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The Impact of Neoadjuvant Chemotherapy on Breast Cancer

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ABSTRACT

Background: Breast cancer (BC) is a heterogeneous disease that requires multimodal treatment. Adoption of neoadjuvant chemotherapy (NACT) as a standard approach for patients with high-risk early-stage or locally advanced breast cancer represents a significant development in breast cancer management.

Objective: This study aimed to evaluate the outcomes of NACT on BC, specifically regarding overall response rate (ORR), breast conservation eligibility rate, overall survival (OS) rate, disease-free survival (DFS) rate, and factors that may influence these outcomes. **Patients and method:** A retrospective study of 200 patients with locally advanced or high-risk early-stage breast cancer who attended Clinical Oncology and Nuclear Department at Mansoura University Hospitals between January 2018 and December 2021 who were treated with neoadjuvant chemotherapy. Response to chemotherapy and survival rates were assessed.

Results: ORR to NACT was 87.5% (175 cases). Breast conservation eligibility was achieved in 27.5% of patients (55 cases). The 5-year OS rate was 90.3%. Higher OS was associated with postmenopausal status, earlier clinical stages, pathologic complete response (pCR), positive hormonal receptors, and absence of recurrence. The 5-year DFS rate was 85.1%, with higher rates associated with high pathological response, hormone receptor (HR) positivity, and receipt of an optimal course of post-operative radiotherapy (PORT). The only independent statistically significant predictive factor for OS and DFS was pathological response, with p-values of 0.007 and 0.02 respectively. **Conclusion:** NACT is generally the preferred treatment for women with locally advanced breast cancer (LABC) and high-risk early BC.

Keywords: Neoadjuvant chemotherapy, Breast cancer, Response rate, Survival rate.

INTRODUCTION

In Egypt, breast cancer is the most common cancer among females, with approximately 28,000 confirmed cases reported annually by National Cancer Institute (NCI), Egypt [1]. Chemotherapy can be used in breast cancer management as neoadjuvant, adjuvant, or palliative treatment. Neoadjuvant chemotherapy is as effective as adjuvant chemotherapy for survival in locally advanced breast cancer [2]. According to National Comprehensive Cancer Network (NCCN) Guidelines Version 5.2024, neoadjuvant chemotherapy is typically used in locally advanced breast cancer to facilitate breast conservation and render inoperable tumors operable. It also allows for delayed decision-making regarding definitive surgery. Additionally, response to neoadjuvant treatment provides valuable prognostic information for individual patients [3]. Other types of neoadjuvant treatments for breast cancer include neoadjuvant endocrine therapy and targeted therapy. Endocrine therapy is effective only for estrogen receptor (ER)-positive disease, while chemotherapy achieves higher pathological complete response (pCR) rates in ER-negative cases [4]. Patients with high-grade tumor differentiation and younger age derive increased benefit from neoadjuvant chemotherapy in ER-negative cases [5]. However, chemotherapy and hormonal therapies yield similar response rates in postmenopausal women with ER-positive cancer [6]. For HER2-positive disease, targeted therapy with trastuzumab, when added to anthracycline-taxane-based chemotherapy, results in a higher pCR rate compared to chemotherapy alone [7].

This study aimed to evaluate the outcomes of NACT on BC, specifically regarding overall response rate (ORR), breast conservation eligibility rate, overall survival (OS) rate, disease-free survival (DFS) rate, and factors that may influence these outcomes.

PATIENTS AND METHODS

Study design and population: This retrospective case series included 200 patients with breast cancer who received neoadjuvant chemotherapy at Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital, from January 2018 to December 2021.

Inclusion criteria: Patients with locally advanced breast cancer and high-risk early breast cancer (stage III: N2, N3, T3N+ & T4), specifically triple-negative early breast cancer or HER2-positive early breast cancer.

Exclusion criteria: Patients with double malignancies and low-risk early-stage breast cancer (T1N0).

Detailed histories and comprehensive clinical examinations were conducted for each patient, alongside routine laboratory investigations. The study assessed overall response rate (ORR), breast conservation eligibility rate following neoadjuvant systemic therapy, OS, and disease-free survival (DFS). These outcomes were analyzed to evaluate their prognostic significance. ORR refers to proportion of patients whose cancer either

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shrinks or disappears after treatment. OS was calculated from start of treatment to time of death or last follow-up visit, while DFS represents period during which the patient shows no evidence of tumor recurrence after starting treatment [8].

Management Protocol

This research comprised a total of 200 participants, and the treatment regimen used was one of the following:

