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Original Research Article

Role of conservative breast surgery in locally advanced breast cancer after neoadjuvant chemotherapy

Alaa A. El Sisi[1], Mahmoud G. Hagag[1], Mohammed G. Hegazi[2]*

[1]Department of General Surgery, Faculty of Medicine, Menoufia University, Menoufia, Egypt
[2]Department of Surgical Oncology, Tanta Cancer Center, El Gharbia, Egypt

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***Correspondence:**
Dr. Mohammed G. Hegazi,
E-mail: mohammedhegazi54@gmail.com

ABSTRACT

Background: Locally advanced breast cancer represents 20%-25% of breast cancer patients at diagnosis. The aim of this prospective study was to assess the feasibility and the oncologic outcome in the treatment of patients of locally advanced breast cancer that had been downstaged by neoadjuvant chemotherapy to the extent that makes them eligible for conservative breast surgery.
Methods: This prospective study was done on 50 female patients who were diagnosed with locally advanced breast cancer and received neoadjuvant chemotherapy to downstage cancer making it eligible for conservation, managed and treated at El Menoufia University Hospital and Tanta Cancer Center from March 2017 to March 2018 after applying inclusion and exclusion criteria. The collected data were organized, tabulated and statistically analyzed using SPSS software.
Results: Significant difference between pre and post-chemotherapy tumor size in patients with locally advanced breast cancer. Conservative breast surgery with intraoperative frozen section assured free margins in all of them with acceptable cosmetic outcome. No local recurrence recorded after one year of follow up.
Conclusions: In the present study, it was observed that conventional neoadjuvant chemotherapy is effective in downgrading the tumor size and axillary lymph nodes in patients with locally advanced breast cancer. Breast conservation after neoadjuvant chemotherapy is safe in terms of local recurrence.

Keywords: Conservative breast surgery, Locally advanced breast cancer, Neo-adjuvant chemotherapy

INTRODUCTION

Breast cancer is the most common site-specific cancer in women and is the leading cause of death from cancer in women aged 20 to 59years.[1]

Locally advanced breast cancer continues to be a significant problem in the United States and a common breast cancer presentation worldwide.[2]

Locally advanced breast cancer is a term that refers to most advanced stage non-metastatic breast tumors and includes a wide variety of clinical scenarios. These tumors remain a difficult clinical problem as most patients with locally advanced disease will experience disease relapse and eventual disease.[3]

Author defined any tumor that is greater than 5cm or that involves the skin or chest wall as locally advanced. The locally advanced disease also includes patients with fixed axillary lymph nodes or ipsilateral supraclavicular, infraclavicular or internal mammary nodal involvement. Thus, all of stage III disease is considered locally advanced as is a subset of stage IIB (T3N0).[4]

In locally advanced breast cancer, one of the goals of the neo-adjuvant chemotherapy is to convert inoperable tumor into an operable tumor. In these patients NACT may allow adequate control of the disease impossible with surgery alone, Moreover, after NACT the patients may be treated with breast-conserving surgery.[5]

Breast-conserving surgery combined with postoperative radiotherapy has become the gold standard of loco-regional treatment for the majority of patients with early-stage breast cancer, offering equivalent survival as compared to mastectomy and improved body image and lifestyle scores. The goals of BCS were to achieve complete removal of the tumor with adequate surgical margins while preserving the natural shape and appearance of the breast. In some cases, achieving both goals may be quite challenging and the need to ensure an oncological safe resection may generate unsatisfying cosmetic results.[6]

Nowadays, up to 80% of patients are treated with breast conservation which is known to be the best method for treating breast cancer when concerning the psychological sequelae to the patient. Large randomized studies have demonstrated that conservative treatment of breast cancer is safe for tumors up to four to five cm. However, a clear margin of 10mm was recommended to keep the local recurrence rate acceptable. With the oncological methods of downstaging large tumors with preoperative chemotherapy or hormonal therapy.[7]

The aim of this work was to assess the feasibility and the oncologic outcome in the treatment of patients with locally advanced breast cancer who had been downstaged by neoadjuvant chemotherapy to the extent that makes them eligible for conservative breast surgery.

