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Neoadjuvant Chemotherapy and Surgical Options for Locally-advanced Breast Cancer: A Single Institution Experience

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Abstract

Background: Neoadjuvant chemotherapy can downstage the size of the tumor, thus allowing some patients with advanced disease with the option of conservative breast surgery. Our study aims to investigate the effectiveness of neoadjuvant chemotherapy in patients with locally advanced breast cancer.

Methods: Fifty-six patients had locally advanced breast cancer. Ten patients (18%) were stage IIB, 32 (57%) were stage IIIA, 9 (16%) were stage IIIB, and 5 (9%) were stage IIIC. Patients received neoadjuvant chemotherapy comprised of cyclophosphamide, doxorubicin, and fluorouracil followed by surgery (15 patients with breast conservative surgery,[11] with skin sparing mastectomy and latesmus dorsi reconstruction, and 30 patients who underwent modified radical mastectomy) and then followed by radiotherapy, 50 Gy with conventional fractionation.

Results: Clinical down staging was obtained in 49 (87.5%) patients: 5 (9%) had complete clinical response, 44 (78.5%) had partial response, 6 (10.7%) had stable disease, and 1 (1.8%) had progressive disease. The primary tumor could not be palpated after chemotherapy in 7 (12.5%) of 56 patients who presented with a palpable mass. Median follow-up was 47.5 months. The factors that correlated positively with locoregional recurrence on univariate analysis included hormonal receptor status and surgical margin status. On multivariate analysis, surgical margin status was the only independent significant factor for locoregional recurrence-free survival. In univariate analysis for distant relapse free survival, factors that correlated positively included disease stage and hormonal receptor status. Multivariate analysis showed that tumor stage and hormonal receptor status were independent significant factors that correlated with distant relapse-free survival.

Conclusion: Neoadjuvant chemotherapy was effective in clinical down staging and should be considered for patients with advanced breast cancer. It improved operability and enhanced local control and increased the possibility of breast-conserving surgery without affecting overall survival. Negative surgical margin was the independent significant factor in terms of locoregional recurrence while tumor stage and hormonal receptor status were the independent significant factors in term of distant relapse free survival.

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Introduction

Locally advanced breast cancer (LABC) represents 20%-25% of breast cancer (BC) patients at diagnosis, with a lower incidence in countries that implement screening programs.[1] Locally advanced breast cancer includes operable (stages IIB, IIIA) and inoperable (stages IIIB, IIIC) BC. In previous decades, most patients underwent mastectomies, with 50% local recurrences (LR) and 2% overall survival (OS). Postmastectomy radiotherapy increased local control (35%-55%) and survival (25%-45%).[1] Adjuvant chemotherapy, hormone therapy, or both further improved local control (LC) and overall survival (OS). Currently, standard of care for LABC patients includes surgery, radiation, and systemic therapy. Patients with stage III disease who underwent neoadjuvant chemotherapy (NAC) followed by surgery and radiotherapy had locoregional recurrence (LRR) in the range of 20%. Neoadjuvant chemotherapy can decrease tumor size, thus decreasing the possibility of positive margins and allows for breast conserving surgery (BCS) in selected LABC cases.[2] The pattern of management and aspects that prompt local treatment after NAC are not well known.[3] Neoadjuvant therapy is a choice for operable BC without compromising survival.[4]

In the current descriptive retrospective study, we aimed to initially explore the effectiveness of NAC in a well-characterized set of patients with LABC at South Egypt Cancer Institute, with particular attention for the surgical options offered to these patients. Secondly, we intended to define the clinical and pathological predictors of recurrence in LABC patients treated with NAC.

Patients and Methods

We retrospectively reviewed data from 56 LABC patients treated with NAC followed by surgery and radiotherapy from January 2007 to January 2014 at South Egypt Cancer Institute, Assiut, Egypt. Locally advanced breast cancer defined as patients with large operable (stages IIB, IIIA) and/or inoperable (stages IIIB, IIIC) tumors with inflammatory BC.[1] Table 1 lists patients' baseline characteristics before NAC. The mean age at presentation was 50.9 years (range: 31 to 64 years). There were 10 (18%) clinical stage IIB patients, 32 (57%) stage IIIA, 9 (16%) stage IIIB, and 5 (9%) stage IIIC. The pathologic diagnosis was obtained from a core biopsy performed before treatment. Patients received 3 to 4 cycles of NAC administered at three weekly intervals. All patients received 5-FU (500 mg/m^2), adriamycin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) as the FAC chemotherapy regimen.[5]