1. **AC regimen:** Administer Doxorubicin at a dosage of 60 mg/m² intravenously, in conjunction with cyclophosphamide at 600 mg/m² intravenously, on day 1, every 3 weeks for a total of 4 cycles.
2. **AC followed by paclitaxel:** Doxorubicin 60 mg/m² IV and cyclophosphamide 600 mg/m² IV administered on day 1 every 3 weeks for 4 cycles, succeeded by dense-dose paclitaxel at 175 mg/m² IV every 3 weeks for 4 cycles or 80 mg/m² IV weekly for 12 weeks. Patients in the paclitaxel cohort received premedication consisting of dexamethasone, diphenhydramine (50 mg), ranitidine (50 mg), and an antiemetic, such as ondansetron, 30 minutes before treatment.
3. **FAC Regimen:** Administer fluorouracil 500 mg/m² intravenously on day 1, along with doxorubicin 50 mg/m² intravenously on day 1, and cyclophosphamide 500 mg/m² intravenously on day 1, to be repeated every 3 weeks for a total of 6 cycles.
4. **FAC followed by taxotere:** Fluorouracil 500 mg/m² IV on day 1, in conjunction with doxorubicin 50 mg/m² IV on day 1, and cyclophosphamide 500 mg/m² IV on day 1, repeated every 3 weeks for 3 cycles, followed by 3 consecutive cycles of docetaxel 100 mg/m² IV, commencing 21 days after the last cycle of FAC. An antiemetic strategy was implemented prior to cycles of doxorubicin, fluorouracil, and cyclophosphamide administration. Patients receiving taxotere regimens were administered pretreatment medications comprising dexamethasone 8 mg intravenously every 12 hours for 3 days (one day prior to and two days following docetaxel infusion), a histamine 1 receptor antagonist such as diphenhydramine (50 mg), a histamine 2 receptor antagonist such as ranitidine (50 mg), and an antiemetic such as ondansetron 30 minutes before chemotherapy. Prophylactic granulocyte colony-stimulating factors (GCSF) were delivered 48 hours post-docetaxel injection, commencing with the second cycle for a duration of 3–5 days.
5. **AC followed by paclitaxel concurrent with trastuzumab:** Alternating current subsequent to paclitaxel administer doxorubicin 60 mg/m² IV and cyclophosphamide 600 mg/m² IV concurrently with trastuzumab on day 1 every 3 weeks for 4 cycles. Paclitaxel was started simultaneously with trastuzumab 21 days after the last treatment of doxorubicin and cyclophosphamide. In the first cycle, trastuzumab was administered as an intravenous dosage of 8 mg/kg on day 1, followed by intravenous paclitaxel at 175 mg/m² on day 2, repeated every three weeks. In later rounds, trastuzumab 6 mg/kg IV every 3 weeks was administered with paclitaxel 175 mg/m² IV for 4 cycles or paclitaxel 80 mg/m² IV weekly for 12 weeks.

Response Assessment: Response was assessed radiologically after 3–4 cycles, according to Response Evaluation Criteria in Solid Tumors (RECIST), which provide an objective measurement of tumor burden in response to systemic therapy (National Cancer Institute) [9]. Responses were categorized as follows:

- **Complete response (CR):** Disappearance of all target lesions.
- **Partial response (PR):** A 30% decrease in sum of the longest diameters of target lesions.
- **Progressive disease (PD):** A 30% increase in sum of the longest diameters of target lesions.
- **Stable disease (SD):** Small changes that do not meet criteria for CR, PR, or PD.

After completion of neoadjuvant therapy, patients were evaluated to determine their eligibility for either conservative breast surgery (CBS) or modified radical mastectomy (MRM). In cases of progression in potentially inoperable disease, systemic therapy continued. Postoperative response was re-evaluated from a pathological perspective.

Ethical considerations: The study protocol was approved by Medical Research Ethical Committee of Institutional Review Board (IRB) of Faculty of Medicine, Mansoura University (MS.22.07.2080). All patients provided written informed consents prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for publication of data, ensuring protection of their confidentiality and privacy. Each patient received a thorough explanation of management protocol and potential complications. This work has been carried out in accordance with The Code of Ethics of World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis and data interpretation:

Data analysis was conducted using SPSS software, version 25 (SPSS Statistics for Windows, Version 25. Chicago: SPSS Inc.). Qualitative data were represented as numbers and percentages, while quantitative data were described by median (minimum and maximum) for non-normally distributed data, and mean ± standard deviation for normally distributed data, after normality evaluation by the Kolmogorov-Smirnov test. Statistical significance was established as a p-value of ≤ 0.05. Chi-Square, Fisher's exact test, and Monte

Carlo tests were used to compare qualitative data across groups where appropriate. For non-normally distributed data, the Mann-Whitney U test was used for comparisons between two groups, while the Kruskall-Wallis test was applied for comparisons across several groups. The Kaplan-Meier technique was used to estimate overall survival (OS) and disease-free survival, using the log-rank χ^2 test to assess the impact of risk factors on survival outcomes. Cox regression analysis was used to identify survival predictors, with hazard ratios calculated.

RESULTS

Patient demographics, tumor characteristics, and treatment: This study included 200 patients with locally advanced breast cancer (LABC) and early-stage high-risk breast cancer who received neoadjuvant chemotherapy. Of these patients, 172 (86.0%) were aged 35 years or older, and 102 (51.0%) were postmenopausal. A majority of patients, 182 (91.0%), were multiparous, and 168 (84.0%) were classified as obese. Most patients had no family history of breast cancer (157 cases, 78.5%), no comorbidities (120 cases, 60.0%), and no use of any contraception method (179 cases, 51.4%) (Table 1).

Table (1): Demographic and Clinical Characteristics of Patients with Locally Advanced and High-Risk Early-Stage Breast Cancer (N=200)

		N=200	%
Age at presentation (Years)	**< 35**	**28**	**14.0**
	≥ 35	**172**	**86.0**
Family history	**-ve**	**157**	**78.5**
	+ve	**43**	**21.5**
Comorbidities	**-ve**	**20**	**60.0**
	+ve	**80**	**40.0**
Contraceptive		**N=179**	
	-ve	**92**	**51.4**
	+ve	**69**	**38.5**
	Unknown	**18**	**10.1**
Parity	**Nullipara**	**10**	**5.0**
	Unipara	**8**	**4.0**
	Multipara	**182**	**91.0**
Menpausal status	**Pre**	**98**	**49.0**
	Post	**102**	**51.0**
Average body	**built**	**32**	**16.0**
	Obese	**168**	**84.0**

N: Number of Patients, %: Percentage, -ve: Negative, +ve: Positive, Menopausal: Menopausal.

As regards tumor's characteristics, most of patients presented with left sided breast cancer (N= 104, 52%), most of them were at Stage IIIA (107 cases, 53.5%) and high-risk early stage (41 cases, 20.5%), rest of cases were stage IIIB or stage IIIC.

