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ORIGINAL ARTICLE

Evaluation of Early Outcome of Breast Surgery after Neoadjuvant Chemotherapy

Heba Al-Hussein Abo-Al-Ella [1*], Khaled Safwat [2], Osama Hassan Gharib [3], Tamer Alsaied Habeeb [4]
[1,2,3,4] General Surgery department, Faculty of medicine Zagazig University,Zagazig, Egypt*

***Corresponding Author:**
Name Heba Al-Hussein Abo-Al-Ella
***Corresponding Author:**
Name Heba Al-Hussein Abo-Al-Ella
Assistant Lecturer of General Surgery Zagazig University, Egypt
01090299263 -
Heba.alhussein.2014@gmail.com / Hhabual-ela@zu.edu.eg

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ABSTRACT

Background: Using neoadjuvant treatment has increased over the past decade due to its ability to assess tumor sensitivity to systemic treatment in vivo, and to downstage breast cancer (BC) for increased breast conserving surgery (BCS)**.** This study aims to compare the efficacy of neoadjuvant chemotherapy (NACT) and adjuvant chemotherapy (ACT) in women with BC stage II-III

Methods: This prospective randomized comparative study included women diagnosed with stage invasive BC and received either NACT or ACT.

Results: The mean age of BC patients in group A was 54.4±12.5 years, while the mean age in group B was 48.7±11.1 years. In group A, 11of cases (61.1%) were grade 2 and 7 were grade 3 (38.9%) and in group B, 9 cases were grade 2 (50%) and 9 were grade 3(50%). The mean initial tumor size was 27.7±11.9 mm (range, 11-60) and after NACT was 20.1±7.5 mm (range, 10-36) (p-value=0.03). In group A the mean disease free survival (DFS) time was 29.8± 6.1months, with a median of 35 months. In group B, the mean was 31.2± 3.8 months, with a median of 34 months (p-value=0.4). The patients outcome among the patients under different types of surgery were stable in 50% and 77.3% of the Breast Conservative surgery (BCS) and Modified Radical Mastectomy (MRM) respectively (p-value =0.7)

Conclusions: NACT followed by surgery is a safe and effective surrogate to conventional method (primary surgery followed by ACT) in treatment of BC stage II-III. NACT is as effective as ACT regarding overal l survival (OS) and DFS.

Keywords: breast cancer; neoadjuvant chemotherapy; adjuvant chemotherapy.

INTRODUCTION

Worldwide, BC is the most frequently diagnosed life-threatening cancer in women and is second only to lung cancer as a cause of cancer deaths [1]. In early BC, NACT has become one of the preferred treatment options. Its efficacy has been proven to be equivalent to adjuvant therapy, in terms of both OS and DFS [2]. NACT offers a unique opportunity for individualized therapy and allows collection of tumor samples before, during, and after treatment. This assessment of tumor behavior in situ during NACT and its correlation with clinical outcome is an excellent model to determine the predictive role of tumor characteristics. In addition, in case of a resistance to therapy, adjusting the dose and/or change to another drug saves patients from the burden of toxicity and side effects [3]. The aim of the study is to investigate the benefits NACT and the influence of tumor characteristics on the outcomes of BC patients and its feasibility as an alternative to the conventional method.

METHODS

This is prospective randomized comparative study included patients with BC stage II/ III (resectable tumor), who presented to Surgery Department of Zagazig University Hospitals during the period from April 2017 to April 2020.

Written informed consent was obtained from all participants with explanation of the management strategy, possible hazards and follow up. 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) for studies involving humans**.**

Patients in this study were divided into 2 groups (18 patients each) group A (Adjuvant group) treated with the conventional method (primary surgery followed by adjuvant therapy) and group B (Neoadjuvant group) treated with NACT protocol.

Group A: ACT started postoperatively within (2-4weeks) after surgical wound healing. Post-operative chemotherapy consists of the same

regimen of NACT.

Group B: protocol assessment was done by clinical examination, and breast U/S that took place after the first cycle and before each of the following cycle. The chemotherapy regimen received included Adriamycin 60 mg/m2, Cyclophosphamide 600 mg/m2 every 3 weeks for four cycles.

Inclusion Criteria were: Female patient with good general condition (adequate hepatic, renal, cardiac and respiratory functions). Patients had clinically and radiologically resectable BC stage IIA/ IIIC, which was confirmed by fine needle aspiration cytology (FNAC) or core biopsy and histopathology.

Females with bad general condition or with brain, bone, and lung metastasis confirmed by CT or MRI or bone scan, patients with associated malignancies or history of either chemotherapy or radiotherapy or previously treated malignancy and patients with complicated BC eg: skin fungation or ulceration extend beyond tumor margin or involve the whole breast were excluded from the study.