According to the WHO criteria, both an oncologist and a surgeon assessed clinical response to NAC. We considered patients qualified for breast surgery when the post-chemotherapy tumor was ≤3 cm. However, we took into account the cosmetic outcome which was related to breast volume percentage. After surgical resection we classified the pathological complete response (PCR) as the complete disappearance of all invasive tumor cells from the breast tissue and regional lymph nodes regardless of the presence of residual ductal carcinoma *in situ*.[6,7]

All patients received radiotherapy (3DCRT) who underwent CBS or mastectomy (50 Gy delivered in 25 fractions over 5 weeks) to the chest wall and supraclavicular lymph nodes. The axillary lymph nodes were irradiated only in cases of residual or incomplete axillary evacuation, while internal mammary nodes did not receive radiation unless positive according to baseline imaging. Patients who underwent CBS received a radiation boost (14 Gy/7fractions). Adjuvant chemotherapy was given to all patients and consisted of 2-3 cycles of FAC. Therefore, patients received 6 cycles of FAC. Tamoxifen or letrazole were given for 5 years to patients who were hormone receptor positive based on menopausal status.

Locoregional control and survival curves were generated by Kaplan-Meier and matched with the log rank test. We defined locoregional control as any repetition in the skin or soft tissue over the chest wall or a repetition in the regional lymphatic sites (axilla, internal mammary, infraclavicular,

and supraclavicular). Multivariate analysis was done using the Cox regression model. Clinicopathologic factors utilized for comparison included: age, menopausal status, histologic type, histological grade, tumor stage, clinical stage, type of surgery, response to chemotherapy, surgical margin status, nodal stage, and hormonal receptor (HR) status.

All statistical tests were two-tailed and differences were considered statistically significant if $P<0.05$. Statistical analysis was done using SPSS software version 16 (Statistical Package for the Social Sciences, Chicago, IL, USA).

Results

Table 2 lists patients' characteristics after NAC. The majority of patients (52/56, 92.8%) had invasive ductal carcinoma, while 4 (7.2%) had invasive lobular carcinoma. A total of 49 (87.5%) patients had clinical downstaging. We observed that 5 (9%) had complete clinical response, 44 (78.5%) had limited response, 6 (10.7%) had stable disease, and 1 (1.8%) patient had progressive disease. The primary tumor could not be palpated after chemotherapy in 7 (12.5%) patients who presented with palpable mass. After NAC, all patients underwent surgery; 15 (27%) had reasonable breast surgery (CBS), 11 (19.5%) underwent skin sparing mastectomy and latissimus dorsi reconstruction, and 30 (53.5%) underwent modified radical mastectomy (MRM). There was pathologic complete response (PCR) noted in 5 (8.9%) patients. The median follow-up time was 47.5 months. There were 19 patients that developed LRR which resulted in recurrence-free survival of 66%, whereas 35 patients had distant metastasis that resulted in a 37.5% distant metastasis-free survival rate. Among all clinicopathologic factors, univariate analysis for LRR-free survival revealed that surgical margin status ($P<0.034$) and HR ($P<0.022$) had positive correlations. Multivariate analysis indicated that the only independent significant factor was surgical margin status. Locoregional recurrence-free survival in patients with negative surgical margins was 76.7% in comparison to 30.7% in those with positive margins ($P=0.034$; Table 3, Figure 1). Univariate analysis showed that tumor stage and HR status correlated positively with distant metastasis-free survival. Table 4 shows that according to multivariate analysis, both disease stage ($P=0.025$) and HR status ($P=0.002$) were the independent significant factors that correlated with distant relapse-free survival.

Table 1. Patients' baseline characteristics.

Characteristic	Patient number (%)
Age (yrs)	
≤50	39 (69.6)
>50	17 (30.4)
Menopausal status	
Premenopausal	37 (66.0)
Postmenopausal	19 (34.0)
Histologic type	
Ductal	52 (92.8)
Lobular	4 (7.2)
Size	
T2	12 (21.4)
T3	30 (53.5)
T4	14 (25.0)
Clinical stage	
IIB	10 (18)
IIIA	32 (57)
IIIB	9 (16)
IIIC	5 (9)
Hormonal status	
ER+/PR+	38 (67.9)
ER-/PR-	18 (32.1)

Discussion

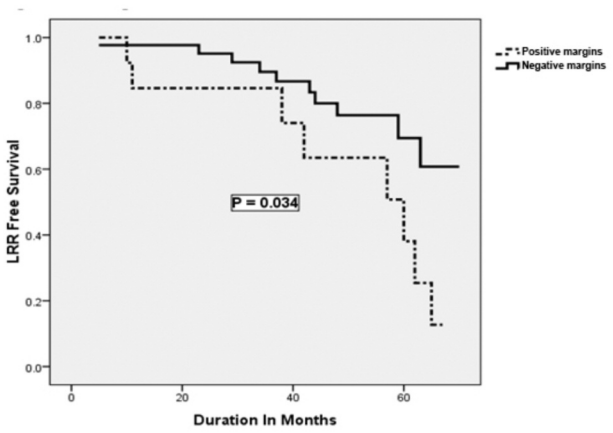

Figure 1. Locoregional recurrence–free survival in relation to surgical margins.

