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ORIGINAL ARTICLE

Role of Neoadjuvant Chemotherapy on the Surgical Treatment of Locally Advanced Breast Cancer

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ABSTRACT

Background: preoperative chemotherapy can reduce the size of the tumor, thus allow some patients with advanced tumors which is common the opportunity of conserving breast surgery. The aim of the study was to evaluate the efficacy of neoadjuvant chemotherapy (NC) on the possibility of breast-conserving surgery (BCS) in patients for whom mastectomy was the only accepted surgical option. **Methods:** thirty patients who had stage III breast cancer received neoadjuvant chemotherapy comprised of doxorubicin and cyclophosphamide, followed by surgery between 2016 and 2019. **Results:** thirty patients included in the study, 27(90%) presented with an invasive ductal carcinoma. The mean tumor size before NC, measured using MRI, was 37 mm (range, 20-75 mm) and 29 mm (range, 12.5-75 mm) after NC. Twenty patients (66.7%) underwent mastectomy while ten patients (33.3%) underwent BCS. The mean follow up survival time for all patients was 32±1.2 months range (29.8-34.8) months with (95% CI; 29.8-34.8).one case (3.3%) of BCS had locoregional recurrence and three cases (10%) had distant metastasis. Patients with IDC had significant higher DFS (33.5 ±1.04) months than patients with combined IDC+ILC (20±6) months and ILC(18) months.Patients with mastectomy had better numerical (not significant) DFS (32.25±1.5) months than patients with BCS (31.6±2.3) months. **Conclusion:** NC had a role in reducing the size of the tumor and could be applied in patients with advanced carcinoma. It increased the chance of BCS without affecting overall survival.

Keywords: Breast cancer, Neoadjuvant chemotherapy, Locally advanced breast cancer, Breast-conserving surgery, Loco-regional recurrence, Survival

INTRODUCTION

Breast cancer is the most common type of malignancies among women all over the world [1]. The incidence of breast cancer varies in the world, as North America, Northern and Western Europe includes high incidence rate for Age-Standardized Rates for Cancers of the Female Breast in 2018 (range ;80-92) , South America and Southern Europe contain intermediate rates (range ;54-79); and Africa and Asia contains lower rates (range ;25-48) [2].

Breast cancer accounts for 38% of all new cancers among women in Egypt [1]. Preoperative chemotherapy is becoming an increasingly popular sequencing strategy in the multimodality treatment of breast carcinoma [3].

The potentiality for converting patients needed mastectomy to breast-conservation, improving the cosmetic appearance following lumpectomy by cutting down the size of the original breast tumor is the main advantage from a surgical therapy point of view even if the patient is a candidate to lumpectomy at time of presentation, sentinel node biopsy instead of axillary dissection is another advantage[4,5].

From time of diagnosis till time of surgery important steps are required to enable successful treatment in patients treated with NC. They include meticulous assessment of the site and extent of original breast mass and axillary nodal status before and after NC [6].

Developing new NC regimens and new imaging techniques will lead to better control of breast cancer surgical management

following NC, including the possibility of even avoiding surgery in cases complete response [7,8].

Several large, well-designed, randomized clinical trials have shown no differences in disease-free and overall survival rates between NC and adjuvant chemotherapy [4].

These trials confirmed that NC increased the proportion of patients with BCS with no significant increase in the local recurrence rates [6].

The aim of this work is to assess the effectiveness of NC on the tumor downsizing for patients with locally advanced breast cancer who needed mastectomy.

METHODS

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) .

The study was executed in the General Surgery and Medical Oncology departments, faculty of medicine, Zagazig University hospitals between the period from June 2016 to June 2019 .

The study included thirty female patients presented with stage III breast cancer all of them were subjected to preoperative chemotherapy.

All patients were histologically confirmed clinical stage III invasive breast cancer. They were more than eighteen years and have Performance status less than 2. Patients unfit for surgery, Patients with inflammatory or multicentric disease, Patients that were already eligible for a conservative treatment before NC and Patients who previously subjected to chemo or radiotherapy for breast cancer were excluded from the study.

All Patients were subjected to Proper and detailed history taking and full clinical examination, Full laboratory tests as CBC, LFT, KFT and Coagulation profile were confirmed.

