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Impact of Neo-Adjuvant Chemotherapy in Triple Negative Breast Cancers

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ABSTRACT

Objective: To evaluate the impact of Neo-Adjuvant Chemotherapy on Pathological Complete Response rates, in patients with Triple-Negative Breast Cancer, focusing on the relationship between tumor size, nodal involvement, type of surgery, and treatment outcomes.

Study Design: Prospective cohort study.

Place and Duration of Study: Pakistan Navy Station Shifa Hospital, Karachi Pakistan, from Feb 2023 to Feb 2025.

Methodology: A total of 88 patients with triple-negative breast cancer who received neoadjuvant chemotherapy were included. Baseline characteristics, including tumor size, nodal involvement, and type of surgery, were recorded. The chi-square test was used to compare pathological complete response rates between subgroups. A *p*-value of <0.05 was considered statistically significant.

Results: The overall Pathological Complete Response rate was 43.18%. Nodal involvement was significantly associated with Pathological Complete Response (p=0.01), with N0 patients achieving higher response rates compared to N1 and N2 patients. Tumor size and type of surgery were not significantly associated with Pathological Complete Response (p=0.13 and p=0.30, respectively). Tumor size and type of surgery did not significantly affect outcomes. Adverse effects were observed in 21.59% of patients, with no significant impact.

Conclusion: Neo-Adjuvant Chemotherapy is effective in achieving Pathological Complete Response in Triple-Negative Breast Cancer patients, particularly in those without nodal involvement.

Keywords: Chemotherapy, Neoadjuvant, Nodal Involvement, Pathological Complete Response, Triple-Negative Breast Cancer.

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INTRODUCTION

Breast cancer is the most common malignancy among women worldwide and remains a leading cause of cancer-related mortality. It is a heterogeneous disease with diverse biological subtypes, each with distinct clinical behaviors, prognoses, and treatment responses.[1] Broadly categorized based on the expression of hormone receptors and HER2 (human epidermal growth factor receptor 2), breast cancer includes hormone receptor-positive (ER/PR-positive), HER2-enriched, and triple-negative subtypes. While hormone receptor-positive breast cancers are associated with favorable outcomes due to the availability of targeted hormonal therapies, HER2-enriched cancers have seen significant survival improvements with the advent of HER2-directed treatments like trastuzumab.[2]

Triple-negative breast cancer (TNBC), however, represents a challenging subset, accounting for 10-20% of all breast cancer cases. It is characterized by the absence of estrogen and progesterone receptors and the lack of HER2 overexpression.[3] This unique molecular profile renders TNBC unresponsive to hormonal or HER2-targeted therapies, leaving chemotherapy as the primary systemic treatment option. TNBC is associated with aggressive biological behavior, rapid growth, higher recurrence rates, and poorer outcomes compared to other breast cancer subtypes.[4]

Neo-adjuvant chemotherapy (NACT) has emerged as a pivotal component in the management of TNBC. Administered before surgical intervention, NACT aims to downstage tumors, increase the feasibility of breast-conserving surgery, and eradicate micrometastases.[5] Pathological complete response (pCR), defined as the absence of invasive cancer in the breast and lymph nodes post-NACT, is a strong surrogate marker for long-term survival. Patients achieving pCR demonstrate significantly reduced risks of recurrence and distant metastasis, underscoring the importance of NACT in improving outcomes.[6]

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Recent studies have further highlighted the clinical benefits of NACT in TNBC. A 2019 prospective analysis reported pCR rates ranging from 30% to 40%, with patients achieving pCR showing a 5-year survival advantage compared to those with residual disease.[7] A 2021 meta-analysis confirmed that pCR was associated with a 60% lower risk of distant metastases and significantly improved disease-free survival rates in TNBC patients.[8]

The propensity of neo-adjuvant chemotherapy (NACT) to convert an in-operable tumor into an operable one is unprecedented. This allows conservative surgery to take place with reduced morbidity and mortality among cancer patients.[9] Despite advances in breast cancer management globally, survival rates in Pakistan remain suboptimal, largely due to late diagnoses and limited access to advanced treatment modalities. A study from Pakistan reported that neoadjuvant chemotherapy is an effective treatment modality in management of triple-negative breast cancer.[10]

Given the aggressive nature of TNBC and the scarcity of treatment options, this study aims to evaluate the impact of NACT on pCR rates, in Pakistani TNBC patients. By analyzing outcomes and predictors of treatment response, the findings will provide valuable insights to optimize TNBC management in resource-limited settings.

METHODOLOGY

This prospective cohort study was conducted to evaluate the impact of neo-adjuvant chemotherapy (NACT) in patients diagnosed with triple-negative breast cancer (TNBC) at PNS Shifa Hospital, Karachi Pakitan. Based on a 60%[8] pathological complete response (pCR) rate in TNBC patients receiving NACT, a sample size of 88 patients was calculated using the WHO sample size calculator, with 10.25% margin of error and 95% confidence level. Participants were selected using consecutive sampling, wherein every patient meeting the inclusion criteria presenting to the oncology department during the study period was included until the desired sample size was achieved. Ethical approval was obtained from the institutional review board and written informed consent was secured from all participants prior to enrollment.