Historically, radical mastectomy alone as treatment for LABC had poor results with a 5-year LR of 46% and a survival rate of 6%.[8] Chest wall radiation was unsuitable in controlling LABC. Studies from the 1970s and 1980s revealed higher rates of LR (46% to 72%) and lower survival rates (16% to 30%).[9] Combined treatment with radiation plus surgery was attempted in this era without significant improvement in local control. Preoperative chemotherapy has revolutionized LABC care; currently, optimal management for LABC is NAC followed by surgery and radiation.[10]

Neoadjuvant chemotherapy in LABC patients can decrease tumor size and makes CBS feasible in selected cases, management of distant undetectable microscopic disease, and assessment of the response to chemotherapy.[11,12] Tumor specimens and blood samples can be evaluated before, during, and after NAC to identify tumor- or patient-specific biomarkers for research. However, NAC changes the histological extent of disease in 80%-90% of cases. Therefore, the decision for postoperative radiotherapy is difficult considered only on postoperative pathology data.[13]

Results of the present study supported these advantages of NAC. The current study data revealed that the use of NAC resulted in clinical downstaging in 49 (87.5%) patients. There were 5 (9%) patients with complete clinical response and 44 (78.5%) with partial response. In 7(12.5%) patients who presented with palpable mass, the primary tumor could not be palpated after chemotherapy. Surgery was possible in all patients after NAC; 15 (27%) underwent CBS, 11 (19.5%) underwent skin sparing mastectomy and latissimus dorsi reconstruction, and 30 (53.5%) patients underwent MRM. Notably, in this study the data revealed that NAC enabled 27% of the patients to undergo CBS. Studies revealed that the use of NAC allowed BCS in 16% and 26% of women candidates for mastectomy without affecting the rate of LR or survival.[14,15]

In selected patients, BCS and adjuvant radiotherapy reported DFS of 54% and OS of 63% at 18 years of follow up. These results were similar to mastectomy.[16]

Table 2. Disease characteristics following neoadjuvant chemotherapy (NAC)*.

Characteristics	Patient number (%)
Histologic type	
Ductal	52 (92.8)
Lobular	4 (7.2)
Tumor grade	
I	2 (3.6)
II	26 (46.4)
III	28 (50.0)
Hormonal status	
ER+/PR+	38 (67.9)
ER-/PR-	18 (32.1)
Lymph node	
N0	3 (5.4)
N1	7 (12.5)
N2	41(73.2)
N3	5 (8.9)
Type of surgery	
CBS	15 (27.0)
Mastectomy & LDR	11 (19.5)
MRM	
Surgical margin	30 (53.5)
Negative margin	43 (76.8)
Positive margin	13 (23.2)
Clinical response to NAC	
Complete	5 (9.0)
Partial	44 (78.5)
Stable	6 (10.7)
Progressive	1 (1.8)
Pathological response	
Complete	5 (8.9)
Incomplete	51 (91.1)

*CBS: Conservative breast surgery; LDR: Latissimus dorsi reconstruction; MRM: Modified radical mastectomy; ER: Estrogen receptor; PR: Progesterone receptor

The observed rates of LRR-free and distant metastasis-free survival were encouraging and compared favorably with those for patients who underwent CBS without NAC.[17,18]

Our results agreed with studies that reported lower LRR rate with CBS after NAC. We reported an LRR of 10.7% with CBS after NAC. Bonadonna et al.[19] reported a 5-year LRR of 7% after CBS and NAC. Buzdar etal.[5] and Cance et al.[20] reported LR rates of 5%, and 10%, respectively.

Factors related with BC recurrence are stage, primary tumor size, presence of nodal involvement, HR and human epidermal growth factor receptor 2 (HER2) status, histological grade,

Table 3. Locoregional recurrence-free survival in relation to clinicopathologic variables.

