World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

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The outcome of breast conservative surgery vs modified radical mastectomy following neoadjuvant therapy among locally advanced breast cancer patients in national cancer institute, Gezira University, Sudan

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World Journal of Biology Pharmacy and Health Sciences, 2025, 21(01), 475-481

Publication history: Received on 11 December 2024; revised on 18 January 2025; accepted on 21 January 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.21.1.0064

Abstract

Background: Locally advanced breast cancer (LABC) is still a common presentation in Sudan. Lack of awareness of guidelines lead to high rates of unnecessary mastectomies among patients with locally advanced breast cancer.

Objective: To compare the outcome of breast conservative surgery and modified radical mastectomy after neoadjuvant therapy for locally advanced breast cancer.

Patients and Methods: Descriptive, cross-sectional, and hospital-based study. Included all the patients with locally advanced breast cancer seen in the National Cancer Institute-University of Gezira from the period of December 2018 to February 2020 and who received neoadjuvant therapy followed by surgery.

Results: Forty-seven patients met the inclusion criteria of the study. The mean age of patients presented with LABC is 47.3 years (+/- 11.6 years) with the majority of patients, 31 patients (66%) less than 50 years and 24 patients (51.1%) are premenopausal. The commonest AJCC stage is stage IIIB in 37 patients (78.7%), 41 patients (87.2%) of tumors are invasive ductal carcinoma and 31 patients (66%) are estrogen receptor and/or progesterone receptor positive. Fortyone patients (87.2%) received anthracycline and taxane-based chemotherapy and 97.9% achieved partial clinical response. Breast conservative surgery was done for 13 patients (27.7%) and modified radical mastectomy for 27 patients (72.3%). There is no statistical difference in the outcome of BCS compared to MRM (P value 0.661). Negative predictive factors of the outcome include skin ulceration, negative ER/PR status, and omission of adjuvant radiotherapy (p-value < 0.05 for each variable).

Conclusion: At 15 months follow-up, there is no difference in the final outcome of BCS and MRM following neoadjuvant therapy in the LABC.

Keywords: Locally advanced breast cancer; Neoadjuvant therapy; Breast conservative surgery; Modified radical mastectomy

1. Introduction

Breast cancer is the most common cancer in females with estimated 2.1 million cases diagnosed in 2018 which represents 23% of all cancers. It is the leading cause of cancer death in more than 100 countries. [1] In Sudan breast cancer

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prevalence was found to be 3.9 cases per 100,000 female populations, with the highest rate in Khartoum state (22.1 per 100,00) and the lowest rate in Gadarif and Western Kordofan (0.3 per 100,000). The median age of diagnosis was 48 years [2]. The national cancer registry found that breast cancer is the most common cancer in females in Khartoum state with an incidence of 25.1 per 100.000 women in 2009 [3].

LABC is defined as a large tumor that has infiltrated into adjacent tissues or tumors with loco-regional lymph node involvement [4]. In Sudan, LABC is the most common presentation of breast cancer with an incidence of 55.4% out of 1255 patients presented to the NCI-Wad Medani in the period from 1999 to 2006 [5]. Another study done in the same institute found that the majority of patients with LABC (62.5%) were premenopausal [6].

The standard of care in patients with LABC is neoadjuvant systemic therapy followed by surgery, adjuvant radiotherapy, and systemic therapy if indicated. Systemic therapy whether it is pre or postoperative, includes chemotherapy, endocrine therapy in hormonal receptor-positive and HER-2 targeted therapy in HER-2 positive patients [7].

A study done in patients with LABC who received NCT to allow BCS found that BCS was feasible in 72.3% of patients with a five-year overall survival equal to MRM and higher five-year free survival in BCS compared to MRM [8]. A metaanalysis of 8 trials concluded that there is no difference between BCS and MRM in terms of local recurrence and fiveyear local recurrence-free survival [9]. A series of systematic reviews agreed that BCS is a safe option for LABC that responded well to NCT, with lower distant recurrence, a higher DFS and a higher overall survival in BCS, and good prognosis seen in patients with pathological complete response (pCR) [10-12].

