

Optimal Time for Conservative Breast Surgery after Neoadjuvant Chemotherapy in Patients with Stage II or III Breast Cancer

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Abstract

Background: During past decades, neoadjuvant chemotherapy (NAC) was limited to inoperable breast cancer, however nowadays, NAC has led to an increase in the rates of breast conserving therapy (BCT), a decrease in the extent of local treatment (e.g. axillary dissection) and as a result, better cosmetic outcomes. Other benefits of NAC that made this method popular include in 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 impact of time to surgery after preoperative chemotherapy in stage II or III breast cancer patients candidate for breast conservative surgery according to: Primary objective: the loco-regional recurrence (include the affected breast and its involved lymph nodes). Secondary objective: the assessment of postoperative complications and healing process of the wound.

Patients and Methods: This study is a prospective randomized study conducted on 60 patients with stage II or III breast cancer indicated for conservative breast 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 conservative breast surgery after neoadjuvant chemotherapy within 3 weeks from the last chemotherapy session (Group A) and 30 female patients who underwent conservative breast surgery after 3 weeks from the last chemotherapy session but not more than 4 weeks. (Group B).

Results: In our study we found that the first group was including patients who did operation after 3 weeks from ending the neoadjuvant chemotherapy & the second group included those who did operation after 4 weeks we followed up them and analyzed different variables like local recurrence, intraoperative blood loss, operative time, delayed wound healing & seroma formation. All of these variables were found statistically non-significant.

Conclusion: There is no difference of doing operations after neoadjuvant chemotherapy either within 3 or 4 weeks as it doesn't affect in the outcome clinically or statistically.

Keywords: Breast cancer, Breast Neoplasm, Breast Tumors, Mammary Cancer, Malignant Neoplasm of Breast, Malignant Tumor of Breast.

Introduction

Breast cancer is the most common cancer diagnosed in women, accounting for more than 1 in 10 new cancer diagnoses each year. It is the second most common cause of death from cancer among women in the world 1 (Mahvi et al., 2018).

Breast cancer always evolves silently. Most of the patients

discover their disease during their routine screening. 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 (Cain et al., 2019).

The WHO has approved breast conservative surgery besides mastectomy in the treatment of malignant breast lesions in 1996 (Lin et al., 2016), which is the entire removal of the tumour with safety margin and preservation of as much breast tissue as possible (confirmed by frozen section followed by adjuvant radiotherapy) (Fajdic et al., 2013).

However not all patients were candidates for breast conservation putting in consideration many factors as breast size, multicentricity and adjacency to the nipple areola complex there was some aesthetic inconvenience (Urban et al., 2011). Aim of the work.

To evaluate the impact of time to surgery after preoperative chemotherapy in stage II or III breast cancer patients candidate for breast conservative surgery according to: (Primary objective) the loco-regional recurrence (include the affected breast and its involved lymph nodes). (Secondary objective) the assessment of postoperative complications and healing process of the wound.

Patients and methods

This study is a prospective randomized study conducted on 60 patients with stage II or III breast cancer indicated for conservative breast 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 patient with breast cancer post neoadjuvant divided into 2 groups: Group A included 30 female patients who underwent conservative breast surgery after neoadjuvant chemotherapy within 3 weeks from the last chemotherapy session. Group B included 30 female patients who underwent conservative breast 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 classify 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. Breast cancer patients' stage 2 or 3 underwent neoadjuvant chemotherapy.

Exclusion criteria: Any female patient indicated for MRM (advanced breast cancer not responding to chemotherapy & Inflammatory breast cancer). Conversion of breast conservative surgery to mastectomy. Failure of downstaging of the breast

tumor after neoadjuvant chemotherapy. Recurrent malignancy following conservative breast surgery. Bilateral female breast cancer

