Optimal time for breast-conserving surgery after neoadjuvant chemotherapy in patients with stage II or III breast cancer

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Background
During past decades, neoadjuvant chemotherapy was limited to inoperable breast cancer; however, nowadays, neoadjuvant chemotherapy has led to an increase in the rates of breast-conserving therapy, a decrease in the extent of local treatment (e.g. axillary dissection), and as a result, better cosmetic outcomes. Other benefits of neoadjuvant chemotherapy that made this method popular include prognostic and therapeutic information based on in vivo tumor response, turning inoperable tumors into operable ones, and providing enough time for genetic testing and breast reconstruction.

Objective
To evaluate the effect of time to surgery after preoperative chemotherapy in patients with stage II or III breast cancer who were candidates for breast-conserving surgery according to the primary objective of the locoregional recurrence (include the affected breast and its involved lymph nodes) and the secondary objective of the assessment of postoperative complications and healing process of the wound.

Patients and methods
This is a prospective randomized study conducted on 60 patients with stage II or III breast cancer indicated for breast-conserving surgery after neoadjuvant chemotherapy at the General Surgery Department at Ain Shams University Hospitals starting from October 2019 to October 2021. Approval of the ethical committee and written informed consent from all participants were obtained. We divided the study sample into two groups: 30 female patients who underwent breast-conserving surgery after neoadjuvant chemotherapy within 3 weeks from the last chemotherapy session (group A) and 30 female patients who underwent breast-conserving surgery after 3 weeks from the last chemotherapy session but not more than 4 weeks (group B).

Results
In our study, the first group included patients who underwent operation within 3 weeks from ending the neoadjuvant chemotherapy and the second group included those who underwent operation within 4 weeks. We followed up them and analyzed different variables like local recurrence, intraoperative blood loss, operative time, delayed wound healing, and seroma formation. All of these variables were found to be statistically nonsignificant.

Conclusion
There is no difference in doing operations after neoadjuvant chemotherapy either within 3 or 4 weeks as it does not affect the outcomes clinically or statistically.

Keywords:
breast cancer, breast neoplasm, breast tumors, malignant neoplasm of breast, malignant tumor of breast, mammary cancer

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Introduction

Breast cancer is the most common cancer diagnosed in women, accounting for more than one in 10 new cancer diagnoses each year. It is the second most common cause of death owing to cancer among women in the world [1].

Breast cancer always evolves silently. Most of the patients discover their disease during their routine screening, whereas others may present with an accidentally discovered breast lump, change of breast shape or size, or nipple discharge. However, mastalgia is not uncommon. Physical examination, imaging especially mammography, and tissue biopsy must

be done to diagnose breast cancer. The survival rate improves with early diagnosis. The tumor tends to spread lymphatically and hematologically, leading to distant metastasis and poor prognosis. This explains and emphasizes the importance of breast cancer screening programs [2].

The WHO has approved breast-conserving surgery besides mastectomy in the treatment of malignant breast lesions in 1996 [3], which is the entire removal of the tumor with safety margin and preservation of as much breast tissue as possible (confirmed by frozen section followed by adjuvant radiotherapy) [4].

However, not all patients were candidates for breast conservation putting in consideration many factors such as breast size, multicentricity, and adjacency to the nipple areola complex, as well as some aesthetic inconvenience [5].

Aim

The aim was to evaluate the effect of time to surgery after preoperative chemotherapy in patients with stage II or III breast cancer candidates for breast-conserving surgery according to the primary objective of the locoregional recurrence (include the affected breast and its involved lymph nodes) and the secondary objective of the assessment of postoperative complications and healing process of the wound.

Patients and methods

This is a prospective randomized study conducted on 60 patients with stage II or III breast cancer indicated for breast-conserving surgery after neoadjuvant chemotherapy at the General Surgery Department at Ain Shams University Hospitals starting from October 2019 to October 2021. Approval of the Ethical Committee and written informed consent from all participants were obtained.

Study sample

This study included 60 female patients with breast cancer after neoadjuvant treatment, who were divided into two groups: group A included 30 female patients who underwent breast-conserving surgery after neoadjuvant chemotherapy within 3 weeks from the last chemotherapy session, and group B included 30 female patients who underwent breast-conserving surgery after 3 weeks from the last chemotherapy session but not more than 4 weeks.

Patient selection

Patients were selected by sealed envelope technique randomization, where the patients were given randomly closed opaque envelopes that classified each patient to either group A or group B.