METHODS

This prospective study was done on 50 patients diagnosed with locally advanced breast cancer who received neoadjuvant chemotherapy to downstage cancer making it eligible for conservation, managed and treated at El Menoufia University Hospital and Tanta Cancer Center from March 2017 to March 2018. Informed consent was taken from all patients and after approval of the ethical committee of the faculty of medicine.

Inclusion criteria were all patients with complete resolution of skin edema, residual tumor size of less than 5cm, no evidence of multicentric cancer, no previous radiation to the breast or chest wall, normal cardiac, hepatic and renal function (chemotherapy), absence of extensive lymph nodes involvement or diffuse microcalcification and negative surgical margins achieved intra-operatively.

Exclusion criteria were patients with T4 tumors with partial or no response to neoadjuvant chemotherapy, patients with a multicentric disease, patients with diffuse malignant mammographic microcalcification, patients with inflammatory carcinoma, previous breast radiotherapy, scleroderma, pregnant women, a large tumor in the small breast and in whom clear margins can't be assessed without performing a mastectomy.

All patients in the study were subjected preoperatively to full history taking, complete examination including (name, age, family history, residence, previous radiation exposure, general and local examination), imaging including (mammography with complementary ultrasound to measure tumor size, CT chest, CT scan of abdomen and pelvis and bone scan) and true-cut biopsy from breast mass.

A radiopaque clip was placed to mark the primary tumor site and the patient was followed with ultrasound imaging during chemotherapy treatment.

Type of surgery was conservative breast surgery with intraoperative frozen section.

Postoperatively, the patients were subjected to early follow-up every week for the first month (with the objective of verifying the surgical incision, local hygiene, presence of hematomas, wound dehiscence, seroma and infection) and late follow up after 3months, 6months and one year as the patients were examined with breast mammography with complementary ultrasonography for evaluation of local recurrence.

During the follow-up, the patients were asked to rate their degree of satisfaction and the overall Cosmetic outcome was evaluated after 6months by the Harvard scale.

Postoperative radiotherapy was given to all of the cases which would reduce the incidence of local recurrence after conservative surgery.

RESULTS

The age of the patients as shown in (Table 1) ranged from 35 to 60 years with a mean value±SD of 47.78±6.85.

Twenty-nine patients had different co-morbidities, 21 of them had more than one co-morbidity. 22 patients were recorded with DM, 24 of them were recorded with hypertension and 9 patients were known to be cardiac with good systolic function as shown in (Table 1).

As regards the risk factors, 3 patients were nulliparous, 10 were on OCP and positive family history was recorded in 8 patients as shown also in (Table 1). 29 patients (58%) were presented with left breast mass and 21 patients (42%) were presented with right breast mass as shown in (Table 2).

In present study, 23 patients (46%) were presented with breast mass in UOQ, 12 patients (24%) were presented with breast mass in LOQ, 10 patients (20%) were

presented with breast mass in UIQ and 5 patients (10%) were presented with breast mass in LIQ (Table 2).

Table 1: Patients demographic characteristics.

Parameters	No.	%
Total patients	50	100.0
Age		
≤45	23	46.0
45-50	10	20.0
>50	17	34.0
Min.-Max.	35.0-60.0	
Mean±SD.	47.78±6.85	
Median	46.50	
Co-morbidity		
Negative	21	42.0
DM	22	44.0
HTN	24	48.0
IHD	9	18.0
Family history		
Positive	8	16.0
Negative	42	84.0
Oral contraceptive pills (OCP)		
No	40	80.0
Yes	10	20.0
Nulliparous		
No	47	94.0
Yes	3	6.0

A true-cut biopsy was done for all studied cases. 44 patients (88%) were IDC, one patient (2%) was ILC and 5 of them (10%) were mixed ductal and lobular carcinoma (Table 2).

Thirty-nine patients (78%) had moderately differentiated tumors G2 and 11 patients (22%) had poorly differentiated tumors G3 (Table 2).