Radiological investigations in the form of mammography ,breast ultrasound and MRI before and after chemotherapy. Core biopsy and receptor examination for (ER,PR , HER2 and ki67), Echocardiography and metastatic work up (CT chest , abdomen and pelvis and bone scan) were done to all patients.

Preoperative chemotherapy:

All patients received 4 cycles of NC (AC regimen: Doxorubicin 60mg/m2 and Cyclophosphamide 600 mg/m2) repeated every 21 days with pre medications and post medications as required.

Response to the NC was evaluated clinically following the first cycle and before each following cycle by physical examination. After neoadjuvant treatment response was evaluated clinically and with diagnostic breast imaging by using imaging techniques (mammography, ultrasound, and MRI). Depending on the tumor response, the patients underwent BCS, or a modified radical mastectomy if they were unsuitable for BCS 3 to 6 weeks after the last NC according to degree of response and breast tumor ratio.

Tumor response was confirmed pathologically after surgery by presence of tumor necrosis and or micrescopic residuals .

Patients received adjuvant chemotherapy was given to all patients 3 cycles of AC (Taxol) weekly as they were all positive nodal mrtastasis.

All patients were planned to adjuvant radiation therapy. Adjuvant hormonal therapy was started at the end of adjuvant chemotherapy for those with positive hormone receptor. Trastuzumab was given to Her2 positive patients.

Three years average follow up was scheduled to detect locoregional recurrence , distant metastasis and disease free survival .

Statistical Analysis:

Data were collected, tabled and analyzed using SPSS. Continuous Quantitative data were expressed as mean ± SD & median (range), and categorical qualitative data were presented as absolute frequencies "number" & relative frequencies (percentage).

A Kaplan-Meier analysis and Log Rank Cox model were used to estimate the main factors related to disease-free survival.

Categorical data were compared using Chi-square test or Fisher's exact test. All tests were two sided. $p< 0.05$ statistically significant (S) and $p \geq 0.05$ non statistically significant (NS) .

RESULTS

Among the 30 patients included 27(90%) patients presented with invasive ductal carcinoma while 2 cases (6.7%) were combined IDC+ ILC and one case(3.3%) was ILC.

The mean age of these patients was 50.8 years (range,26-75). Fifteen tumors (50%) were grade III, 16 were ER positive (53.3%) and 10 patients were HER2 positive (33.3%).

The mean Ki 67 was 22.5% ranged from 10 to 70%. The patients' demographic characteristics and pathological features are presented in **Tables1,2.**

All patients received 4 cycles of NC (AC regimen) repeated every 21 days. Among 30 cases 24 patients (80%) obtained partial clinical response. stable disease was in 4 cases(13.3%) while 2 cases(6.7%) had disease progression. **(Table 3)**

It was noticed that stable and progressive diseases were grade 2, hormonal receptor positive and HER 2 negative. There was significant association between tumor response to chemotherapy and tumor grade (p-value=0.02) and ER status (p-value=0.037).

The mean tumor size before NC, measured using MRI, was 37 (range, 20-75) mm and 29 (range, 12-75) mm after NC without significant difference according to subtype of breast cancer.

Ten patients (33.3%) underwent BCS, one patient who treated with BCS (wide local excision) needed additional surgery because of positive surgical margin.

The mean follow up survival time for all patients was 32±1.2 (range; 29.8-34.8) months with (95% CI; 29.8-34.8). locoregional recurrence was diagnosed in one case (3.3%) and distant metastasis in 3 cases (10%).

There is significant association between locoregional recurrence and high ki67 percentage and positive marginal status (p-value =0.11, 0.1) respectively.

There is significant association between distant metastasis and tumor pathological type ILC (p-value=0.14).

There is significant relation between grade III tumors and negative estrogen receptor tumors with response to NC (p-value=0.2,0.37) respectively.