Inclusion criteria

Female patients ranging from age of 18–60 years old, co-operative patients, psychologically stable patients, and patients with breast cancer stage II or III who underwent neoadjuvant chemotherapy were included.

Exclusion criteria

Any female patient indicated for MRM (advanced breast cancer not responding to chemotherapy and inflammatory breast cancer), conversion of breast-conserving surgery to mastectomy, failure of downstaging of the breast tumor after neoadjuvant chemotherapy, recurrent malignancy following breast-conserving surgery, and bilateral female breast cancer were the exclusion criteria.

Methods

All patients included in the study were candidates for the following:

Clinical assessment

It included detailed medical (any chronic diseases) and surgical history; menstrual history, that is, last menstrual period – date of first day of bleeding, cycle length and frequency, for example, 5/28, 5 days of bleeding every 28 days, heaviness of bleeding. (number of tampons per day/clots/flooding/need for double protection), and presence or absence of intermenstrual bleeding; family history (any family member with breast cancer or any other type of cancer); history of intake of oral contraceptive pills or hormonal replacement therapy with estrogen and progesterone; and general examination. Full breast and axillary examinations were done as follows: the examiner introduced himself/herself to the patient and explained to the patient what the examination involved. It is important to check the patient's understanding of the examination. Then, the patients were positioned at 45°. A chaperone was present during the examination. The patients were asked to remove their clothing to expose their chest, from above the waist. A blanket was provided for the patients to cover themselves when not required to expose the breast. The patients were inspected from the end of the bed. Any obvious masses, scars, or asymmetries were checked. The patients were asked to place their hands by their sides to compare both breasts. Any obvious scars or masses present; the size and position of any observed masses; any skin changes or ulcerations; erythema, puckering, or peau d'orange (orange peel appearance due to edema); and any nipple changes, nipple discharge, or inversion were noted. The patients were asked to place both their hands behind their head, and this inspection was repeated to

accentuate any asymmetry. The axillae are inspected for any obvious masses. Each quadrant of the breast was examined in turn, including the axillary tail (also termed the 'Tail of Spence'). Using a flat hand, the breast was pressed against the underlying chest wall, rolling the underlying tissue. The examination was started with the 'normal' side first, while examining any painful areas last. If there are any lumps, their position, size, shape, consistency, overlying skin changes, and mobility were noted. The fixity of lumps to pectoralis muscles was examined by asking the patients to push against the examiner's hand with their hand outstretched. Both axillae were examined in turn. When examining the right axilla, the examiner held the patients' right arm with his/her right hand and examined the axilla with his/her left hand. When examining the left axilla, the examiner held the patients' left arm with his/her left hand and examined the axilla with his/her right hand. Palpation was done for any lymphadenopathy (five sets of axillary lymph nodes are present: apical, anterior, central, posterior, and medial). To fully examine a breast, one should also remember to assess for potential metastasis by palpating the spine for tenderness, palpating the abdomen for hepatomegaly, and performing percussion and auscultation of the lungs for lung masses. The patients were thanked and asked redress.

Investigations

Routine laboratory investigations, such as bilateral sonomammography, abdominal and pelvic ultrasound, chest radiograph/computed tomography chest, MRI if needed, and bone scan if patients complained of bone aches or stage III breast cancer, were done. Histopathological examination of the suspicious breast mass was done by ultrasound-guided tru-cut needle biopsy, and also histopathological examination for suspicious axillary lymph nodes was done. Immunohistochemical examinations were done (ER, PR, and Her2).

Multidisciplinary team

To take any medical or surgical decision for any patient in the breast unit at the General Surgery Department of Ain Shams University Hospitals, the decision was discussed with a group of senior staffs from the oncology, radiology, pathology, and surgery departments. The discussion was done with a power-point presentation of data that showed a detailed history of the patient and images of the suspicious breast mass. After the discussion, all of the lines of treatment were revealed and discussed with the patient, so that the patient could participate in the study fully informed and oriented to their treatment modality. The patients provided their consent.

Intervention

Patients were subjected to conventional breast-conserving surgery after a fixed regimen of neoadjuvant chemotherapy: four cycles anthracycline and taxane-containing regimen (four AC–three TAX), with addition of a specific regimen for HER2-positive patients (herceptin/perjeta).

All of the patients underwent re-assessment for their breast lesion after the neoadjuvant chemotherapy to detect its downstaging effect.