Evaluation of the tumor size before receiving neoadjuvant chemotherapy revealed that 3 patients (6%) had T1 lesion, 5 patients (10%) had T2 lesion, 29 patients (58%) had T3 lesion and 13 patients (26%) had T4 lesion (Table 2).

Evaluation of lymph node status before receiving neo-adjuvant chemotherapy revealed also that 8 patients (16%) had N0, 27 patients (54%) had N1 and 15 patients (30%) had N2 as shown in Table 2.

Present study had shown that 7 patients (14%) with locally advanced breast cancer were presented with (Stage IIB), 30 patients (60%) were presented with (Stage IIIA) and 13 patients (26%) were presented with (Stage IIIB) as shown in (Table 2). Intraoperative frozen section was done and free margins were assured in all of the 50 patients as shown in Table 2. There were 39 patients (78%) were categorized as luminal A, 5 patients (10%) as luminal B, triple negative in 5 patients (10%) and Her2+ in 1 patient (2%) as shown in (Table 2). Evaluation of pre and post-chemotherapy tumor size was done for the 50 patients who received neoadjuvant chemotherapy.

Table 2: Distribution of the studied cases according to tumor characteristics.

Parameters	No.	%
Side		
Right	21	42.0
Left	29	58.0
Tumor site		
UOQ	23	46.0
LOQ	12	24.0
UIO	10	20.0
LIQ	5	10.0
TRU-CUT		
IDC	44	88.0
ILC	1	2.0
Mixed ductal and lobular ca.	5	10.0
Nuclear grading		
II	39	78.0
III	11	22.0
Clinical tumor stage (pre-chemotherapy)		
T1	3	6.0
T2	5	10.0
T3	29	58.0
T4	13	26.0
Clinical lymph node stage (pre-chemotherapy)		
N0	8	16.0
N1	27	54.0
N2	15	30.0
Tumor stage (pre-chemotherapy)		
3A	30	60.0
2B	7	14.0
3B	13	26.0
Pathological tumor size		
Min.-Max.	1.0-3.80	
Mean±SD.	2.29±0.72	
Median	2.30	
Pathological N staging		
Negative	14	28.0
Positive	36	72.0
Hormone receptor		
Luminal A (ER+PR+HER-)	39	78.0
Luminal B (ER+PR+HER+)	5	10.0
Triple -ve (ER-PR-HER-)	5	10.0
HER2 +ve (ER-PR-HER+)	1	2.0
Safety margin		
Negative	50	100.0
Positive	0	0.0

Mean tumor size prior to chemotherapy was 4.65±1.65cm ranging from 1.5 to 7cm. However, mean tumor size after neo-adjuvant therapy was 2.32±0.8cm ranging from 1cm to 4cm. Statistical analysis of those results revealed a

significant statistical difference where P value <0.001 as shown in Table 3.

Table 3: Comparison between pre-chemo tumor size, post-chemo tumor size and pathological tumor size.

Chemotherapy radiological tumor size	Pre-chemo tumor size (n = 50)		Post-chemo tumor size (n = 43)		Pathological tumor size (n= 43)		P
	No.	%	No.	%	No.	%	
<2	3	6.0	13	25.6	15	30.2	
2-5	16	32.0	37	74.4	35	69.8	<0.001*
>5	31	62.0	0	0.0	0	0.0	
Sig.bet.Grps	p_1<0.001*, p_2<0.001*, p_3=0.746						
Min.-Max.	1.50-7.0		1.0-4.0		1.0-3.80		
Mean±SD.	4.65 1.65		2.32±0.80		2.29±0.72		<0.001*
Median	5.30		2.10		2.30		
Sig.bet.Grps	p_1<0.001*, p_2<0.001*, p_3=0.332						

p1: p value for comparing between pre-chemo tumor size and post-chemo tumor size, p2: p value for pre-chemo tumor size and Pathological tumor size p3: p value for Post-chemo tumor size and Pathological tumor size, *: Statistically significant at P ≤0.05.