The mean DFS was 28±0.7 months, with a median of 28 months and a range between (26.6-29.4) months with (95% CI; 26.7-29.2) **(Fig.1).**

Patients with IDC had significant higher DFS (33.5 ±1.04) months than patients with combined IDC+ILC (20±6) months and ILC(18) months (p-value=0.003) **(Fig.2)**

Patients with mastectomy had better DFS (32.25±1.5) months than Patients with BCS (31.6±2.3) months but there is no significant relation between type of surgery and DFS (p-value=0.75) **(Fig. 3).**

There is no significant association between DFS and patients' age (p-value=0.2) menstrual status(p-value=0.6) tumor grade (p-value=0.9) ER status(p-value=0.38) and PR status(p-value=0.64).

Table 1. Demographic data of the breast cancer patients (N=30).

Demographic data	All patients (N=30) %	
Age (years)		
Mean ± SD	50.8 ± 14	
Range	(26 – 75)	
Menstrual state		
Premenopausal	11	36.7%
Postmenopausal	19	63.3%
Family History		
Negative	28	93.3%
Positive	2	6.7%

Table 2. Pathological features of studied patients (N=30).

	All patients (N=30) %	
Tumor site		
Rt	12	40%
Lt	18	60%
Tumor type		
IDC	27	90%
ILC	1	3.3%
IDC+ILC	2	6.7%
Tumor grade		
Grade II	15	50%
Grade III	15	50%
ER status		
Negative	14	46.7%
Positive	16	53.3%
PR status		
Negative	11	36.7%
Positive	19	63.3%
HER2neo status		
Negative	20	66.7%
Positive	10	33.3%
KI 67		
Mean ± SD (range)	22.5 ± 15.6 (10_70)	
Median	17.5	

IDC: Invasive Ductal Carcinoma
ILC: Invasive Lobular Carcinoma
ER: Estrogen Receptor
PR: Progesterone Receptor
HER2: Human Epidermal Growth Factor Receptor

Table 3. Post neoadjuvant chemotherapy findings (N=30).

	(N=30)	%
Response		
Complete response	0	0%
Partial response	24	80%
Stable disease	4	13.3
Progressive disease	2	6.7%
LN metastasis		
Negative	0	0%
Positive	30	100%
Positive LN		
Mean ± SD		9.75 ± 8.08
Median (Range)		8 (1 – 29)
Dissected LN		
Mean ± SD		18.06 ± 5.99
Median (Range)		19 (5 – 32)
Type of surgery		
MT	20	66.7%
BCS	10	33.3%
Marginal status		
Negative	28	93.3%
positive	2	6.7%
Additional surgery (re excision)		
No	28	93.3%
Done	2	6.7%

MT :Mastectomy
BCS :Breast Conserving Surgery

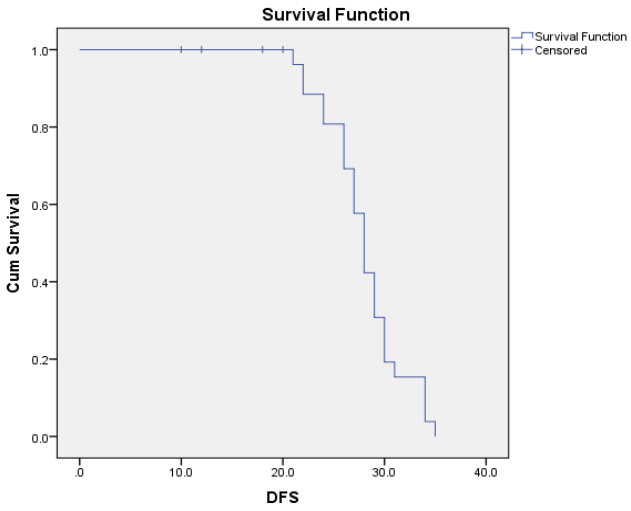


Figure 1. Disease free survival for all patients.