Operative techniques: before the surgery, all of the patients were consented to undergoing breast-conserving surgery with the possibility of mastectomy if the surgeon failed to eradicate the tumor with a suitable safety margin (tumor-free area in the frozen section intraoperatively). All of the patients were told to fast for at least 8 h before the surgery. The suspicious breast mass was marked either with a colored marker when it was palpable or when the mass was not palpable, localization was performed either preoperatively by stereotactic guide-wire placement or by placement of wire and needle on the operating table using a high-resolution ultrasonography. The surgery began by marking out the wise pattern. The next step was to excise it with wide margins by going through one of the limbs of the wise pattern. The tumor and its quadrant were then widely excised through either circumareolar excision or radial line. After this step, the shaved margins of the cavity were further excised and sent for frozen sections. Once clarity about the tumor margins of the excision cavity was achieved, the surgeon could declare the tumor was grossly removed, as our surgical technique encompasses excision of a suitable volume of breast mass dictated by the extent and site of the tumor.

Postoperative care: the National Canadian clinical practice guidelines recommend that RT should be given less than 12 weeks after breast-conserving surgery to keep the incidence of local failure and disease-free survival (DFS) similar to that of mastectomy.

Follow-up

Short-term follow-up (within 3 months)

All patients were followed after intervention every week for the first 2 weeks and then every 2 weeks for wound healing assessment and early wound complications either hematoma or postoperative infection.

Long-term follow-up (within 2 years)

Follow-up time for the patients had been every 3 months for the following: loco-regional recurrence and aesthetic satisfaction.

Statistical analysis

Data were collected, revised, coded, and entered to the Statistical Package for the Social Sciences (IBM SPSS), version 26 (IBM Inc., Chicago, IL, USA). The quantitative data were presented as mean, SDs, and ranges. Moreover, qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done using χ^2 test and/or Fisher exact test when the expected count in any cell was found to be less than 5. Independent *t* test was used to compare between two quantitative parameters with parametric distribution. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *P* value was considered significant as follows: *P* value more than 0.05: nonsignificant, *P* value less than 0.05: significant, and *P* value less than 0.01: highly significant.

Results

Our study was done on 60 patients who were divided into two groups: group A included 30 female patients who underwent breast-conserving surgery after neoadjuvant chemotherapy within 3 weeks from the last chemotherapy session, and group B included 30 female patients who underwent breast-conserving surgery after 3 weeks from the last chemotherapy session but not more than 4 weeks. The mean age in group A was 42.35 ± 10.6 years, whereas that of group B was 42.93 ± 9.81 years, as shown in Table 1.

No patients had local recurrence within the first year of follow-up in our study.

Table 2 shows the difference between the two groups regarding different variables, which are intraoperative time, intraoperative blood loss, hospital stay, intraoperative blood transfusion, seroma formation, delayed wound healing, and immunohistopathology. All of them was statistically nonsignificant. However, the difference between both groups regarding tumor size after neoadjuvant chemotherapy was statistically significant, with *P* value of 0.049, where size in patients who had neoadjuvant chemotherapy within 3 weeks was larger than that of 4 weeks.

Figure 1 shows the cosmetic outcome for the patients who had operations after 3 weeks of chemotherapy. Regarding delayed wound healing, we found that two patients had delayed wound healing but their cosmetic outcome was good, whereas three of 28 patients who did not experience delayed wound healing had poor cosmetic outcome, seven had fair cosmetic outcome, eight had good cosmetic outcome, and 10 had excellent outcome. The total number of patients who had good and excellent cosmetic outcome was 33% for both groups. Figure 2 shows the cosmetic outcome for the patients who had operations after 4 weeks chemotherapy. Regarding delayed wound healing, we found that two patients had delayed wound healing, but their cosmetic outcome was fair, two had good cosmetic outcome, and one excellent cosmetic outcome. However, one of 28 patients who did not experience delayed wound healing had poor cosmetic outcome, nine had fair cosmetic outcome, 11 had good cosmetic outcome, and four had excellent outcome. The total number of patients who had fair and good cosmetic outcomes was 36.7 and 43.3% for groups A and B, respectively.

Table 3 represents the number of patients having a family history of cancer breast in both groups.