2. Methodology

This study is a cross-sectional, prospective, and hospital-based study. It included all patients with locally advanced breast cancer who received neoadjuvant therapy during the period from December 2018 to February 2020 and then received surgery The patients were followed in NCI for a mean of 15 months up to November 2021. The data of the study was collected by the researcher herself using a data collection sheet from hospital records, the patients were followed using their phone number till November 2021 to document the outcome.

The data collection sheet covered all the variables including demographical data, TNM staging, response to neoadjuvant therapy, and outcome of both BCS and MRM after neoadjuvant therapy for all the patients included in the study. Data were entered, cleaned, and analyzed using Statistical Package for Social Sciences (SPSS) version 26.

Descriptive statistics were presented in terms of frequency tables with percentages and graphs. Means and standard deviations were presented with relevant graphical representations for quantitative data. Bivariable analysis between different variables and the two groups (BCS and MRM) was done using an independent chi-squared statistical test to compare the two groups. A p-value of 0.05 or less is considered statistically significant.

3. Results

From December 2018 to February 2020; one hundred and sixty patients were diagnosed with LABC, and 88 of them underwent surgery without neoadjuvant therapy. The remaining 69 received neoadjuvant therapy, of which 47 patients completed their therapy and underwent surgery, 14 developed disease progression on treatment, 8 achieved complete clinical response; received radical radiotherapy, and were put on close follow-up (those patients were counseled to do surgery or to have radical radiotherapy and they has chosen radical radiotherapy).

Only one of the 47 patients is male and the remaining are females. Patients less than 50 years are 31 (66%) patients, with the mean age being 47.3 (±11.6) years. Most of the patients are from Gezira state 32 (68.1%) patients, and 30 (63.8%) patients are from rural areas. Regarding the educational levels, 59.5% are illiterate or have just basic education and only 19.1% have higher levels of education. The majority of patients are married 39 (83%). Regarding the TNM classification and AJCC staging, most tumors are T4b, 30 (63.8%) patients. The majority of patients are stage IB, 34 (78.7%) patients. Skin ulceration is found in 12 (25.5%) patients. (Table 1).

Table 1 Demographic Characteristics of Patients (n=47)

Characteristic	Frequency	Percentage
Age (years)		
≤ 50	31	66%
> 50	16	34%
Menopausal Status		
Premenopausal	31	66%
Postmenopausal	16	34%
Rural	30	63.8%
Urban	17	36.2%
Education Level		
Illiterate	12	25.5%
Basic Education	16	34%
Secondary Education	10	21.3%
University/Postgraduate	9	19.2%
Marital Status		
Married	39	83%
Single/Divorced/Widow	8	17%
Family History of Breast Cancer	7	14.9%

The most common histopathological presentation of the tumor is invasive ductal carcinoma which represents 41 (87.2%) patients. According to Nottingham histological grading, grades II and III represent 44.7% and 42.6% respectively. Thirty (63.8%) patients have ER-positive tumors, 19 (40.4%) patients have PR-positive tumors and only 11 (23.4%) have HER-2-positive tumors. Whereas six (12.8%) patients have triple-negative tumors. Four patients (8.5%) have their hormonal receptors not done.

Regarding neoadjuvant therapy, only one patient received combined hormonal therapy (in the form of Tamoxifen) and chemotherapy while the remaining 46 (97.9%) patients received only chemotherapy. Most of the patients 46 (97.9%) patients received anthracycline-based chemotherapy. Thirty-two (68.1%) patients completed the regimen of chemotherapy (eight cycles), whereas ten patients showed improvement after six cycles or less. On the other hand, some showed response only after the addition of more cycles or after the change to second-line chemotherapy (five patients). Thirty-nine patients (83%) had a partial clinical response, seven had a complete clinical response, one had no response, and none of them developed disease progression.