Regarding tumor grade, 171 cases, 85.5% of cases were grade II, rest of cases were Grade III (29 cases, 14.5%).

The most dominant histopathological type was Invasive Ductal Carcinoma (IDC) (196 cases, 98.0%), while ILC (Invasive Lobular Carcinoma) was 4 cases, 2.0%, while ILC (Invasive Lobular Carcinoma) was 4 cases (2.0%).

The molecular subtype most distributed among cases was luminal B her2 +ve (80 cases, 40%), luminal B her2 –ve (55 cases, 27.5%), luminal A (25 cases, 12.5%) then enriched her2 (20 cases, 10%) and triple negative breast cancer (TNBC) (20 cases, 10%).

Different neoadjuvant protocols utilized among studied cases. The number of cases used each protocol was: AC 79 cases (39.5%), AC+taxans 50 cases (25.0%), FAC 31 cases (15.5%) FAC+taxans 18 cases (9.0%), AC+taxan+antiher2 22cases (11.0%). 186 cases (93%) received postoperative radiotherapy (PORT).

Two types of surgery were performed; 145 (72.5%) cases underwent MRM Vs 55 (27.5%) underwent CBS.

For adjuvant chemotherapy (Adj cth), 94 (47.0%) cases had already finished course of NACT preoperatively, and 106 (53.0%) completed it postoperatively. 186 cases (93.0%) received post-operative radiotherapy (PORT).

Furthermore, for adjuvant anti-HER2 therapy, (71 cases, 35.5) cases received it either (as continuation of preoperative course or starting it postoperatively).

Table (2): Clinical and Pathological Characteristics of Patients with Locally Advanced and High-Risk Early-Stage Breast Cancer (N=200)

		N=200	%
Side	**Lt**	**104**	**52.0**
	Rt	**94**	**47.0**
	Bilateral	**2**	**1.0**
Clinical stage	**High-risk**	**41**	**20.5**
	Early stage	**107**	**53.5**
	IIIA	**28**	**14.0**
	IIIB	**24**	**12.0**
	IIIC		
Grade	**G1**	Zero	**zero**
	G2	**171**	**85.5**
	G3	**29**	**14.5**
Pathological subtype	**IDC**	**196**	**98.0**
	ILC	**4**	**2.0**
Molecular subtype	**LA**	**25**	**12.5**
	LB her2-ve	**55**	**27.5**
	LB her+ve	**80**	**40.0**
	her2 enrich	**20**	**10.0**
	TNBC	**20**	**10.0**
Neoadj protocol	**AC**	**79**	**39.5**
	AC+taxans	**50**	**25.0**
	FAC	**31**	**15.5**
	FAC+taxans	**18**	**9.0**
	AC+taxan+antiher2	**22**	**11.0**
Surgery	**MRM**	**145**	**72.5**
	CBS	**55**	**27.5**
Adj cth	**-ve (**finished cth course preoperatively)	**94**	**47.0**
	+ve	**106**	**53.0**
PORT	**No**	**14**	**7.0**
	Yes	**186**	**93.0**
Adj anti-HER2	**No**	**29**	**14.5**
	Yes	**71**	**35.5**
	not indicated	**100**	**50.0**

Lt: Left, Rt: Right, IDC: Invasive Ductal Carcinoma, ILC: Invasive Lobular Carcinoma, LA: Luminal A, LB her2-ve: Luminal B HER2-negative, LB her2+ve: Luminal B HER2-positive, her2 enrich: HER2-enriched, TNBC: Triple-Negative Breast Cancer, Neoadj: Neoadjuvant, AC: Doxorubicin and Cyclophosphamide, FAC: Fluorouracil, Doxorubicin, and Cyclophosphamide, Anti-HER2: Anti-Human Epidermal Growth Factor Receptor 2, MRM: Modified Radical Mastectomy, CBS: Conservative Breast Surgery, Ads cth: Adjuvant Chemotherapy, PORT: Postoperative Radiotherapy.

Response to neoadjuvant chemotherapy and factors affecting it:

Most cases got partial response (PR) (141 cases, 70.5%), some of them got CR (34 cases, 17.0%), few cases progressed during neoadjuvant therapy (16 cases, 8 %), while only 9 cases (4.5%) had no response. 55 cases (27.5%) had successful downstaging (P-value=0.037) to undergo CBS Vs 145 (72.5%) cases underwent MRM. Regarding effect of NST on failure rate (P value=0.018). Only 30.5% (61 cases) experienced recurrence, 17 cases (8.5%) of them were local recurrence while 56 cases (28.0%) showed systemic recurrence. We analysed data to determine what clinical factors predicted for pathological response and hence ability to attempt BCT in these patients and found that initial clinical stage and type of neoadjuvant protocol significantly affected pathological response (as their P value (0.015, 0.02 respectively), while age, family history, comorbidities, contraception, parity, menopausal status, body built and side of tumor had no statistical significance as their P values were 0.374, 0.532, 0.901, 0.327, 0.430, 0.322 & 0.332 respectively (Tables 2 & 4).

Table (3): Outcome response to neoadjuvant systemic NST

	N=200	%
Pathological response		
SD	**9**	**4.5**
PR	**141**	**70.5**
CR	**34**	**17.0**
progression	**16**	**8.0**
		Test of significance
Surgery		
MRM	**145 (72.5%)**	χ^{2MC}**=10.18**
CBS	**55 (27.5%)**	**P=0.037***
Failure	**51 (25.5%)**	χ^{2MC}**=11.86** **P=0.018***
local Recurrence	**17 (8.5%)**	χ^{2MC}**=2.42** **P=0.660**
Systemic recurrence	**34 (17%)**	χ^{2MC}**=11.87** **P=0.018***

SD: Stable Disease, PR: Partial Response, CR: Complete Response, MRM: Modified Radical Mastectomy, CBS: Conservative Breast Surgery, χ^2MC: Chi-Square Monte Carlo, P: P-value.