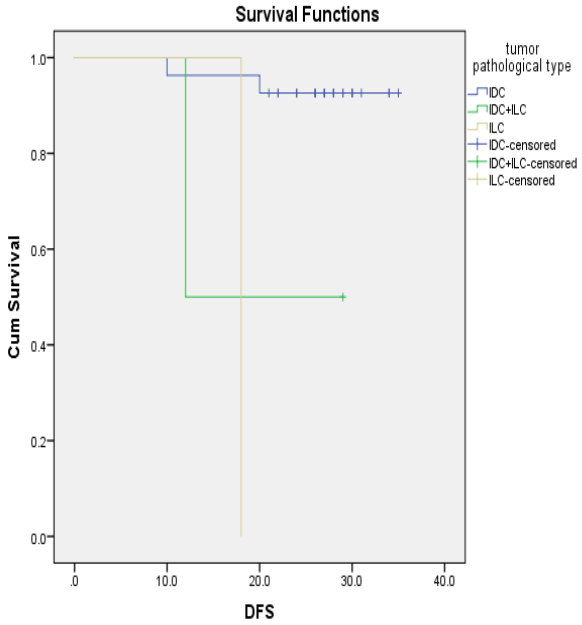
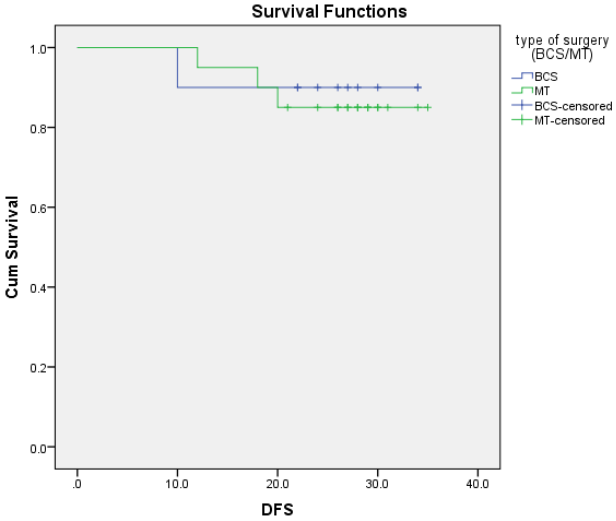


Figure 2. Disease free survival as a function of tumor pathological type.

IDC: Invasive Ductal Carcinoma ILC: Invasive Lobular Carcinoma



BCS: Breast conserving surgery MT: mastectomy

Figure 3. Disease free survival as a function of type of breast surgery.

DISCUSSION

Neoadjuvant chemotherapy was used as a treatment for patients with locally advanced breast cancer to convert inoperable cancers into operable ones [9].

Sooner, the concept was expanded to earlier stages, to increase the rate of (BCS) [10].

The main advantage of NC is reducing the size of the tumor allowing BCS and so less morbidity and better cosmosis compared to mastectomy [11].

However, current practice patterns of NC are not well described in the literature and not taken into consideration the major changes of the surgical treatment of cancer during the past 20 years [12,13].

Different results for various factors could be related to different patient selection criteria, different therapeutic approaches, and type of surgery, margins taken, and

chemotherapeutic drugs used. Thus, in clinical practice, the oncology team should review each patient in a multidisciplinary fashion and discuss complete multimodality management according to the individual patient's prognostic predictive factors.

In this study we evaluated the safety of BCS following NC instead of mastectomy in LABC.

This is done by history taking and clinical examination of 30 female patients with LABC then we searched for the response of the tumor to neoadjuvant chemotherapy by measuring the tumor size before and after NC and then evaluate the eligibility of conversing mastectomy to BCS .

In this study the mean initial tumor size was 3.7 cm (range, 2-7.5) and after NC was 2.9 cm (range ,1.25-7.5) which considered statistically significant (p value=0.03) a close range reported by **Emmanuel et al.** [14] who reported that tumor size before NC was 41.6 mm (range, 15-110) and 25.3 mm (range, 0-90) after NC.

In our study the mean age of breast cancer patients with locally advanced breast cancer was 50.8 years (range, 26-75). 22 patients were ≤60 and 8 patients were >60. There was statistically non significant association between age groups and DFS (p-value=0.6).

In this study premenopausal women were 11 (36.7%) and postmenopausal were 19 cases (63.3%) there was statistically non significant association between menstrual state and DFS (p-value= 0.6) this coincides with **Mohamed et al.** [15]

In this study, upper outer quadrant was the most affected one (18 patients with 60 % incidence). This matches with **Skandalakis et al.** [15] and **Hunt et al.** [16] who reported that upper outer quadrant contains the main bulk of breast tissue and thus it is the most usual site for both breast cancer and most benign breast pathologies .