Inclusion Criteria: Eligible participants were female patients aged between 18 and 70 years, with histologically confirmed triple-negative breast cancer. This was defined by the absence of estrogen receptors (ER), progesterone receptors (PR), and HER2 expression. Patients with performance 1 and 2 included in the study had tumor stages I, II & III based on the TNM classification at the time of diagnosis, and they were all candidates for neo-adjuvant chemotherapy, as determined by the hospital's multidisciplinary oncology team.

Exclusion Criteria: Patients with performance status 3 and 4 were excluded from the study if they had metastatic disease (stage IV) at the time of diagnosis. Additionally, those with a prior history of breast cancer or other malignancies were not eligible to participate. Patients who had undergone chemotherapy, radiotherapy, or hormonal therapy for any condition prior to the study were also excluded.

Baseline demographic information, clinical characteristics (such as tumor size and nodal involvement), and relevant medical history were recorded at the time of recruitment. Patients underwent a triple assessment that included clinical examination, radiological imaging (mammography and ultrasound), and pathological evaluation via biopsy to confirm the diagnosis of TNBC.

All patients received neoadjuvant chemotherapy (NACT) with a standard regimen of anthracyclines (doxorubicin) and taxanes (paclitaxel or docetaxel). The chemotherapy was administered in 4-6 cycles, depending on the clinical and radiological response. The response to NACT was evaluated after every two cycles using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, incorporating clinical examination, mammography, and ultrasound findings.

Patients demonstrating progression despite NACT were considered for alternative management strategies, while those completing NACT were assessed for surgery. The decision for surgery was made within 4-6 weeks following the final cycle of chemotherapy.

Surgical interventions included breast-conserving therapy (BCT) and modified radical mastectomy (MRM), with the choice guided by tumor response, residual disease, and patient preference.

Among the 88 patients, 39(44.32%) underwent BCT, while 49(55.68%) required MRM. Surgical outcomes, including margin status and axillary lymph node involvement, were recorded. Pathological complete response (pCR), defined as the absence of

invasive cancer in the breast and lymph nodes, was assessed on histopathology of surgical specimens.

Post-surgical outcomes, including rates of pCR, residual disease, and complications, were documented. Regular follow-up was maintained to monitor for recurrence, outcomes, and long-term side effects.

Data were analyzed using Statistical Package for Social Sciences version 26.0. Descriptive statistics summarized demographic and clinical characteristics, with continuous variables presented as Mean±SD, and categorical variables as frequencies and percentages. The chi-square test was used to compare pathological complete response (pCR) rates among different subgroups. Statistically significant differences were identified with a *p*-value threshold of ≤0.05, highlighting the impact of neo-adjuvant chemotherapy in triple-negative breast cancer.

RESULTS

A total of 88 patients were included in the study. The mean age of the patients was 44.34±16.01 years.

Most patients had tumor sizes categorized as T2 (59.09%), followed by T1 (25.00%) and T3 (15.91%). Nodal involvement showed that 43.18% of patients had no nodal involvement (N0), while 30.68% had N1, and 26.14% had N2 involvement. Regarding the response to NACT, 43.18% of patients achieved pCR, while 56.82% did not. Additionally, 55.68% of patients underwent mastectomy, and 21.59% of patients experienced adverse effects (Table-I).

Table-I: Clinical Characteristics of Patients (n=88)

Variable	Categories	n(%)
Age	<50 Years	53(60.2%)
	>50 Years	35(39.8%)
	Total	88(100%)
Tumor Size	T1	22(25.00%)
	T2	52(59.09%)
	T3	14(15.91%)
	Total	88(100%)
Nodal Involvement	N0	38(43.18%)
	N1	27(30.68%)
	N2	23(26.14%)
	Total	88(100%)
Response to NACT	pCR	38(43.18%)
	No pCR	50(56.82%)
	Total	88(100%)
Type of Surgery	Breast-Conserving Surgery	39(44.32%)
	Mastectomy	49(55.68%)
	Total	88(100%)
Adverse Effects	Yes	19(21.59%)
	No	69(78.41%)
	Total	88(100%)

For age groups, pCR rates were 41.5% for patients under 50 and 45.7% for those over 50, showing no significant difference (p=0.696). Tumor size categories T1, T2, and T3 demonstrated pCR rates of 54.55%, 36.54%, and 50.00% respectively, without significant differences (p=0.13). Nodal involvement showed significant variation; N0 patients had the highest pCR rate of 60.53% (p=0.01). Breast-conserving surgery and mastectomy yielded similar pCR rates (p=0.30). Adverse effects appeared to influence pCR rates slightly, though not significantly (p=0.10). These results highlight critical factors affecting treatment efficacy and patient outcomes in the context of neo-adjuvant chemotherapy for breast cancer. (Table-II).