Methods

All patients included in the study will be candidates for

Clinical assessment: Detailed medical (any chronic diseases), surgical history, menstrual history (Last menstrual period (LMP) - date of first day of bleeding. Cycle length and frequency - eg, 5/28, 5 days of bleeding every 28 days. Heaviness of bleeding. (Number of tampons per day/clots/flooding/need for double protection.) Presence or absence of intermenstrual bleeding (IMB) and 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. General examination. Full breast and axillary examination: Introduce oneself to the patient. Explain to the patient what the examination involves. Important to check the patients understanding of the examination. Position the patient at 45°. Ensure a chaperone is present during the examination. Ask the patient to remove their clothing to expose their chest, from above the waist. Provide a blanket for the patient to cover themselves when not required to expose the breast. Inspect the patient from the end of the bed. Check for any obvious masses, scars, or asymmetry. Ask the patient to place their hands by their sides, comparing both breasts. Check for any obvious scars or masses present. Note the size and position of any observed. Look for any skin changes or ulceration. Erythema, puckering, or peau d'orange (orange peel appearance due to oedema). Look for any nipple changes, nipple discharge or inversion. Ask the patient to place both hands behind their head and repeat this inspection to accentuate any asymmetry. Inspect the axillae for any obvious masses. Examine each quadrant of the breast in turn, including the axillary tail (also termed the "Tail of Spence"). Using a flat hand, press the breast against the underlying chest wall, rolling the underlying tissue. Start with the 'normal' side first, examining any painful areas last. If there is any lumps, note their position, size, shape, consistency, overlying skin changes, and mobility. Examine their fixity to pectoralis muscles by asking the patient to push against your hand with their hand outstretched. Examine both axilla in turn. When examining the right axilla, hold the patients right arm with your right hand and examine the axilla with your left hand. When examining the left axilla, hold the patients left arm with your left hand and examine the axilla with your right hand. Palpate for any lymphadenopathy (5 sets of axillary lymph nodes are present: apical, anterior, central, posterior, and medial). To fully examine a breast, you should also remember to assess for potential metastasis: Palpate the spine for tenderness. Palpate the abdomen for hepatomegaly. Percuss and auscultate the lungs for lung masses. Thank the patient and ask them to redress.

Investigations

Routine laboratory investigations. Bilateral sonomammography. Abdominal and pelvic ultrasound. Chest x-ray / CT chest. MRI if needed. Bone scan if patient complain of bony aches or

stage 3 breast cancer. Histopathological examination for the suspicious breast mass by Ultrasound guided trucut needle biopsy / Histopathological examination for the suspicious axillary LN. Immuno-histochemical examination (ER, PR, Her2).

MDT (multidisciplinary team)

To take any medical or surgical decision for any patient in breast unit at the General Surgery Department of Ain Shams University Hospitals, the decision must be discussed by a group of senior staffs from the oncology, radiology, pathology and surgery departments. The discussion is done in the presence of a power-point data show includes a detailed history of the patient and images of the suspicious breast mass. After the discussion, all the lines of treatment are revealed and to be discussed with the patient so the patient can involve in the study fully consented and oriented to their treatment modality.

Intervention

Patients subjected to conventional breast conservative surgery after a fixed regimen of neoadjuvant chemotherapy; 4 cycles anthracycline and taxane containing regimen (4 AC - 3TAX), with adding specific regimen for HER2 positive patients (herceptin /perjeta).

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

Operative techniques: Before the surgery all the patient is consented to do conservative breast surgery with the possibility of mastectomy if surgeon failed to eradicate the tumor with suitable safety margin (tumor free area in the frozen section intraoperative). All the patients to be told about fasting at least 8 hours before the surgery. Marking of the suspicious breast mass either by a colored marker if it is palpable or if the mass is not palpable localization is 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 begins by marking out the wise pattern. The next step is to excise it with wide margins by going through one of the limbs of the wise pattern.. The tumor and its quadrant are then widely excised either circumareolar excision or radial line. After this step, the shaved margins of the cavity are further excised and sent for frozen sections. Once clarity

about the tumor margins of the excision cavity is achieved, the surgeon can declare the tumor is grossly removed, as our surgery technique encompasses excision of suitable volume of the breast mass dictated by the extent and site of the tumor.

Postoperative: National Canadian clinical practice guidelines recommend that RT should be given <12 weeks after BCS 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 had been followed after intervention every week for the first 2 weeks, then every 2 weeks for: Wound assessment regarding healing. 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. Aesthetic satisfaction.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 26. The quantitative data were presented as mean, standard deviations and ranges. Also qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using **Chi-square test and/or Fisher exact test** when the expected count in any cell found 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 the following: P-value > 0.05: Non significant (NS). P-value < 0.05: Significant (S). P-value < 0.01: Highly significant (HS).