In our study, we found that patients having a positive family history of cancer breast was 10 in group A and four in group B, with a total of 14 (23.3%) patients in the whole sample having family history of cancer

Table 1 Patient characteristics

	Neoadjuvant chemotherapy within 3 weeks [*n* (%)]	Neoadjuvant chemotherapy within 4 weeks [*n* (%)]	Test value	*P* value	Significance
	N=30	*N*=30			
Age					
Mean±SD	42.35 ± 10.6	42.93 ± 9.81	–0.218•	0.828	NS
Co-morbidities					
No	24 (80)	20 (66.7)			
HTN	2 (6.7)	7(23.3)	4.141*	0.247	NS
DM	3 (10)	3 (10)			
HTN and DM	1 (3.3)	0			
Neoadjuvant target therapy					
No	29 (48.3)	28 (46.7)	0.3509*	0.553167	NS
Yes	1 (1.7)	2 (3.3)			
Tumor size after neoadjuvant chemotherapy					
Mean±SD	1.980 ± 1.137	1.4 ± 1.097	2.010•	0.049	S

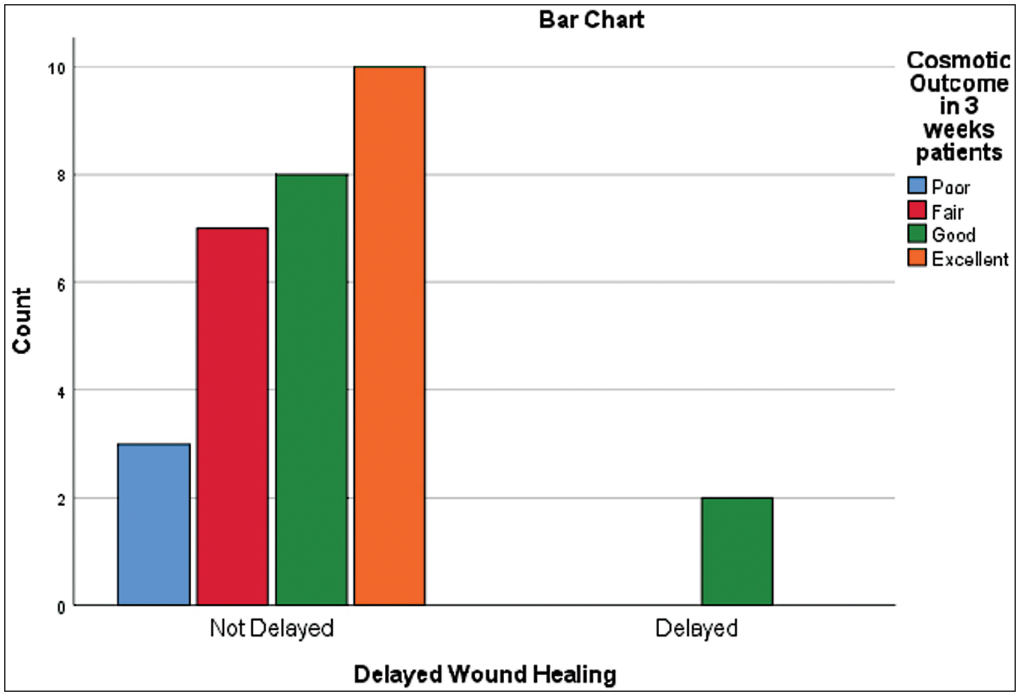
*χ^2 test.
•Independent *t* test.
P value more than 0.05: nonsignificant; *P* value less than 0.05: significant; *P* value less than 0.01: highly significant.

Table 2 Analysis between both groups with regard to different variables

		Neoadjuvant chemotherapy within 3 weeks	Neoadjuvant chemotherapy within 4 weeks	*t* test value	*P* value	Significance
Size after neoadjuvant chemotherapy	Mean	1.980000	1.400000	0.5800•	0.049	S
Intraoperation time	Mean	2.636667	2.305000	0.33167•	0.088	NS
Intra-blood loss	Mean	208.333333	227.333333	−19.000•	0.299	NS
Hospital stay	Mean	1.950000	1.766667	0.1833•	0.214	NS
Intra-blood transfusion						
No	Number	26	24		0.488	NS
Yes		4	6	0.480≠		
Seroma formation						
No	Number	26	27	0.162≠	0.688	NS
Yes		4	3			
Delayed wound healing						
No	Number	28	25	1.456≠	0.228	NS
Yes		2	5			
Immunohistopathology						
Luminal A		21	24			
Luminal B	Number	4	3	2.457π	0.514	NS
Her+		1	2			
Triple −ve		4	1			

•Independent *t* test.
≠χ^2 test,
πFisher exact test.
P value more than 0.05: nonsignificant; *P* value less than 0.05: significant; *P* value less than 0.01: highly significant.