After neoadjuvant therapy and assessment of operability in the combined onco-surgical clinic; 13 patients (27.7%) had undergone BCS while 34 (72.3%) had undergone MRM. Thirty-eight (80.9%) patients received adjuvant radiotherapy to the chest wall and the supraclavicular area, 40.5Gy, five sessions per week for three weeks. Only four (8.5%) patients received adjuvant chemotherapy, either taxane alone, trastuzumab alone, or taxane followed by trastuzumab

The patients were followed up until November 2021 with a mean follow-up of 15 months, twenty-seven (57.4%) patients were found alive without residual disease, six patients developed local recurrence; five of them were alive till the follow-up time they were seen in the combined onco-surgical clinic treated by chemotherapy, surgical excision or both; and one patient died 15 months after recurrence. Twelve (25.5%) patients developed distant metastasis, seven of them died of metastasis with the interval between metastasis and death ranging from one day to 18 months. Two patients died within the first six months of follow-up

Comparing the outcome of BCS and MRM following neoadjuvant therapy the study found that there is no statistical difference in the outcome of BCS and MRM, including local recurrence, distant metastasis, and death (Table 2)

Table 2 Correlation between surgical margins, type of surgery, and outcome of patients diagnosed as LABC after complete management

Presentation	**Type of surgery**	**MRM**		**BCS**	
	Surgical Margins	**Free Frequency (%)**	**Involved Frequency (%)**	**Free Frequency (%)**	**Involved Frequency (%)**
Alive	Without residual disease	16 (34%)	01 (2.1%)	10 (21.3%)	00 (0%)
	With local recurrence	04 (8.5%)	00 (0%)	00 (0%)	01 (2.1%)
	With distant metastasis	04 (8.5%)	00 (0%)	00 (0%)	01 (2.1%)
Death	Local recurrence	01 (2.1%)	00 (0%)	00 (0%)	00 (0%)
	Distant metastasis	06 (12.8%)	00 (0%)	01 (2.1%)	00 (0%)
	undiagnosed	02 (4.3%)	00 (0%)	00 (0%)	00 (0%)
Total		33 (70.2%)	01 (2.1%)	11 (23.4%)	02 (4.3%)
P value		0.96		0.005	

Demographic characteristics of the patients, clinical characteristics of the tumor (except skin ulceration), and histology of the tumor have no significant effect on the outcome of both MRM and BCS (P value > 0.05 for each).

Skin ulceration was found to impact the outcome significantly (88.9% of patients who are alive without residual disease have no history of skin ulceration) (P value 0.010) .The presence of skin ulceration significantly increases local recurrence (66.7% of patients with local recurrence have a history of skin ulceration)

Hormonal receptor status strongly correlates with the outcome, the percentage of patients alive without residual and having ER±PR positive is 21 patients out of 27 (77.8%) (P value 0.014). In contrast, patients with negative ER/PR are found to have local recurrence in four out of six patients (66.7%) (P value 0.044).

Adjuvant radiotherapy has been shown to affect the outcome (P value < 0.001). Distant metastasis occurs in 55.6% of patients who did not receive adjuvant therapy (P value 0.022)

Surgical margins were found to have an impact on the outcome of BCS (P value 0.005) but not MRM (P value 0.96). The presence of the involved margin increases the local recurrence rate in BCS (P value 0.015)

4. Discussion

The study has shown that the mean age of the patients at diagnosis was 47.3 (±11.6) years, which is consistent with the presenting age in previous studies done in Sudan in LABC, which showed the mean age of presentation of 47 years [6]. Twenty-five patients (51%) were premenopausal is equal to what was found by Mohamed AA, et al. 53.7% (44and less than the incidence concluded by Ahmed AA, et al. which showed that 62.5% of LABC were premenopausal [6] and what was found by Abuidris DO, et al. that found 72.7% of patients were less than 50 years [12].

Regarding the TNM staging, T3 had six patients (12.8%), T4b which was the commonest 29 patients (61.7%), T4c had ten patients (21.3%), and T4d were two patients (4.3%); with overall percentage of T4 is 87.3%. This is almost close to the percentage found by Gogia A., et al. which showed the T4 percentage in LABC to be 80%, and T3 to be 15% [13], and it is less than Ahmed AA, et al. result where T4b represents 78.5% [6]. N1 is found to be 40.4%, N2 (25.5%), N0 (25.5%), and N3 (8.5%) which is different from what was found by Gogia A, et al. which showed the highest percentage of N2 43% [13].

