Upper and lower inner quadrants	2	2
	Lower outer and inner quadrants or lower half	1	1
Stage	IIIA	51	51
	IIIB	24	24
	IIIC	25	25
Histopathological Type	Ductal	91	91
	Lobular	4	4
	Medullary	1	1
	Mucious	1	1
	Papillary	2	2
	Tubular	1	1
Immuno histochemistry	ER+PR+HER2-	29	29
	ER+PR+HER2+	5	5
	ER-PR-HER2-	28	28
	ER-PR-HER2+	12	12
	ER+PR-HER2+	4	4
	ER+PR-HER2-	18	18
	ER-PR+HER2-	3	3
	ER-PR+HER2+	1	1
Duration of symptom (months)	2.87 ± 2.19		

All patients within the study cohort underwent neoadjuvant chemotherapy (NACT), with 69% of them receiving Cisplatin + Doxorubicin + Docetaxel, and the remaining 31% receiving Cyclophosphamide + Doxorubicin + 5-fluorouracil. On average, patients underwent three cycles of chemotherapy, and surgery was performed 30 days after the completion of these chemotherapy cycles. Clinical response was observed in 92% of patients with locally advanced breast cancer (LABC). This response was characterized by 10% achieving a complete response, 82% exhibiting a partial response, and 8% showing no response or stable disease. Post NACT clinical response among LABC patients, categorized according to RECIST criteria, is detailed in Table 2.

Table 2: Clinical Response Rate post NACT according to RECIST criteria

RECIST 1.1	CR (Complete Response)	10	10%
	PR (Partial Response)	82	82%
	SD (Stable Disease or no response)	8	8%
	Total	100	100%

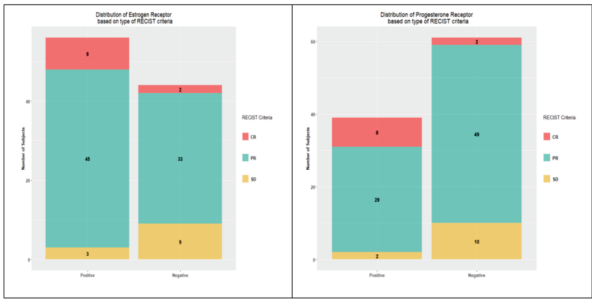
Table 3 provides an overview of the post-NACT clinical response rates across various parameters, including age, stage, histopathology, receptor status, and the feasibility of breast-conserving surgery (BCS). Notably, response rates demonstrated significance in relation to ER status and PR status ($p < 0.05$).

However, statistical significance was not observed when comparing age, Her2/neu status, histopathology, stage, and the feasibility of BCS.

Table 3: Comparison of Post NACT Clinical response with various parameters

		CR (Complete Response)	PR (Partial Response)	SD (Stable Disease)	Total
Age (P = 0.81)	≤40	3	21	1	25
	41-50	3	27	6	36
	51-60	2	18	2	22
	≥61	2	12	3	17

ER Status (P = 0.03)	Positive	8	45	3	56
	Negative	2	33	9	44
PR Status (P = <0.0001)	Positive	8	29	2	39
	Negative	2	49	10	61
HER2/neu (P = 0.72)	Positive	2	21	2	25
	Negative	2	8	57	75
Histopathological Type (P = 0.93)	Ductal	10	69	12	91
	Lobular	0	4	0	4
	Medullary	0	1	0	1
	Mucious	0	1	0	1
	Papillary	0	2	0	2
	Tubular	0	1	0	1
Stage (P = 0.52)	IIIA	7	40	4	51
	IIIB	2	18	4	24
	IIIC	1	20	4	25
BCS (P = 0.17)	Feasible	7	43	10	60
	Not Feasible	3	35	2	40



Graph 1: Distribution of ER and PR based on RECIST criteria

Table 4 provides a comprehensive overview of the changes observed in patients with locally advanced breast cancer (LABC) following neoadjuvant chemotherapy (NACT). These changes include reductions in lump size and lymph node size, evaluations of organ toxicity, assessments of pathological response, and the feasibility of breast-conserving surgery (BCS).