Figure 1



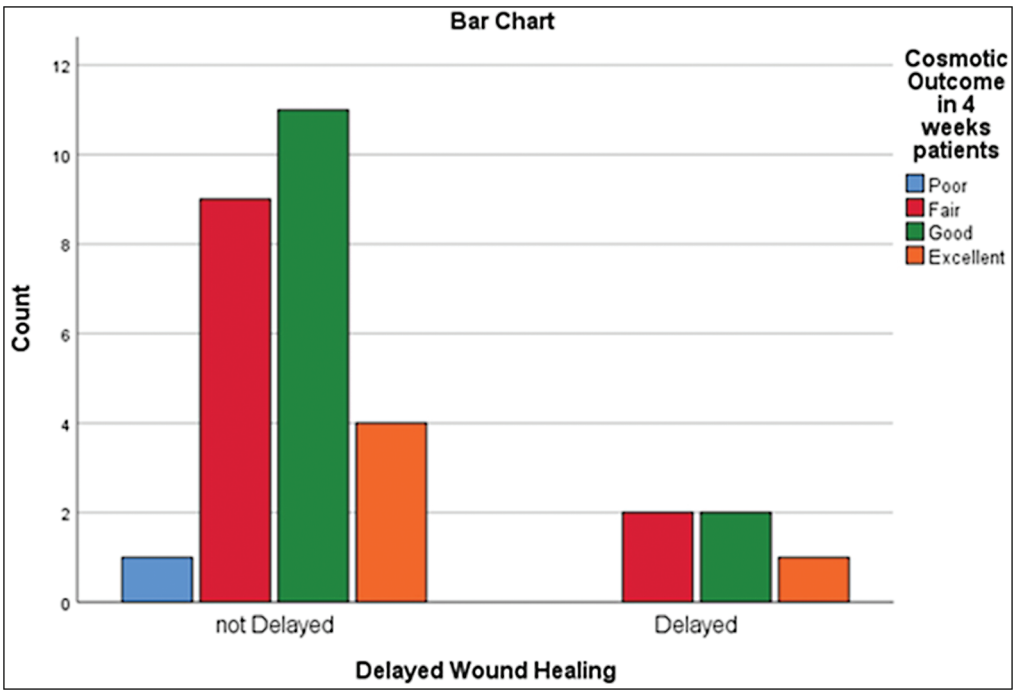
Cosmetic outcome among patients in the 3-week group regarding delayed wound healing.

breast. The difference between the two groups was statistically nonsignificant.

Discussion

Breast cancer has threatened human health for a long time, and many trials have been carried out to discover the mechanism of its occurrence and its treatment [6]. Time interval to treatment is an important question asked by patients every day but also a question without a definite answer. Clinical practice guidelines do not present specific guidelines on a maximum interval, and conflicting results are reported in numerous studies. This question has also been discussed in various intervals, as of time interval between diagnosis to surgery, and surgery to adjuvant chemotherapy or radiotherapy [7].

Figure 2



Cosmetic outcome for patients in the 4-week group regarding delayed wound healing.

Table 3 The number of patients having family history of cancer breast in both groups

	Patients		Total	χ^2 test	*P* value	Significance
	Neoadjuvant chemotherapy within 3 weeks	Neoadjuvant chemotherapy within 4 weeks				
Family history						
No	20	26	46	3.354	0.067	NS
Yes	10	4	14			
Total	30	30	60			

A total of 60 patients in our study underwent Zinedine breast-conserving surgery after neoadjuvant chemotherapy.

We divided the study sample into two groups: 30 female patients who underwent breast-conserving surgery after neoadjuvant chemotherapy within 3 weeks from the last chemotherapy session (group A) and 30 female patients who underwent breast-conserving surgery after 3 weeks from the last chemotherapy session but not more than 4 weeks (group B).

No significant statistical difference between the two groups was found regarding patients' age (mean=42.35 ± 10.6 and 42.93 ± 9.81 years in group A and group B, respectively), which is consistent with the demographic data published by National Cancer Institute at 2013 by Zeeneldin *et al.* [8], who claimed that the peak incidence of breast carcinoma is between 40 and 59 years of age.

In our study, we found that 10 patients had a positive family history of cancer breast in group A and four in group B, with a total of 14 (23.3%) patients in the whole sample having a family history of cancer breast. Unfortunately, BRCA gene test, which is significantly related to positive family history, was not available in our hospitals during this study.