The most common histological tumor type is IDC 87.2%, similar to the result of Sengal AT, et al. 86% [14] and slightly higher than Elbasheer MM, et al. 79.5% 5, Elamin AA, et al. 82% 68 and Elgaili EM, et al. 82% 23. ILC was found to be

4.3%, which is slightly higher than in Gogia et al 2.5% [13]and Abuidris DO, et al. 3.6% [15]. Grade II and grade III were 44.7% and 42.6 respectively, which is different from other studies done in LABC that showed the dominance of grade III, followed by grade II and the lowest percentage of grade I [2,6].

Neoadjuvant therapy given was chemotherapy only in 46 patients (97.9%) and only one patient (2.1%) received combined chemotherapy and hormonal therapy (Tamoxifen). The most commonly used regimen is mixed anthracyclines and taxanes based chemotherapy in 85% with the commonest being EC followed by Docetaxel in 53.2%, 6.4% received anthracycline and taxane and shifted to the second line (vinorelbine/cisplatin), 6.4% received anthracycline-based chemotherapy, and 2.1% received taxane-based chemotherapy. This is consistent with NCCN Clinical Practice Guidelines in Oncology which indicate a preference for neoadjuvant regimens that contain both an anthracycline and taxane for patients with LABC given the superior outcome of these regimens in the adjuvant setting for patients with lymph node-positive disease [7].

BCS was done in 13 patients (27.7%) and MRM in 34 patients (72.3%). The percentage of BCS is still lower than the percentage which was found to be 44.5% in a meta-analysis of 16 studies (3531 patients) (55), and 64.5% according to a cohort study done by Simons JM, et al. [16].

Twenty-seven patients (57.4%) were found alive without residual disease, six patients developed local recurrence; five of them were alive till the follow-up time they were seen in the combined onco-surgical clinic treated by chemotherapy, surgical excision, or both; and one patient died 15 months after recurrence. Twelve patients (25.5%) developed distant metastasis, seven of them died of metastasis with the interval between metastasis and death ranging from one day to 18 months. Two patients died within the first six months of follow-up.

In comparison between the outcome of BCS and MRM following neoadjuvant therapy, there is no statistical difference in the final outcome of both BCS and MRM (p-value = 0.661). This is similar to what was concluded by several studies done in this era that showed equal disease-free survival and overall survival in both types of surgery [11,16,17].

Skin ulceration is found to have a negative impact on the outcome of both BCS and MRM; it is found that it is associated with increased incidence of local recurrence (P value 0.013), Huang, et al. have found a negative effect of skin involvement on local recurrence [18].

ER/PR negative status is associated with a higher recurrence rate (66.7%) while ER and/or PR positive associated with a lower recurrence rate (P value 0.044), this was also stated by Angelucci D, et al. and Huang, et al. [18,19].

Adjuvant radiotherapy is found to affect the final outcome regardless of the type of surgery (P value < 0.001). Distant metastasis is seen in 58.3% of patients who did not receive adjuvant radiotherapy (P value 0.022). But-Hadžić, et al. found that adjuvant radiotherapy increases DFS and OS in patients with LABC and concluded that adjuvant radiotherapy should be given regardless of the response to neoadjuvant chemotherapy (58).

The outcome of BCS was found to be affected negatively by an involved surgical margin in that it increased the local recurrence rate (P value 0.015). Beriwal S, et al. stated that a positive margin is significantly correlated with ipsilateral breast recurrence (73).

Abbreviations

- BCS=Breast conservative surgery
- IDC=Invasive ductal carcinoma
- LABC =Locally advanced breast cancer
- MRM =Modified radical mastectomy
- NAT= Neoadjuvant therapy
- NCCN= National Comprehensive Cancer Network NCI =National Cancer

5. Conclusion

At 15 months follow-up, there is no difference in the final outcome of BCS and MRM following neoadjuvant therapy in the LABC.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Statement of ethical approval

Ethical approval was optainned from the Research and Ethics committee of Sudan medical specialization board .

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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