Table-II: Comparison of pCR Rates Between Different Subgroups Using Chi-Square Test (n=88)

Subgroup	Category	pCR n(%)	No pCR n(%)	*p*-value
Age Group	<50 Years	22(41.5%)	31(58.5%)	0.696
	>50 Years	16(45.7%)	19(54.3%)	
	Total	38(43.2%)	50(56.8%)	
Tumor Size	T1	12(54.55%)	10(45.45%)	0.13
	T2	19(36.54%)	33(63.46%)	
	T3	7(50.00%)	7(50.00%)	
	Total	38(43.18%)	50(56.82%)	
Nodal Involvement	N0	23(60.53%)	15(39.47%)	0.01
	N1	11(40.74%)	16(59.26%)	
	N2	4(17.39%)	19(82.61%)	
	Total	38(43.18%)	50(56.82%)	
Type of Surgery	Breast-Conserving Surgery	19(48.72%)	20(51.28%)	0.30
	Mastectomy	19(38.78%)	30(61.22%)	
	Total	38(43.18%)	50(56.82%)	
Adverse Effects	Yes	5(26.32%)	14(73.68%)	0.10
	No	33(47.83%)	36(52.17%)	
	Total	38(43.18%)	50(56.82%)	

DISCUSSION

The results of this study showed that 43.18% of triple-negative breast cancer (TNBC) patients achieved a pathological complete response (pCR) after receiving neo-adjuvant chemotherapy (NACT). This finding is consistent with recent studies, such as the one by Li *et al*., who reported a pCR rate of 35% in TNBC patients receiving anthracycline and taxane-based NACT[7]. A slightly higher pCR rate in our study could be due to differences in chemotherapy regimens or patient selection criteria. Another study by Sharma *et al*., demonstrated a 40% pCR rate in TNBC patients treated with similar regimens[8], further aligning with our findings.

Nodal involvement was significantly associated with pCR rates in our study, with patients who had no nodal involvement (N0) showing the highest pCR rates. This is in agreement with findings by Bianchini *et al*., where N0 patients had better response rates to NACT[9]. The lower pCR rates in N1 and N2 patients may be attributed to the more aggressive biology of the disease in patients with nodal involvement, as highlighted by Hanif *et al*., who suggested that tumor burden plays a crucial role in response to chemotherapy.[10]

Our study found no significant association between tumor size and pCR rates (p=0.13), which contrasts with the findings of Spring *et al*., where smaller tumor sizes (T1) were significantly associated with higher pCR rates.[11] This discrepancy could be due to differences in the tumor biology of the study populations, or the chemotherapy protocols used. Additionally, we observed no significant difference in pCR rates between patients who underwent breast-conserving surgery and those who underwent mastectomy, which aligns with recent findings by Voduc *et al*., who concluded that the type of surgery does not significantly impact pCR outcomes.[12]

Adverse effects were reported in 21.59% of patients, with no significant impact on pCR. This is consistent with findings by Chu *et al*., who also found that chemotherapy-related adverse effects did not significantly alter the outcomes in TNBC patients.[13] However, the slightly lower adverse effect rate in our study compared to global figures could be attributed to better management protocols or patient compliance in our setting, as highlighted by Herrero-Vicent *et al*.[14] Furthermore, Zhang *et al*., showed similar results where adverse effects were not found to have a significant impact on long-term outcomes.[15] A systematic search was done in 2018 in which role of platinum based neoadjuvant chemotherapy was assessed in TNBC patients. An increased incidence of haematological adverse effects were noted but at the same time, this regimen was associated with significantly increased pCR rates. It supports the concept of neoadjuvant chemotherapy in TNBC patients despite haematological adverse effects.[16]

Overall, our study adds to the growing body of evidence on the efficacy of NACT in TNBC patients. Although certain factors like nodal involvement play a significant role in predicting outcomes, others like tumor size and type of surgery do not seem to influence pCR significantly in our cohort. This emphasizes the need for individualized treatment approaches, particularly in patients with advanced nodal disease, to optimize their treatment outcomes. Further research into the molecular characteristics of TNBC and its relationship with treatment response is warranted to better tailor therapies to specific patient populations. Recent studies, such as one by Anderson *et al*., further support this, as they call for a deeper understanding of TNBC's heterogeneity in relation to treatment response.[17] An important factor that needs to be emphasized is recurrence rate following this modality of treatment. Although no longterm followup was done in our study but literature shows a significantly decreased rate of recurrence in ten years in patients who receive neoadjuvant chemotherapy compared to those who don`t.[18]

CONCLUSION

This study demonstrates that neoadjuvant chemotherapy (NACT) is effective in achieving pathological complete response (pCR) in a significant proportion of triple-negative breast cancer (TNBC) patients. The findings highlight the potential of NACT to enhance surgical outcomes and long-term prognosis in TNBC, particularly in resource-limited settings. However, the variability in response underscores the need for further research to identify predictive biomarkers and optimize treatment regimens to improve outcomes in this aggressive breast cancer subtype.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SHS & MU: Data acquisition, data analysis, critical review, approval of the final version to be published.

UZF & AT: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

YA & LBS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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