The difference between the two groups was statistically nonsignificant.

Cosmetic outcomes

The total number of patients who had good and excellent cosmetic outcome was 33% each in group A, whereas it was 43.3 and 16.7%, respectively, in group B, which reveals 76.3% had good in all of the study sample, whereas 49.7% had excellent cosmetic outcome. This is in contrast to Denewer *et al.* [9], who reported 64% had excellent and 30% had good outcome. Of the patients, 5–14% had a poor cosmetic outcome following OPS. Our results are very similar to the published literature

in this aspect. This is far less than the possible poor cosmetic outcome associated with wide local excision with no attempt at breast reconstruction.

The rate of surgical site complications was 11.6%, which is different to that reported by Crown *et al.* [10] (26.1%).

In our study, there was no local recurrence during the 12-month follow-up period. This could be owing to the fact that assessments were done for only 12 months due to lack of available resources. However, Niinikoski *et al.* [11] reported the local recurrence rate of 2.3% during a median of 75 months of follow-up. Moreover, Romics *et al.* [12] reported a 2.7% recurrence during a median of 30 months of follow-up, and Clough *et al.* [13] reported 2.2% during a median of 55 months of follow-up.

There are too few studies, all retrospective, addressing time interval after completion of neoadjuvant chemotherapy for breast cancer. In 2014, Borna *et al.* [14] presented the results of a study at the annual meeting of the American Society of Breast Surgeons, demonstrating that patients undergoing surgery within 40 days after completion of neoadjuvant chemotherapy showed greater reductions in the final Ki-67, a marker of proliferative activity, which was associated with decreased recurrence rates.

A total of 1101 patients were identified. Median time to surgery was 33 days (range, 8–159 days). A total of 335 (30.4%) patients had surgery within 4 weeks of their last dose of neoadjuvant chemotherapy, 524 (47.6%) within 4–6 weeks, and 242 (22.0%) after more than 6 weeks. Median follow-up was 94 months (range, 3–178 months). The 5-year overall survival (OS) estimates were 79, 87, and 81% in patients who underwent surgery less than or equal to 4, 4–6, and more than 6 weeks after neoadjuvant chemotherapy, respectively (P=0.03). The three groups did not differ in 5-year recurrence-free survival (RFS) or locoregional RFS. In multivariable analysis, compared with an interval of less than or equal to 4 weeks, patients who underwent surgery at 4–6 or more than 6 weeks had equivalent OS, locoregional RFS, and RFS; a sensitivity analysis suggested worse OS in patients who underwent surgery at more than 8 weeks [15].

The 5-year OS rate was 89.6% and the 5-year DFS rate was 74%. OS and DFS were not significantly different when stratified according to timing of surgery; however, the trends of OS and DFS were poor when surgery was delayed for more than or equal to 8 weeks. Median OS and median DFS have not yet been reached. Of the 17% of patients who had surgery after more than or equal to 8 weeks, 12.9% had pathological complete response, whereas among those who received surgery 4–7 weeks and less than 4 weeks after neoadjuvant chemotherapy, 26 and 21% had pathological complete response, respectively (P=0.02) [16].

The study has many limitations, mainly the small number of cohort. This is a feature of most of OPS studies where randomized trial data are still lacking. The other limitation of our study is the very simplified cosmetic outcome scale. This is owing to the social and demographic properties of the study population and the relatively new concept of cosmetic preservation in breast cancer surgery in developing countries and the fact that all the available cosmetic assessment scales are developed from the West. We acknowledge the need to develop a local cosmetic outcome scale specific to the population of the study. We also recognize the limitation of our study with regards the follow-up time. Longer follow-up may be needed to ascertain local failures. We continue to monitor our patients for further results.

Conclusion

Our study included 60 patients who were divided into two groups: group A included 30 female patients who underwent breast-conserving surgery after neoadjuvant chemotherapy within 3 weeks from the last chemotherapy session, and group B included 30 female patients who underwent breast-conserving surgery after 3 weeks from the last chemotherapy session but not more than 4 weeks. We followed them up and analyzed different variables like intraoperative blood loss, operative time, delayed wound healing, and seroma formation. All of these variables were statistically nonsignificant, so there is no difference of doing operations after neoadjuvant chemotherapy either within 3 or 4 weeks as it does not affect the outcome clinically or statistically.

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Nil.

Conflicts of interest

The author declares that there is no conflict of interest.

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