Table (4): Factors affecting the pathological response of our studied cases to NST

		Pathological response				Test of significance
		SD N (%)	PR N (%)	CR N (%)	Progression N (%)	
Age at presentation (Years)	**<35**	**0**	**19(13.5)**	**5(14.7)**	**4(25.0)**	χ^{2MC}**=3.12**
	≥35	**9(100)**	**122(86.5)**	**29(85.3)**	**12(75.0)**	**P=0.374**
Family history	**-ve**	**8(88.9)**	**113(80.1)**	**25(73.5)**	**11(68.8)**	χ^{2MC}**=2.20**
	+ve	**1(11.1)**	**28(19.9)**	**9(26.5)**	**5(31.2)**	**P=0.532**
Comorbidities	**-ve**	**5(55.6)**	**87(61.7)**	**19(55.9)**	**9(56.2)**	χ^{2MC}**=0.578**
	+ve	**4(44.4)**	**54(38.3)**	**15(44.1)**	**7(43.8)**	**P=0.901**
Contraceptive	**-ve**	**4(44.4)**	**63(50.4)**	**19(59.4)**	**6(46.2)**	χ^{2MC}**=6.93**
	+ve	**3(33.3)**	**51(40.8)**	**8(25.0)**	**7(53.8)**	**P=0.327**
	Unknown	**2(22.2)**	**11(8.8)**	**5(15.6)**	**0**	
Parity	**Nullipara**	**0**	**8(5.7)**	**2(5.9)**	**0**	χ^{2MC}**=5.93**
	Unipara	**1(11.1)**	**4(2.8)**	**3(8.8)**	**0**	**P=0.430**
	Multipara	**8(88.9)**	**129(91.5)**	**29(85.3)**	**16(100)**	
Menopausal status	**Pre**	**2(22.2)**	**71(50.4)**	**18(52.9)**	**7(43.8)**	χ^{2MC}**=3.07**
	Post	**7(77.8)**	**70(49.6)**	**16(47.1)**	**9(56.2)**	**P=0.380**
	Average	**0**	**24(17)**	**7(20.6)**	**1(6.2)**	χ^{2MC}**=3.48**
	Obese	**9(100)**	**117(83)**	**27(79.4)**	**15(93.8)**	**P=0.322**
Side	**Lt**	**7(77.8)**	**74(54.5)**	**13(38.2)**	**10(62.5)**	χ^{2MC}**=6.88**
	Rt	**2(22.2)**	**66(46.8)**	**20(58.80**	**6(37.5)**	**P=0.332**
	Bilateral	**0**	**1(0.7)**	**1(2.9)**	**0**	
Clinical stage	**High-risk Early stage**	**1(11.1)**	**26(18.4)**	**18(52.9)**	**3(18.8)**	χ^{2MC}**=20.48**
	IIIA	**1(11.1)**	**80(56.7)**	**11(32.4)**	**8(50)**	**P=0.015***
	IIIB	**3(33.3)**	**21(14.9)**	**1(2.9)**	**3(18.8)**	
	IIIC	**4(44.4)**	**14(9.9)**	**4(11.8)**	**2(12.5)**	
Grade	**G1**	**5(55.6)**	**122(86.5**	**29(85.3)**	**15(93.8)**	χ^{2MC}**=7.51**
	G2	**4(44.4)**	**19(13.5)**	**5(14.7)**	**1(6.2)**	**P=0.057**
	G3					
Pathological subtype	**IDC**	**8(88.9)**	**138(97.9**	**34(100)**	**16(100)**	χ^{2MC}**=4.84**
	ILC	**1(11.1)**	**3(2.1)**	**0**	**0**	**P=0.184**
Molecular subtype	LA	**1(11.1)**	**19(13.5)**	**3(8.8)**	**2(12.5)**	χ^{2MC}**=7.18**
	LB her2-ve	**2(22.2)**	**38(27)**	**4(11.8)**	**7(43.8)**	**P=0.846**
	LB her+ve	**3(33.3)**	**59(41.8)**	**13(38.2)**	**5(31.2)**	
	her2 enrich	**1(11.1)**	**12(8.5)**	**8(23.5)**	**1(6.2)**	
	TNBC	**2(22.2)**	**13(9.2)**	**6(17.6)**	**1(6.2)**	
Neoadj protocol	**AC**	**3(33.3)**	**60(42.6)**	**9(26.5)**	**7(43.8)**	
	AC+taxans	**2(22.2)**	**35(24.8)**	**10(29.4**	**3(18.8)**	χ^{2MC}**=24.2**
	FAC	**2(22.2)**	**24(17.0)**	**1(2.9)**	**4(25.0)**	**P=0.02***
	FAC+taxans	**2(22.2)**	**10(7.1)**	**4(11.8)**	**2(12.5)**	
	AC+taxan+antiher2	**0**	**12(8.5)**	**10(29.4)**	**0**	

SD: Stable Disease, PR: Partial Response, CR: Complete Response, χ^2MC: Chi-Square Monte Carlo, P: P-value, Lt: Left, Rt: Right, IDC: Invasive Ductal Carcinoma, ILC: Invasive Lobular Carcinoma, LA: Luminal A, LB her2-ve: Luminal B HER2-negative, LB her2+ve: Luminal B HER2-positive, her2 enrich: HER2-enriched, TNBC: Triple-Negative Breast Cancer, Neoadj: Neoadjuvant, AC: Doxorubicin and Cyclophosphamide, FAC: Fluorouracil, Doxorubicin, and Cyclophosphamide, Anti-HER2: Anti-Human Epidermal Growth Factor Receptor 2.