Table 4: Post NACT changes observed in study population

Parameters		Type of NACT			
		Cisplatin+ Doxorubicin +Docetaxel		Cyclophosphamide + Doxorubicin + 5 fluorouracil	
Haematological Toxicity		Frequency	Percentage (%)	Frequency	Percentage (%)
	Grade I	42	60.87	19	61.29
	Grade II	22	31.88	10	32.26
	No Toxicity	5	7.25	2	6.45
	Total	69	100.00	31	100.00
	p-value	0.99			
GI Toxicity (Post NACT)	Grade I	56	81.16	21	67.74
	Grade II	6	8.70	4	12.90
	No Toxicity	7	10.14	6	19.35
	Total	69	100.00	31	100.00
	p-value	<0.0001			
Skin Toxicity (Post NACT)	Grade I	58	84.06	18	58.06
	Grade II	11	15.94	13	41.94
	Total	69	100.00	31	100.00
	p-value	0.01			
Pathological response (MP GRADE)	GRADE I	1	1.45	3	9.68
	GRADE II	26	37.68	12	38.71
	GRADE III	30	43.48	10	32.26
	GRADE IV	7	10.14	1	3.23
	GRADE V	5	7.25	5	16.13
	Total	69	100.00	31	100.00
	p-value	0.12			
BCS feasibility	Feasible	40	66.67	20	33.33
	Not Feasible	29	72.50	11	27.50
	Total	69	100.00	31	100.00
	p-value	0.54			
Lump Size Reduction	Mean ± S.D.	4.28 ± 2.31		4.15 ± 2.16	
	p-value	0.79			
Lymph Size Reduction	Mean ± S.D.	28.41 ± 16.94		26.94 ± 19.86	
	p-value	0.72			

DISCUSSION:

The average age of our study participants was 49.43 years, which closely aligns with the findings of Raina et al. (27). Our study's assessment of menstrual status corresponds with the observations made by Cuen et al. (28). Among the patients with locally advanced breast cancer (LABC), 61% were identified as pre-menopausal, surpassing the results of Mohapatra et al. (29) (54.7%) but falling short of the figures reported by Mona M Rashed et al. (30) (70%).

Interestingly, a protective role was noted for women with multiple pregnancies. Specifically, the majority of patients exhibited a parity of 2 [41 (41%)], a statistically significant finding ($p < .00001$). Within our cohort, there was one grand multipara (1%), and 11 (11%) were nulliparous. In accordance with Lambe Met al.'s study (31), we found that increasing parity was linked to a notable reduction in breast cancer risk, with each additional birth leading to a 10 percent decrease in risk (odds ratio 0.90 [95% CI 0.88-0.91]).

Additionally, our analysis revealed that 43% (43%) of patients had never used hormonal contraception. Morch LS and Skovlund CW (32) demonstrated that the overall relative risk of invasive breast cancer was 1.20 (95% CI 1.14–1.26) among women using or having recently used hormonal contraception. The relative risk grew with prolonged use, ranging from 1.09 (95% CI 0.96–1.23) for durations of less than 1 year to 1.38 (95% CI 1.26–1.51) for use exceeding 10 years. Notably, the risk was comparable across various formulations or types of combined oral contraceptives.

In our study, a total of 87% of patients had no family history of malignancy, indicating that breast malignancy was predominantly sporadic in nature. Conversely, 13% had a positive family history. Notably, Helmrich et al. (33) reported a higher incidence of 5.6% positive family history of breast cancer in their patient series, which could potentially be attributed to their smaller patient cohort. Out of the total patients, 73% presented with painless lumps, while the remaining 27% had other symptoms.

Our findings revealed that the majority of patients displayed symptoms for a duration of 1-3 months, with an average symptom duration of 2.87 months. Moreover, a significant proportion of cases (59%) involved the left breast, a notable difference from the right breast, with a p-value of less than 0.0001. This preference for the left side could be linked to the larger amount of breast tissue in the upper outer region, which is a common location for breast malignancies. Correspondingly, the upper outer quadrant was identified as the most frequent position for lumps, accounting for 38% of cases.

According to our study, 51% of patients were categorized as Stage IIIA based on the American Joint Committee on Cancer (AJCC) classification. In contrast, Mohapatra et al. (29) found that LABC cases predominantly fell into the AJCC clinical stage IIIB.

Comparing our results with Mohapatra et al. (29) study, the mean lump size in our cohort was 8.34 cm, with a substantial 88% having lump sizes exceeding 5 cm, a difference that was statistically significant ($p < 0.0001$). This contrasts with Azizun-Nisa et al. (34), where 52.7% of tumors were between 2-5 cm and 35.3% were larger than 5 cm. Similarly, Mona M Rashed et al. (30) reported that 54% of cases had tumor sizes ranging from 2-5 cm, and 36% exhibited tumor sizes larger than 5 cm. This variance may be attributed to our study's focus solely on LABC cases.