In present study, 11 cases (22%) were complicated with seroma that was detected clinically and confirmed by U/S. Wound infection occurred in 4 patients (8%) and Hematoma occurred in two cases (4%) as shown in Table 4.

Table 4: Distribution of the studied cases according to complication.

Complications	No.	%
Post-operative wound infection	4	8.0
Seroma	11	22.0
Hematoma	2	4.0

Regarding the postoperative follow up after three, six months and one year, one case (2%) missed the following up postoperative with author. The 49 remaining cases (98%) were followed up with no local recurrence recorded. According to response to chemotherapy, partial response was observed in 41 patients (82%), complete response was detected in 7 patients (14%) and two cases (4%) were presented with a stationary disease as shown in Table 5.

Table 5: Distribution of the studied cases according to response to chemotherapy.

Response to chemo	No.	%
PR	41	82.0
CR	7	14.0
SD	2	4.0

All the 50 followed up cases were evaluated for the cosmetic outcome by Harvard scale, 43 (86%) of them were with excellent outcome. Good outcome was in 4 (8%) patients and 3 (6%) cases with a fair outcome as shown in Table 6.

Table 6: Distribution of the studied cases according to the cosmetic outcome.

Cosmetic outcome	No.	%
Poor	0	0.0
Fair	3	6.0
Good	4	8.0
Excellent	43	86.0

All the 50 followed up cases were asked to rate their degree of satisfaction, accordingly, graded into good, fair and poor satisfaction. 27 (54%) patients rated excellent satisfaction, 16 (32%) patients rated good satisfaction with only 5 (10%) with fair satisfaction and the poor score was rated in two cases (4%) as shown in Table 7.

Table 7: Distribution of the studied cases according to patient satisfaction.

Patient satisfaction	No.	%
Poor	2	4.0
Fair	5	10.0
Good	16	32.0
Excellent	27	54.0

DISCUSSION

Breast conservation is indeed a wise and attractive option in patients with early breast cancer. With the development of active chemotherapy regimens, it is now possible to extend breast conservative treatment to some patients with locally advanced breast cancer.[8] Overall outcome and local control rates have improved markedly with multimodal therapy, including neo-adjuvant chemotherapy plus surgery and loco-regional radiation.[7] This study aimed to assess the feasibility and the oncologic outcome in the treatment of patients with

locally advanced breast cancer that had been downstaged by neoadjuvant chemotherapy to the extent that makes them eligible for breast conservative surgery. In this study, 46% of patients were <45years old, 20% of patients were 45-50years old and 34% of patients were >50years old with mean of age was 47.78years, That was close to the results of the study done by Barranger E et al, which was conducted on 119 female patients with a mean of 49.6years old and close to the results of Mashoori N et al, that stated that mean of age was 43.52.[9,10]

In the present study, 6% of patients had T1 lesion, 10% of patients had T2 lesion, 58% of patients had T3 lesion and 26% had T4 lesion. This doesn't agree with Parmar V et al, who stated that 30.9% of patients had T1-T3 lesion and 69.1% of patients had T4 lesion, there was a significant difference because of the higher rates of lymph node involvement in the present study.[11] This study was close to the results of Sweeting RS et al, that stated that 6% of patients had T1 lesion, 24% of patients had T2 lesion, 63% of patients had T3 lesion and 7% of them had T4 lesion.[12] Evaluation of pre and post-chemotherapy tumor size was done for the 50 patients who received neoadjuvant chemotherapy. Mean tumor size prior to chemotherapy was 4.65cm. However, mean tumor size after neo-adjuvant therapy was 2.32cm. This was close to the results of Parmar V et al, who stated that mean tumor size prior to chemotherapy was 6cm and mean tumor size after neoadjuvant chemotherapy was 1.5cm.[11]