The survival Figures:

Figure (1) showed OS of all cases. the 5-Year OS rate among the studied cases was 90.3%.

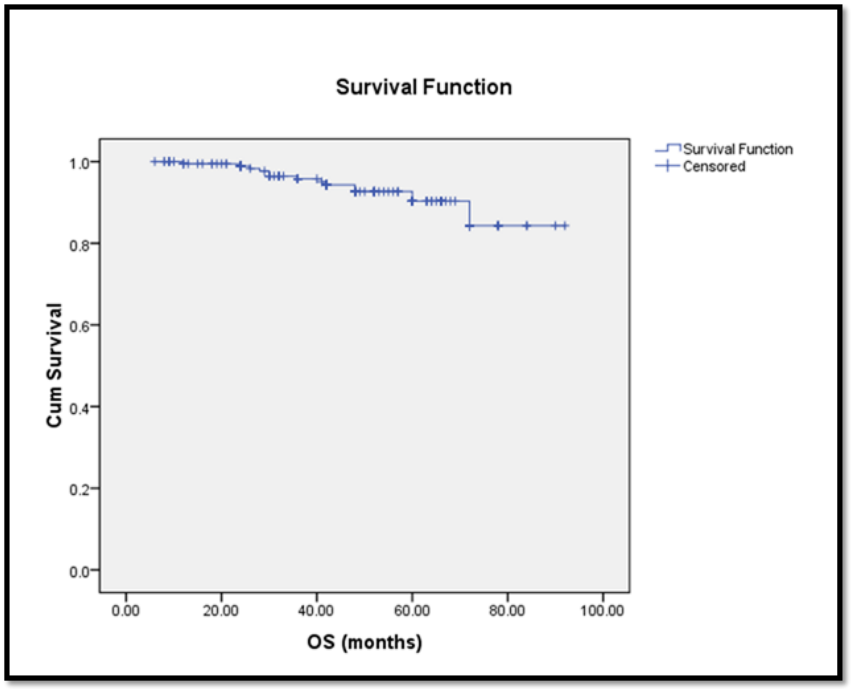

Figure (1): Kaplan -Miere curve showing OS of all studied cases.

Figure (2) showed PFS curve for all cases. The 5-Year DFS rate among studied cases was 85.1%.

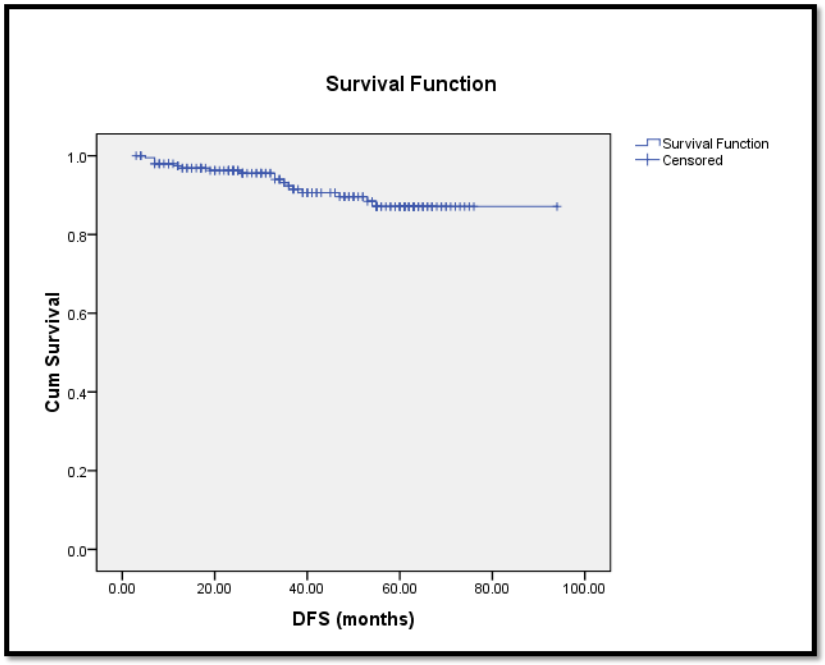

Figure 2: Kaplan -Miere curve showing disease free survival.

Starting with univariate analysis, factors that were associated with good prognosis with a statistically significant correlation with OAS, were early initial clinical stage, HR positive subtype, pCR to neoadjuvant systemic therapy (NST) and non-relapsed cases (Table 5).

Table (5): Univariate analysis detecting factors affecting (OS) among our studied cases