All patients were subjected to history taking including age, menstrual status, gravidity, breast-feeding, oral contraception/hormonal therapy intake, family history of ovarian cancer or BC, general and abdominal clinical examinations and laboratory investigation including complete blood picture, blood sugar level, hepatic and renal function tests, coagulation profile. Radiological imagings as breast U/S and mammogram or/ MRI, chest x-rays, pelvi-abdominal U/S and bone scan were performed to exclude distant metastasis. Histopathological examination of the tumor and immunophenotyping (estrogen receptor (ER), progesterone receptor (PR), HER2 and KI 67) were performed.

Tumor response after NACT was classified to:

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. (Note: the appearance of new lesions is considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Post-operative follow-up: By clinical examination that was performed every 3 months following surgery. Breast U/S and Mammogram was performed 6 months after the operation. MRI was performed in case of abnormalities that may be seen on mammogragm. Bone scan if there was bone pain or increase alkaline phosphatase. If there was any suspicion of metastasis, PET- CT scan was perfomed.

Operative technique: MRM was done by classic technique, some cases breast conserving surgery was done in the form of quadrentectomy or lumbectomy with safety margin and axillary clearance was done

Statistical analysis:

The collected data were analyzed by computer using Statistical Package of Social Services version 23 (SPSS), Data were represented in tables, Continuous Quantitative variables e.g. age were expressed as the mean ± SD & median (range), and categorical qualitative variables were expressed as absolute frequencies (number) & relative frequencies (percentage).

Suitable statistical tests of significance were used after checked for normality. Categorical data were cross tabulated and analyzed by the Chi-square test, Continuous data were evaluated by Mann Whitney test. The results were considered statistically significant when the significant probability was less than 0.05 ($P < 0.05$), and P-value $\geq$ 0.05 was considered statistically insignificant (NS).

RESULTS

This is prospective randomized comparative study including 36 patients with BC stage II/ III (resectable tumor) who presented to Surgery Department of Zagazig University. Patients were divided into two groups (adjuvant and neoadjuvant group).

There was no statistically significant difference between the two studied groups regarding age, parity, family history, lactation history and menstrual state table (1)

Tumor characteristics and type of surgery is presented in tables (1). There was no statistically significant difference between the two studied groups regarding tumor type, tumor grade, LN status, KI 67, PR status, ER status, HER2 and type of surgery needed while comparing between the two studied groups.

Tumor size before and after the NACT among group B is presented in table (2) there was statistically significant decrease in tumor size after the NACT from (27.7±11.9 cm) to (20.1±7.5 cm).

Post NACT response among group B is presented in table (3) (50.0%) of the patients had partial response followed by (33.35%) had stationary disease then disease progression on (11.1%) and lastly (5.6%) had complete response.

Patients outcome is presented in tables (4) there

was no statistically significant difference between the two studied groups regarding the outcome with (61.1%) and (72.2%) of group A and B respectively were stable.

Disease free survival time is presented in table (5) .

there was no statistically significant difference between the two studied groups (p-value=0.4). In group A, the mean DFS time was 29.8± 6.1 months and In group B, the mean DFS time was 31.2± 3.8 months

Table (1): Comparing socio-demographic characteristics between the two studied groups:-

Variables	Adjuvant Group (A) (18)		Neoadjuvant Group (B) (18)		Test	p-value
Age						
mean ± SD	54.4±12.5		48.7±11.1		1.4	
(Range)	(28-75)		(33-71)			0.2
Median	50		50			
Variables	**Group A**		**Group B**			
	No(18)	**%**	**No(18)**	**%**	**χ^2**	**p-value**
Parity					**FET**	
Nulliparous	2	11.1%	2	11.1%		1
Multiparous	16	88.9%	16	88.9%		
Menstrual state					**FET**	
premenopausal	5	27.8%	6	33.3%		0.2
Postmenopausal	13	72.2%	12	66.7%		
Lactation history					**FET**	
No	2	11.1%	4	22.2%		0.3
Yes	16	88.9%	14	77.8%		
Family history					**FET**	
Negative	15	83.3%	17	94.4%		0.6
Positive	3	16.7%	1	5.6%		
Tumor type	16	88.9%	14	77.8%	**FET**	
IDC	2	11.1%	4	22.2%		0.7
ILC						
Tumor grade	11	61.1%	9	50%	**1.3**	
II	7	38.9%	9	50%		0.5
III						
LN metastasis	4	22.2%	8	44.4%	**FET**	
Negative	14	77.8%	10	55.6%		0.14
Positive						
Tumor size	6	33.3%	7	38.9%	**0.1**	
<2 Cm	10	55.6%	9	50.0%		
2-5 Cm	2	11.1	2	11.1%		0.9
>5 Cm						
PR status	11	61.1%	10	55.6%	**0.9**	
Positive	7	38.9%	8	44.4%		1
Negative						
ER status	10	55.6%	9	50%	**0.7**	
Positive	8	44.4%	9	50%		0.5
Negative						
HER2 status	6	33.3%	7	38.9%	3.1	
Positive	12	66.7%	11	61.1%		0.4
Negative						
KI 67 (%)	31.4±19.3		24.1±15.6		M.W	0.2
mean ± SD	(12-65)		(13-62)		1.2	
(Range)	21		18			
Median						
Type of surgery	14	77.8%	13	72.2%	0.1	0.7
MRM	4	22.2%	5	27.8%		
BCS						