Factor	LRR-free No (%)	*P*-value
Age (yrs)		0.322
≤50	27/39 (69.2)	
>50	10 /17 (58.8)	
Menopausal status	0.263	
Premenopausal	26/37 (70.2)	
Postmenopausal	11/19 (57.8)	
Histologic type		0.582
Ductal	34/52 (56.3)	
Lobular	3/4 (75)	
Tumor stage		0.084
T2-T3	25/42 (59.5)	
T4	12/14 (85.7)	
Stage		0.072
II	9/10 (90)	
III	28/46 (60.8)	
Surgery		0.222
CBS	9 /15 (60)	
Mastectomy	31/41 (75.6)	
Pathologic response		0.058
Complete	4/5 (80)	
Incomplete	33/51 (64.7)	
Histological grade		0.330
I	2/2 (100)	
II	18/26 (69.2)	
III	17/28 (60.7)	
N-stage		0.235
N0-1	9/10 (90)	
N2-3	28/46 (60.8)	
Margins		0.034*
Negative	33/43 (76.7)	
Positive	4/13 (30.7)	
Hormonal status		0.022
ER+/PR+	32/38 (84.2)	
ER-/PR-	5/18 (27.7)	

*Significant on multivariate analysis.; ER: Estrogen receptor; PR: Progesterone receptor.

and response to NAC.[2,5,17] With the exception of response to NAC, these factors were independent of the influence of systemic adjuvant therapy and correlated with the natural history of the disease. HR status and HER2 status were both prognostic and predictive, as these factors determined the patient population at risk of recurrence (prognostic) but identified patients which might benefit from certain types of the systemic therapy (predictive).[2,5]

Results of this study showed that at the middle follow-up of 47.5 months, factors correlated positively with LRR on univariate analysis which included HR status and surgical margin status. Multivariate analysis showed that surgical margin status was the only independent significant factor for LRR-free survival. In a similar study, Buzdar et al.[5] retrospectively reviewed the outcome of 141 patients with stage II to stage III BC after NAC and found that the significant independent factors for LRR were tumor and pathological nodal stage. Data from the M.D. Anderson Cancer Center has suggested that even amongst patients with complete response to NAC, the disease stage is predictive for risk of locoregional failure. This should be taken into account when deciding on

Table 4. Distant metastasis-free survival (DFS) in relation to clinicopathologic variables.

Factor	DFS No (%)	*P*-value
Age (yrs)		0.303
≤50	16/39 (41)	
>50	5/17 (29.4)	
Menopausal status		0.321
Premenopausal	15/37 (40.5)	
Postmenopausal	6/19 (31.5)	
Histologic type		0.483
Ductal	19/52 (36)	
Lobular	2/4 (50)	
Tumor stage		0.512
T2-T3	17/42 (40.4)	
T4	4 /14 (28.5)	
Stage		0.025*
II	8/10 (80)	
III	13/46 (28.2)	
Surgery		
CBS	7/15 (46.6)	0.060
Mastectomy	14/41 (34.1)	
Pathologic complete response		0.290
Complete	3 /5 (60)	
Incomplete	18 /51 (35.2)	
Histologic grade		0.876
I	1/2 (50)	
II	9/26 (34.6)	
III	11/28 (39.2)	
Margins		0.134
Negative	13/43 (30.2)	
Positive	8/13 (61.5)	
Hormonal status		
ER+/PR+	18/38 (47.3)	0.002*
ER-/PR-	3/18 (16.6)	

*Significant on multivariate analysis.

radiation needs.[21] Buchholz et al.[22] have stated that the pathologic tumor size and lymph node status predicted different rates of LRR after mastectomy for BC patients treated with neoadjuvant versus adjuvant chemotherapy.

The current study data showed that disease stage and HR status were independent significant factors for distant relapse-free survival. Yadav et al. observed that, in univariate analysis, factors that correlated for distant relapse were tumor stage, response to chemotherapy, type of surgery, extracapsular extension, and tamoxifen therapy. However, multivariate analysis showed that only extracapsular extension was a significant factor related to distant relapse-free survival.[5]

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.

The current study has three main possible limitations. First, we included a relatively low number of patients. Second, we did not assess HER2 neu status due to financial issues. Hence, anti-Her 2 neu therapy was not administered in the study patients' cohort. Lastly, we lacked access to frozen sections to evaluate surgical margins at the time of surgery. Larger studies that assess

HER2 neu status and possibly imply relevant molecular markers with subsequent classification of BC into different biologic subtypes are warranted for accurate correlation with different clinicopathological factors.

Conclusion

Neoadjuvant chemotherapy was effective in clinical downstaging in the majority of our patients' cohort. This could be taken into consideration as a reasonable alternative treatment for patients with advanced BC. Neoadjuvant chemotherapy contributes to improved operability, enhanced local control, and makes breast-conserving surgery possible for many patients without affecting OS. Negative surgical margins are an independent significant factor for LRR. Hormonal receptor status and tumor stage are independent significant factors in terms of distant relapse. Further studies with larger numbers of patients, multicenter-based and implementation of different therapeutic strategies are warranted.

Conflicts of interest

No conflict of interest is declared.

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