	Median overall survival (months), (95%CI)	Log Rank χ^2	P value
Age at presentation (Years)			
<35	**76.8(74.53-79.07)**	**0.952**	**0.329**
≥35	**85.19(81.8188.59)**		
Family history			
-ve	**86.5(83.40-89.6)**	**1.17**	**0.280**
+ve	**76.84(70.26-83.42)**		
Comorbidities			
-ve	**87.22(84.06-90.39)**	**0.643**	**0.423**
+ve	**73.15(69.71-76.58)**		
Contraceptive			
-ve	**No statistics computed**	**1.22**	**0.543**
+ve			
Unknown			
Parity			
Nullipara	**66.67(56.81-76.52)**	**0.976**	**0.614**
Unipara	**64.5(58.26-70.74)**		
Multipara	**86.09(83.0-89.18)**		
Menpausal status			
Pre	**82.65(77.76-87.55)**	**5.52**	**0.019***
Post	**87.37(84.42-90.32)**		
Average built	**71(69.12-72.88)**	**0.779**	**0.377**
Obese	**85.28(81.94-88.63)**		
Side			
Lt	**84.56(80.24-88.88)**	**3.15**	**0.207**
Rt	**86.54(83.25-89.84)**		
Bilateral	**69(56.52-81.47)**		
(T) stage			
T1	**87.13(80.67-93.59)**	**0.402**	**0.040***
T2	**86.06(76.17-81.95)**		
T3	**84.8(77.99-93.61)**		
T4	**82.83(82.85-88.83)**		
Axillary LN	**No statistics computed**	**5.67**	**0.029***
N0			
N1			
N2			
N3			
Clinical stage			
High risk-early stage	**78.8(68.48-73.12)**		0.035*
IIIA	**85.95(81.69-90.22)**	**5.18**	
IIIB	**70.38(72.39-84.37)**		
IIIC	**63.76(56.42-71.09)**		
Grade			
G1	**zero**	**zero**	
G2	**85.79(82.55-89.03)**	**0.008**	**0.929**
G3	**68.17(63.09-73.24)**		
Pathological subtype			
IDC	**86.14(83.19-89.09)**	**3.49**	**0.062**
ILC	**54(34.79-73.20)**		
ER			
-VE	**83.14(74.84-91.43)**	**0.280**	**0.597**
+VE	**86.66(81.65-87.68)**		
PR			
-VE	**84.71(78.65-90.77)**	**0.053**	**0.817**
+VE	**84.41(81.09-87.73)**		

	Median overall survival (months), (95%CI)	Log Rank χ^2	P value
Her-2			
-VE	**84.09(77.08-83.11)**	**1.01**	**0.315**
+VE	**80.32(79.59-89.05)**		
Ki67			
Unknown	**No statistics computed**	**5.87**	**0.118**
Low			
high			
Molecular subtype	**No statistics computed**	**10.87**	
LA			**0.028***
LB her2-ve			
LB her+ve			
her2 enrich			
TNBC			
Neoadj protocol types			
AC	**No statistics computed**	**1.56**	**0.816**
AC+taxans			
FAC			
FAC+taxans			
AC+taxan+antiher2			
Neoadj combination protocol			
Single	**79.87(77.14-82.59)**		
Combined	**84.98(80.0-89.9)**	**0.285**	**0.594**
Surgery			
MRM	**86.44(83.14-89.74)**	**0.335**	**0.563**
CBS	**68.96(65.73-72.19)**		
Pathological response			
no response	**51.14(38.70-63.58)**		
PR	**84.67(83.33-90.02)**	**15.12**	**0.002***
CR	**87.62(79.87-97.38)**		
progression	**79.50(70.96-88.04)**		
Adj cth			
-ve	**84.37(79.36-89.37)**	**0.824**	**0.364**
+ve	**80.19(77.50-82.89)**		
PORT			
No	**68.25(56.38-80.12)**	**3.41**	**0.07**
Yes	**86.58(83.74-89.43)**		
adj anti Her2			
No	**83.04(75.53-90.59)**	**1.08**	**0.584**
Yes	**85.17(78.36-89.99)**		
not indicated	**80.31(77.48-83.14)**		
Failure			
No	**88.46(88.39-90.52)**	**30.02**	**<0.001***
Yes	**74.49(66.98-82.02)**		
local Recurrence			
no	**87.68(84.92-90.46)**	**22.18**	**<0.001***
yes	**59(47.46-70.56)**		
Systemic	**No statistics computed**	**41.64**	**<0.001***
No			
yes			

CI: Confidence Interval, χ^2: Chi-Square, P: P-value, Lt: Left, Rt: Right, T: Tumor, LN: Lymph Node, IDC: Invasive Ductal Carcinoma, ILC: Invasive Lobular Carcinoma, ER: Estrogen Receptor, PR: Progesterone Receptor, Her-2: Human Epidermal Growth Factor Receptor 2, Ki67: Proliferation Index, LA: Luminal A, LB her2-ve: Luminal B HER2-negative, LB her2+ve: Luminal B HER2-positive, her2 enrich: HER2-enriched, TNBC: Triple-Negative Breast Cancer, Neoadj: Neoadjuvant, AC: Doxorubicin and Cyclophosphamide, FAC: Fluorouracil, Doxorubicin, and Cyclophosphamide, Anti-HER2: Anti-Human Epidermal Growth Factor Receptor 2, MRM: Modified Radical Mastectomy, CBS: Conservative Breast Surgery, Adj cth: Adjuvant Chemotherapy, PORT: Postoperative Radiotherapy.

Prognostic factors that had a statistically significant negative correlation with DFS in univariate analysis were HR positive subtype, pCR and receiving PORT (Table 6).

Table (6): Univariate analysis detecting factors affecting (DFS) among our studied cases