In our study two (6.7%) patients out of 30 had positive family history. There was no significant association between family history and DFS (p-value=0.6)

there was statistically non significant association between ER, PR ,HER2 status and DFS. (p-value=0.28,0.64and 0.27) respectively.

And this may be due to neutralization by post operative hormonal and target therapy. This differs with **Mohamed et al.** [15] who reported that hormonal receptor status was a significant factor in term of distant relapse [15].

In our study Mean Ki 67 was 22.5 ranged from 10 to 70% There was a statistically significant association between ki 67 and locoregional recurrence (p-value=0.011) this matches with **Shin et al.** [18].

In our study two cases had positive marginal status one of them had locoregional recurrence. There was a statistically significant association between positive surgical margins and DFS (p-value=0.04) this matches with **Mohamed et al.** [15] who reported that negative margin was to locoregional recurrence.

In this study 10 (33.3%) cases had BCS and 20 (66.7%) cases had mastectomy (mastectomy to BCS conversion rate). This differs with **Emmanuel et al.** [14] who reported 72.3% of cases had BCS the high conversion rate was explained by that they selected breast tumors with high potentiality for complete response ; IDC (99%), high grades tumors (93.3%) and hormone receptor negative (49.6%).Also their frequent usage of oncoplastic techniques (33.6% of the cases).

The review published by **Mieog et al.**[19] included 5 randomized studies and reported a modification of local treatment after NC in 16% of the cases (mastectomy converted to BCS). The low BCS conversion rate was explained by the difference of breast tumor characteristics in these series. A meta-analysis published by **Mauri et al.** [20] found important differences across studies in the rates of BCS with NC (ranging from 28% to 98%).

In our study one case (3.3%) had locoregional recurrence. This matches with **Emmanuel et al.** [14] who reported 3.4 % locoregional recurrence and differs with **Chen et al.** [21] who showed a locoregional recurrence rate 8.5% and **Parmar et al.** [22] who reported a locoregional recurrence rate of

8% after BCS versus 10.7% after mastectomy and **Mohamed et al.** [15] who reported locoregional recurrence 34%.this may be due to longer period of follow up which is considered an important factor for developing more cases of locoregional recurrence or different regimens of NC.

In our study 3 cases (10%) had DM this differs with **Mohamed et al.**[15] who reported 62.5% distant metastasis in a period of median follow up 47.5 months.

Patients with BCS their mean DFS = 31.6±2.3 . while Patients with mastectomy their mean DFS = 32.25±1.5 there is no significant relation between type of surgery and DFS (p-value=0.75). this coincide with with **Emmanuel et al.** [14] **and Mohamed et al.** [15]

In our study non of patients had complete response to NC and this differs with **Iqbal et al.** [23] who reported that 44.4 of patients achieved complete pathological response and with **Mohamed et al.** [15] who reported 9% of patients achieved complete response. This may be due to applying different regimens of neoadjuvant chemotherapy .

In our study the mean follow up survival time for all patients was 32±1.2 months range (29.8-34.8) months with (95% CI; 29.8-34.8). This differs with **Emmanuel et al.** [14]**, Chen et al.** [21]**, Parmar et al.** [22]**, Mauri et al.** [20] and **Mohamed et al.** [15] who reported longer follow up period .

In our study the mean DFS was 28±0.7 months, with a median of 28 months and a range between (26.6-29.4) months with (95% CI; 26.7-29.2). This differs with **Emmanuel et al.** [14]**, Chen et al.** [21]**, Parmar et al.** [22]**, Mauri et al.**[20] and **Mohamed et al.**[15] who reported different DFS due to different follow up period , larger sample size and different NC regimens.

According to our study the ideal patients for BCS after NCT should have these criteria: tumor type IDC, tumor grade 3, hormonal receptor negative, low ki67 and negative surgical margin. This coincides with **Emmanuel et al.**[14]**, Chen et al.**[21]**, Parmar et al.**[22]**, Mauri et al.** [20] and **Mohamed et al.** [15]**.**

CONCLUSION

The results of this study suggest that NC can help in downsizing LABC and offer the chance to BCS instead of mastectomy. The accurate selection of patients can lead to a high conversion rate.

Conflict of Interest: Nothing to declare.
Financial Disclosures: Nothing to declare.

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