In the present study, 16% of patients had N0, 54% of patients had N1 and 30% of patients had N2. This agrees with El-Sayed MI et al, study that stated that 20% of patients had N0, 55% of them had N1 and 25% of them had N2.[13] This study included 14% of patients who were presented with locally advanced breast cancer stage IIB, 60% of them with stage IIIA and 26% of them with stage IIIB. Similar to Shin HC et al, study which stated that 63.5% of patients presented with stage IIIA and 36.5% with stage IIIB, however they had excluded Stage IIB group in their study and close to Salem MA et al, study which stated that 18% of patients presented with stage IIB, 57% of patients presented with stage IIIA, 16% with stage IIIB and 9% were stage IIIC.[14,15]

In this study 88% of patients had IDC, 2% of patients had ILC and 10% of patients had mixed ductal and lobular carcinoma. This agrees with Mashoori N et al, who stated that 91.2% of patients had IDC and 8.8% of them had ILC and close to the results of Rahman MS et al, study which stated that 80.45% were classified as IDC, 13.64% as ILC and 5.91% as mixed invasive patterns.[10,16] Intraoperative frozen section was a method for margin evaluation which allowed us for resection of suspicious or positive margins at the time of lumpectomy and therefore free margins were assured in all of the 50 patients resulting in low rates of local recurrence and re-excision. This was similar to the results of Costa SD study.[17] While Mittra I et al, reported that 2.4% of patients with BCS showed positive margins.[18] This difference may be explained by a large number of patients in their study (726 patients) than in this study (50 patients). In this study, 88% were ER/PR-positive and 12% were Her2-positive, this doesn't agree with Vieira RA et al, that stated that 61.5% were ER-positive, 52.6% were PR-positive and 23.1% were Her2-positive and close to the results of El-Sayed et al, study who stated that 21% of patients were Her2-positive and very near to results reported by Rahman MS et al, which stated that 69.09% were found estrogen receptor positive tumor.[13,16,19]

According to response to chemotherapy, partial response was observed in (82%) of patients, complete response was detected in (14%) of patients and (4%) of them were presented with stationary disease, this agree with Rahman MS et al, study that stated that 18% had CR, 75% had PR and 7% had SD and agree with Salem MA et al, study that stated 9% had complete response, 79% had partial response and 10% had stationary disease and 2% had progressive disease.[15,16] In the present study, 22% of cases were complicated with seroma that was detected clinically and confirmed by U/S and wound infection occurred in 8% of them. When compared to Ranisavljević M et al, study, seroma was seen in 10% and wound infection in 6% of cases.[20] Meaning that seroma was the most frequent complication in present study like (Ranisavljević M et al) study. Obesity, older age and diabetes mellitus were recognized as risk factors for early postoperative complications and the use of preoperative antibiotic coverage was noticed to minimize infection rates. Meticulous manipulation of breast tissue, following the strict rules in Conservative breast surgery, the duration of surgery, closing the dead space with sutures and the use of electrocautery could explain the difference in seroma incidences.

In this study, postoperative radiotherapy was given to all of the cases which reduce the incidence of local recurrence after conservative surgery. No local recurrence was observed after 3, 6 and 12months in the 49 followed up cases. Compared to Mashoori N et al, study with a longer follow up period for 1.5year, local recurrence was reported in one case and when compared to the results of Levy A et al, that reported local recurrence in 9% of cases, There was a significant difference because of the long period of follow up for 5years and the larger number of cases.[10,21] Therefore, breast preservation should be an appropriate option of loco-regional treatment as local recurrence rate risk seemed to be more related to histologic patterns when loco-regional management was optimal (negative margins, postoperative radiotherapy). The followed-up cases were evaluated for the cosmetic outcome by Harvard scale, 86% of them were with excellent outcome. Good outcome was in 8% patients and 6% cases with fair outcome compared to the results of Tewari M et al, which found a good to excellent cosmetic result in 73% of patients and a fair result in 27%.[8]

CONCLUSION

Patients of locally advanced breast cancer who were included in this study and underwent treatment with neo-adjuvant chemotherapy had shown excellent response through downstaging the tumor size, axillary lymph nodes and pathological response. So, author may conclude that the conventional neoadjuvant chemotherapy is effective in this study. Breast conservation after neo-adjuvant chemotherapy is safe in terms of local recurrence in women with locally advanced breast cancer during the limited follow-up time of this study.

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