		Median DFS survival (95%CI)	Log Rank χ^2	P value
Age at presentation (Years)	**<35** **≥35**	**69.04(63.68-74.38)** **85.71(81.76-89.66)**	**0.168**	**0.682**
Family history	**-ve** **+ve**	**86.50(82.66-90.35)** **61.24(55.89-66.59)**	**0.365**	**0.546**
Comorbidities	**-ve** **+ve**	**86.53(82.17-90.89)** **67.88(63.58-72.17)**	**0.165**	**0.685**
Contraceptive	**-ve** **+ve** **Unknown**	**70.03(66.17-73.89)** **65.88(61.93-69.82)** **88.88(79.15-98.89)**	**0.09**	**0.952**
Parity	**Nullipara** **Unipara** **Multipara**	**No statistics computed**	**1.77**	**0.413**
Menpausal status	**Pre** **Post**	**69.86(66.05-73.67)** **86.55(81.66-91.42)**	**0.132**	**0.716**
	Average **Obese**	**69.95(63.78-76.11)** **86.32(82.49-90.14)**	**0.045**	**0.832**
Side	**Lt** **Rt** **Bilateral**	**71.22(68.06-74.38)** **86.75(81.60-91.89)** **27(11.32-42.68)**	**33.59**	**0.656**
CLINICAL STAGING	**Early stage high risk** **IIIA** **IIIB** **IIIC**	**70.44(65.44-75.38)** **85.98(81.03-90.95)** **65.92(60.57-71.32)** **62.14(55.75-68.54)**	**0.176**	**0.981**
Grade	**G2** **G3**	**86.33(82.52-90.13)** **66.44(59.54-73.34)**	**0.140**	**0.708**
Pathological subtype	**IDC** **ILC**	**No statistics**	**0.318**	**0.573**
Molecular subtype	LA LB her2-ve LB her+ve her2 enrich TNBC	**85.97(51.85-66.11)** **74.951(72.92-76.98)** **65.709(79.91-91.50)** **59.88(53.96-65.82)** **57.05(46.19-67.93)**	**10.58**	**0.032***
Neoadj protocol	**AC** **AC+taxans** **FAC** **FAC+taxans** **AC+taxan+antiher2**	**No statistics computed**	**1.36**	**0.852**
Surgery	**MRM** **CBS**	**86.18(81.99-90.37)** **70.31(65.63-74.99)**	**0.005**	**0.942**
Pathological response	**no response** **PR** **CR** **progression**	**45.0(39.91-50.09)** **71.06(68.29-73.84)** **88.58(81.36-95.81)** **53.76(42.32-65.2)**	**14.43**	**0.021***
Adj cth	**-ve** **+ve**	**45.0(39.81-50.07)** **70.27(66.87-73.66)**	**18.26**	**0.134**
PORT	**No** **Yes**	**33.34(23.04-43.63)** **88.09(84.89-91.30)**	**37.17**	**<0.001***
adj anti Her2	**No** **Yes** **not indicated**	**68.05(80.14-95.97)** **71.11(63.67-72.55)** **70.26(66.72-73.81)**	**0.256**	**0.880**

DFS: Disease-Free Survival, CI: Confidence Interval, χ^2: Chi-Square, P: P-value, Lt: Left, Rt: Right, IDC: Invasive Ductal Carcinoma, ILC: Invasive Lobular Carcinoma, LA: Luminal A, LB her2-ve: Luminal B HER2-negative, LB her2+ve: Luminal B HER2-positive, her2 enrich: HER2-enriched, TNBC: Triple-Negative Breast Cancer, Neoadj: Neoadjuvant, AC: Doxorubicin and Cyclophosphamide, FAC: Fluorouracil, Doxorubicin, and Cyclophosphamide, Anti-HER2: Anti-Human Epidermal Growth Factor Receptor 2, MRM: Modified Radical Mastectomy, CBS: Conservative Breast Surgery, Adj cth: Adjuvant Chemotherapy, PORT: Postoperative Radiotherapy.

It was detected that only statistically significant independent OAS and DFS in multivariate analysis was the pathological response (Tables 7 & 8)).

Table (7): Multivariate cox regression showing prognostic factors of overall survival among studied cases

	β	p value	Hazard ratio (95%CI)
Menpausal status			
Pre (r)	**-1.13**	**0.206**	**1**
Post			**0.322(0.056-1.87)**
(T) stage			
T1 (r)			**1**
T2	**-0.658**	**0.069**	**0.518(0.02-13.33)**
T3	**3.53**	**0.751**	**0.029(0.002-0.375)**
T4	**2.29**	**0.164**	**0.100(0.004-2.56)**
Axillary LN			
N0 (r)			**1**
N1	**1.71**	0.302	**0.908(0.048-17.35)**
N2	**0.68**	0.060	**1.18(0.039-35.79)**
N3	**0.74**	0.180	**3.72(0.909-15.22)**
Clinical stage			
High risk-early stage (r)			**1**
IIIA	3.17	0.84	**5.54(0.98-29.28)**
IIIB	2.81	0.078	**1.25(0.04-15.68)**
IIIC	2.46	0.062	**1.87(0.98-17.8)**
Molecular subtype			
LA (r)		**0.089**	**1**
LB her2-ve	**-0.241**	**0.850**	**0.786(0.178-3.57)**
LB her+ve	**1.71**	**0.08**	**5.54(0.97-29.28)**
her2 enrich	**0.68**	**0.07**	**1.75(0.04-15.68)**
TNBC	**0.74**	**0.15**	**1.77(0.98-17.8)**
Pathological response			
no response (r)			
PR	**-0.096**	**0.007***	**1**
CR	**0.169**	**0.923**	**0.908(0.048-17.35)**
progression	**-0.633**	**0.713**	**1.18(0.039-35.79)**
Failure			
No (r)	**0.210**	**0.898**	**1.23**
Yes			**(0.05-30.29)**
local Recurrence			
no (r)	**1.31**	**0.068**	**3.72(0.909-15.22)**
yes			
Systemic failure			
No (r)	**12.66**	**0.902**	**UBDEFINED**
yes			

β: Beta Coefficient, p: P-value, CI: Confidence Interval, LN: Lymph Node, T: Tumor, LA: Luminal A, LB her2-ve: Luminal B HER2-negative, LB her2+ve: Luminal B HER2-positive, her2 enrich: HER2-enriched, TNBC: Triple-Negative Breast Cancer, PR: Partial Response, CR: Complete Response, r: Reference.