Furthermore, post-neoadjuvant chemotherapy (NACT), 66% of cases were categorized within the 2-5 cm lump size range, with a mean lump size of 4.11, signifying statistical significance at $p < 0.0001$. Clinically, the lymph node size was 36.70 prior to NACT and decreased to 8.75 post-NACT, which aligns with findings from Viswambharan JL et al. (35).

Regarding lymph nodal status, 10% of patients were classified as N0, a significant finding with a p-value of less than 0.0001. Post-neoadjuvant chemotherapy (NACT), 32% were categorized as T2N0M0, also demonstrating statistical significance at $p < 0.0001$.

Analysis of post-NACT lymph node size indicated that the majority of nodes fell within the 0-15 mm range, with a mean size of 8.75 mm. This measurement was employed to determine clinical response using the RECIST 1.1 criteria.

Clinical response was evaluated by comparing the pre and post-NACT measurements of breast lump and axillary lymph node size using slide calipers. When considering both factors, clinical response was determined according to the RECIST 1.1 criteria. Among the patients, 82% exhibited partial response, while 10% showed complete response after NACT. These results exhibited variation based on different NACT regimens, aligning with the observations of Cleator SJ et al., Chang J et al., and Colleoni M et al. (36, 37, 38).

In terms of histological subtype, 91% were diagnosed with invasive ductal carcinoma – not otherwise specified (NOS), a significant finding with $p < 0.001$, followed by 4% with the lobular type. This distribution is in line with the findings of Yerraguntla Subramanya et al. (29), where 89% were identified as invasive ductal carcinoma.

Immunohistochemistry analysis revealed that the majority, 29%, were categorized as ER+PR+Her2-, followed by 28% with triple negative breast cancer. Post-NACT, breast-conserving surgery (BCS) was feasible for 60% of patients, consistent with the findings of Yixuan Suna et al. (39). Karanlik Ozgur et al. (40) suggested that NACT could enhance BCS success with negative margins for tumors larger than 2 cm, a concept supported by our study wherein 60% were suitable for BCS.

A similar trend was observed in the study by Zhou B, Yang DQ, Qiao XM, Tong FZ, Cao YM et al. (41), where 63% were candidates for breast-conserving therapy. Among our patients, 69% received cisplatin, doxorubicin, and docetaxel as neoadjuvant chemotherapeutic agents, while 31% received cyclophosphamide, doxorubicin, and 5-fluorouracil.

Toxicity due to chemotherapeutic agents was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. We found that 61% experienced grade I hematological toxicity. Gastrointestinal toxicity was absent in 13%, whereas 77% had grade I toxicity, and 76% exhibited grade I skin toxicity.

Among the total of 100 patients, 55% had an ECOG performance status score of 0, followed by 37% with a score of 1. Furthermore, this study illustrated a relatively low incidence of surgical morbidity. A majority of patients, 12%, experienced seroma after surgery.

Neoadjuvant chemotherapy is increasingly utilized in locally advanced breast carcinoma cases, offering several advantages. From a surgical perspective, it can reduce surgical morbidity in the breast and axilla. Tumor downstaging through NACT can potentially convert mastectomy candidates into candidates for breast-conserving surgery, leading to smaller excision volumes and improved cosmetic outcomes. Additionally, NACT can downstage the axilla, potentially avoiding axillary lymph node dissection. However, in cases of clinically and radiologically negative axilla, sentinel lymph node biopsy (SLNB) is pursued based on our institutional practices.

CONCLUSION:

Locally advanced breast cancer (LABC) constitutes a significant portion, around 40-50%, of breast cancer cases in India. Our research revealed that neoadjuvant chemotherapy effectively reduced the size of tumors in the majority of cases, although a complete clinical response was less frequent. Notably, our study demonstrated that a decrease in tumor size facilitated a shift from mastectomy to breast conservation surgery. The understanding of receptor status proved valuable in anticipating the response to chemotherapy. To address the existing gap in information regarding neoadjuvant chemotherapy followed by breast conservation surgery for LABC patients in India, a comprehensive and standardized approach is imperative. A protocol-driven multimodal strategy for individuals with LABC would contribute significantly to addressing this knowledge deficit.

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