FET= Fischer Exact test.
M.W= Mann-Witenney U test
SD = standard deviation

P ≤ 0.05 is Statistically significant difference.
PR =Progesterone Receptor
ER =Estrogen Receptor
IDC= Invasive duct carcinoma
ILC= Invasive lobolar carcinoma
LN =lymph node
MRM =Modified Radical Mastectomy
BCS =Breast conservative surgery

Table (2): Comparing tumor size before and after the NACT among Group B:

Variables	Before NACT (18)	After NACT (18)	W.S.R Test	p-value
Size *(cm)* *mean ± SD* *(Range)* *Median*	27.7±11.9 (11-60) 23.5	20.1±7.5 (10-36) 19.5	3.5	**0.003***

P ≤ 0.05 is Statistically significant difference.
P ≤ 0.001 is Statistically highly significant difference*
W.S.R=Wilcoxon Signed rank
NACT= neoadjuvant chemotherapy

Table (3): Post-NACT response among Group B:

Variable	NO(18)	%
Response		
Complete response	1	5.6%
Partial response	9	50.0%
Stationary disease	6	33.3%
Progressive disease	2	11.1%

Table (4): Patients outcome among the two studied groups:

Variables	Group A		Group B		χ^2	p-value
	No(18)	**%**	**No(18)**	**%**		
Disease free survival	11	61.1%	13	72.2%	2.1	0.7 (NS)**
Local recurrence	2	11.1%	2	11.1%		
Lung metastasis	2	11.1%	1	5.6%		
Bone metastasis	3	16.7%	2	11.1%		

(NS) is Not significant**
P ≤ 0.05 is Statistically significant difference.

Table (5): Comparing disease free survival time between the two studied groups:-

Variables	Group A (18)	Group B(18)	T- Test	p-value
Disease free survival time *(months)* *mean ± SD* *(Range)* *median*	29.8± 6.1 (18-36) 35	31.2± 3.8 (18-36) 34	0.8	0.4

In this table, there was no statistically significant difference between the two studied groups regarding disease free survival time.

DISCUSSION

In this study, we evaluated the oncological safety of the conventional method (primary surgery followed by adjuvant therapy) versus NACT followed by surgery, so we divide the patients into two groups; adjuvant group treated with conventional method (primary surgery followed by ACT and neoadjuvant group, consisted of the same number patients who were given preoperative NACT then subjected to surgery and then evaluate oncological safety of both methods. In line with our study, both LeVasseur et al. [4] and Bagegni et al. [5] performed a similar study.

The chemotherapy regimen received in our study includes Adriamycin 60 mg/m2, Cyclophosphamide 600 mg/m2 (AC) every 3 weeks for four cycles. This coincides with a study conducted by Javan- Noughabi et al. [6] that show that this NACT regimen is the most appropriate. The results of this study showed that the response to treatment in AC chemotherapy regimen 84% and according to the findings of this study, AC is more effective and low cost compared to other NACT regimens.

In this study, the mean age of BC patients in adjuvant group was 54.4±12.5 years (range, 28-75). While the mean age of BC patients in neoadjuvant group was 48.7±11.1 years (range, 33-71).There was no statistically significant difference between the two studied groups regarding age (p-value=0.2). This coincides with median age was 49 years (37-68) in the neoadjuvant group vs 49 (37-65) in the adjuvant group (p- value = 0.71) that was reported by LeVasseur et al. [4].

In our study, in regards to the tumor type, in the adjuvant group 16 cases (88.9%) were IDC while 2 cases (11.1%) were ILC and in the neoadjuvant group 14 cases were IDC while 4 cases (22.2%) were ILC. There was no statistically significant difference between the two studied groups regarding tumor type (p-value=0.7). This matched with Yousefi Kashi et al. [7] in which in the adjuvant group 86% of the patients had IDC and in neoadjuvant group 85% of the patients had IDC.

In our study, in the adjuvant group 11of cases (61.1%) were grade 2 and 7 were grade 3 (38.9%) and in the neoadjuvant group 9 cases were grade 2 (50%) and 9 were grade 3(50%). there was no statistically significant difference between the two studied groups regarding tumor grade (p value=0.5). This differs with LeVasseur et al. [4] who reported that the majority had stage 3 disease, 64% in both groups (p-value = 1.0).