Table (8): Multivariate cox regression showing predictors of disease-free survival among studied cases

	β	P value	Hazard ratio (95%CI)
Molecular subtype			
LA (r)		**0.086**	**1**
LB her2-ve	**-0.241**	**0.750**	**0.786(0.178-3.47)**
LB her+ve	**1.71**	**0.08**	**5.54(0.98-29.28)**
her2 enrich	**0.68**	**0.07**	**1.25(0.04-15.68)**
TNBC	**0.74**	**0.14**	**1.87(0.98-17.8)**
Pathological response			
no response (r)			**1**
PR	**-1.9**	**0.09**	**0.145(0.016-1.33)**
CR	**-2.99**	**0.034***	**0.05(0.015-0.17)**
progression	**-2.44**	**0.001***	**0.087(0.009-0.830)**
PORT			
No (R)	**-0.892**	**0.192**	**1**
Yes			**0.410(0.107-1.57)**

β: Beta Coefficient, P: P-value, CI: Confidence Interval, LA: Luminal A, LB her2-ve: Luminal B HER2-negative, LB her2+ve: Luminal B HER2-positive, her2 enrich: HER2-enriched, TNBC: Triple-Negative Breast Cancer, PR: Partial Response, CR: Complete Response, r: Reference, PORT: Postoperative Radiotherapy.

DISCUSSION

Our study involved 200 patients with locally advanced breast cancer and high-risk early-stage breast cancer having different patient characteristics, receiving different neoadjuvant protocols and yielding variable degrees of response and survival rates.

Regarding outcome response, overall response rate (ORR) was 87.5%, partial response (PR) was 70.5%, CR was 17.0%, and progression rate was 8 %, while 4.5% had no response. breast conservation was eligible in 27.5% of patients, recurrence rate (RR) affected significantly by NST (P value= 0.018) where 25.5% developed relapse, 8.5% developed locoregional relapse, while 17% developed systemic relapse, which is near to results of **Pramesh *et al.*** [10] who reported that ORR (80.4%), PR was 62.2%, CR was 18.2%, SD was 13% and PD was 7%. Breast conserving surgery was allowed in 28.4% of cases and 24.3% of cases relapsed later on, of which 5.05% developed locoregional recurrence (LRR), while 20.25% developed distant metastases.

Regarding factors affecting pathological response, the current study showed that age, family history, comorbidities, contraception, parity, menopausal status, body built, side of tumor and histopathological subtype had no statistically significant effect on pathological response, which is correlated with results of **Xu *et al.*** [11] who reported also that family history was a non-statistically significant parameter and **Verdial *et al.*** [12] who reported that overall pCR rates did not differ by age. On the other hand, menopausal status was reported by **Kunnuru *et al.*** [13] to be a significant parameter as response rate was higher in post-menopausal group (P-value < 0.05). Obesity was reported by **Gourgue *et al.*** [14] to be associated with poorer pCR rates. Regarding laterality of tumor, **Abdou *et al.*** [15] reported that left sided breast tumors have a more proliferative genomic profile and lower responses to neoadjuvant chemotherapy compared to right sided breast cancer (15.4% versus 29.9% respectively, p = 0.036). Moreover, histopathological subtype was reported by **O'Connor *et al.*** [16] to be significant, as patients with IDC were more likely to achieve breast pCR (22% vs 7%), more likely to undergo BCS (46% v 33%) and to get higher rates of obtaining free margin at surgery (86% Vs 64%) when compared to ILC. This difference in factors affecting pathological response may be explained by difference in races and availability of more advanced research fields.

Our study showed also that tumor (T) stages and overall clinical stages were statistically significant (P-value= 0.036, 0.015 respectively) where the smaller the tumor was, the higher pCR could be achieved as pCR in T1 was (52.9%), T2 was (29.4%), T3 was (14.7%) and T4 was (2.9%). This goes parallel with results of **Goorts *et al.*** [17] who reported that cT-stage was an important predictor of pCR (p < 0.001) as response rate was higher in lower cT-stage as well as T1, T2, T3, T4 yielded 31%, 22%, 18%, and 17% response rate respectively.

Our present study showed that taxol containing regimens significantly (P=0.02) had highest pCR (29.4%), while highest progression rate was observed in non taxol-containing regimens; AC (43.8%) and FAC (25%) which is comparable to results of **Subbiah *et al.*** [18] who reported that taxol-containing regimen had a pCR higher than non-taxol-containing regimen (33.3% Vs 7%) respectively.

Regarding survival rates and factors affecting them, our study showed that 5-Year OS rate was 90.3%, 5-Year DFS was 85.1%, which is correlated with results of **Zheng *et al.*** [19] and **Domingo *et al.*** [20] where 5-year

OS was 89.5% and 83.2% respectively. OS was higher in postmenopausal, high-risk early stage, stage IIIA and cPR, hormonal receptors positive and non-relapsed cases, which is comparable with results of **Öztürk *et al.* [21].** DFS was higher in HR positive subtypes, pCR and cases received PORT, which is mostly consistent with **Shohdy *et al.* [22].** The only independent significant OAS and DFS predictive factor is pathological response. This is in agreement with the results of **Zheng *et al.* [19]** and **Shohdy *et al.* [22]**.

Limitations: The limitations of this study included its retrospective design, which may introduce selection bias and limit the ability to establish causality. Additionally, being conducted at a single institution, which restricts generalizability of our findings to a broader population. The study's reliance on available patient records may lead to incomplete data for some variables, potentially affecting accuracy of analysis. Lastly, despite efforts to control for confounding variables, residual confounders cannot be entirely ruled out, which may impact validity of associations that were found in this study.

CONCLUSION

The results of the current study suggested that there are many factors affecting prognosis of patients receiving NST for LABC or high-risk early-stage breast cancer, and most important factor that improved OS and DFS independently was pCR.

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