In this study the mean initial tumor size was 27.7±11.9 mm (range, 11-60) and after NACT was 20.1±7.5 mm (range , 10-36) which considered statistically significant (p value=0.03) a close range reported by Barranger et al. [8] who reported that tumor size before NACT was 41.6 mm (range, 15-110) and 25.3 mm (range, 0-90) after NACT.

Yoo et al. [9] revealed ER, PR and HER 2 were the same in neoadjuvant and adjuvant group. These findings were consistent with our study that showed ER positive 50% and 55.6%, PR positive 55.6% and 61.1% and HER 38.9% and 33.3 % in neoadjuvant and adjuvant group, respectively. There was no statistically significant difference between the two studied groups regarding ER status, PR status, HER2

According to Spronk et al. [10], primary surgery without NACT was performed in which 65% were treated with BCS and 35% with a mastectomy. In neoadjuvant group; of which 50.9% were treated with BCS and 49.1% with a mastectomy. This can be explained by the fact that in NACT followed by BCS the tumor characteristics are associated with high potential for pathological complete response; IDC subtype, no multi-focality, a cT1-2 clinical tumor stage and cN0 disease. An important result of this nationwide data is that BCS after NACT leads to equal surgical outcomes for cT2 and improved outcomes for cT3 invasive BC compared to primary BCS. This differ from our study in which BCS was performed in 22.2% in the adjuvant and in 27.8% in neoadjuvant group.

In our study, in the adjuvant group, the mean DFS time was 29.8± 6.1 months, with a median of 35 months and a range between (18-36) months. In the neoadjuvant group, the mean DFS time was 31.2± 3.8 months, with a median of 34 months and a range between (18-36) months (p-value=0.4). This differs with Barranger et al. [8] and Salem et al. [11] who reported different DFS due to different follow up period, larger sample size, different NACT regimens and different tumor characteristics such as tumor size, stage of tumor and hormone receptors.

In our study, 50% of the patients who received NACT had partial response followed by 33.35% had stationary disease then disease progression on 11.1% and lastly 5.6% had complete response. This differs with Asselain et al. [12] who reported that 28% of patients achieved complete pathological response and with Salem et al. [11] who reported 9% of patients achieved complete response. This may be due to applying different regimens of NACT and different tumor characteristics.

In our study, there was statistically significant decrease in tumor size after the NACT from

27.7±11.9 mm, with a median of 23.5 mm and a range between (11-60) mm to 20.1±7.5 mm, with a median of 19.5 mm and a range between (10-36) mm (p-value=0.003). A close range reported by Barranger et al. [8] who reported that tumor size before NC was 41.6 mm (range, 15-110) and 25.3 mm (range, 0-90) after NACT. Man et al. [13] published in his study that the mean tumor size reduced by more than half, from 4 cm to <2 cm. The HER2-positive group showed a relatively greater tumor size reduction to almost 75%. On the contrary, the mean tumor size in luminal A BCs remained relatively static despite NACT.

In our study, there was no statistically significant difference between the two studied groups regarding the outcome with (61.1%) and (72.2%) of the adjuvant and neoadjuvant group respectively were stable (p-value =0.7). This matches a review published by Shin et al. [14], which found that DFS was 71.9 % in the neoadjuvant group and 72.7 % in the adjuvant group (p-value = 0.552).

Mauri and colleagues [15] evaluated 9 randomized trials showing no difference in overall survival, disease progression and distant disease recurrence. There was a 22% increased relative risk of local regional recurrence in the neoadjuvant group. However, this was attributed to inclusion of 3 trials which did not require surgery after achieving a complete clinical response thereby underscoring the significance of definitive local therapy.

In our study, there was no statistically significant difference in the patients outcome between the patients under different types of surgery with (50.0%) and (77.3%) of the BCS and MRM respectively were stable (p-value =0.7). This concides with Shin et al. [14], in which the BCS groups and the mastectomy group were not significantly different (p-value = 0.669).

Maishman et al. [16] study demonstrated worse DFS and OS for mastectomy compared with BCS (p-value < 0.001). This is almost certainly because of imbalances in prognostic features between the two groups. Patients treated with mastectomy presented with more high-risk features such as significantly larger tumors than BC tumor size ≥20 mm, positive lymph nodes, high tumor grade and negative hormone receptor status. This matches with Corradini et al. [17] results.

CONCLUSION

So we conclude that that NACT followed by surgery is a safe and effective alternative to conventional method (primary surgery followed by ACT) in treatment of early stage BC (stage II - III). Its efficacy has been proven to be equivalent to adjuvant therapy, in terms of both DFS and OS.

Conflicts of interest

There are no conflicts of interest.

Financial Disclosures

Non

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