Results

Our study was done on 60 patients divided to 2 groups one group included patients taken chemotherapy after 3 weeks and the other one included patients taken chemotherapy after 4 weeks, 30 patients each. The mean age in group A was 42.35± 10.6 while that of group B was 42.93± 9.81 as seen in Table 1.

		neoadjuvant chemotherapy within 3 weeks	neoadjuvant chemotherapy within 4 weeks	Test value	P-value	Sig.
		No. = 30	No. = 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%)	4.141*	0.247	NS
	HTN	2 (6.7%)	7(23.3%)			
	DM	3 (10%)	3 (10%)			
	HTN & DM	1 (3.3%)	0 (0.0%)			
Neoadjuvant target therapy	No	29(48.3%)	28 (46.7%)	0.3509*	0.553167	NS
	Yes	1 (1.7%)	2(3.3%)	0.3509*	0.553167	
Tumor size after neoadjuvant chemotherapy	Mean ± SD	1.980 ± 1.137	1.4 ±1.097	2.010*	0.049	S

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.
 *: Chi-square test; •: Independent t-test.

Table 1 : Patient characteristics.

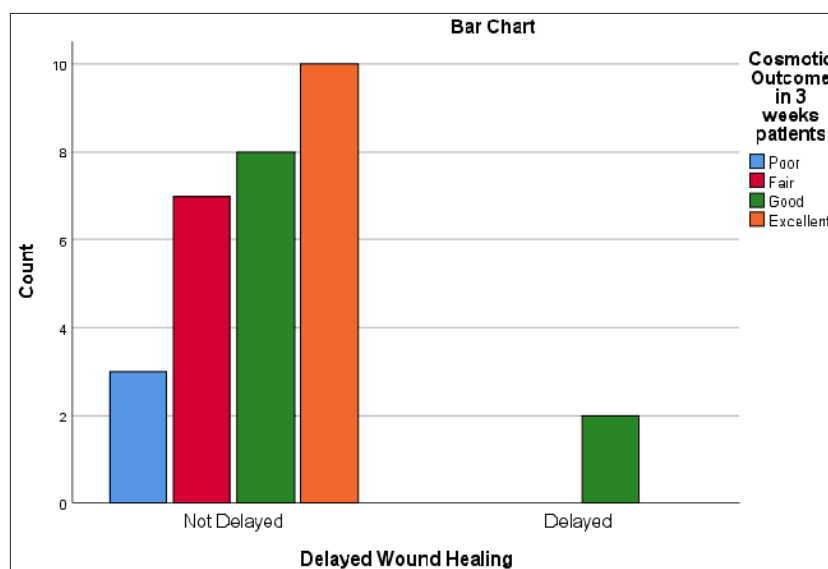


Figure 1: representing Cosmetic out come in the 3 weeks patients with regard to delayed wound healing .

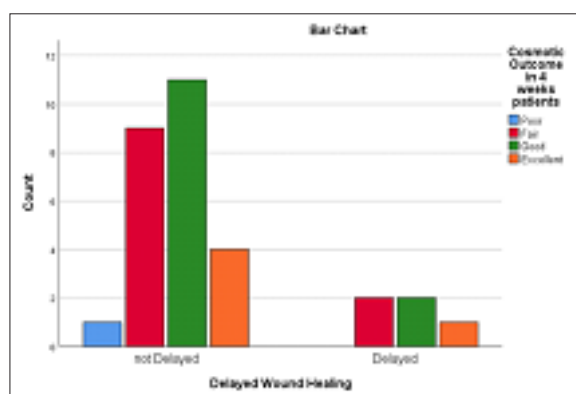


Figure 2: representing Cosmetic outcome for patients who chemotherapy within 4 weeks with regard to delayed wound healing.

There was no patients in our study had local recurrence within the first year of follow up.

		neoadjuvant chemotherapy within 3 weeks	neoadjuvant chemotherapy within 4 weeks	T test Value	p-value	Sig.
size after neoadj chemo	MEAN	1.980000	1.400000	0.5800	0.049	S
intra-operation 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 trasfusion						
No	number	26	24	0.480 ≠	0.480	NS
Yes		4	6			
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			
Immnohistopathology						
Luminal A	Number	21	24	2.457 π	0.514	NS
Luminal B		4	3			
Her +		1	2			
Triple -ve		4	1			

p-value > 0.05: non-significant, p-value <0.05: significant, p-value <0.0001: highly significant.

Independent t-test, ≠Chi square test, π Fisher exact test.

Table 2: Representing analysis between both groups with regard to different variables

Table 2 shows the difference between the two groups with regard to different variables which are intraoperative time, intraoperative blood loss, hospital stay, intraoperative blood transfusion, seroma formation, delayed wound healing & immunohistopathology, all of them was statistically nonsignificant while the Difference between both groups with regard to tumor size after neoadjuvant chemotherapy we found that it was statistically significant with p value= 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 chemotherapy with regard to delayed wound healing we found that 2 patients had delayed wound healing but their cosmetic outcome was good while 3 out of 28 patients who didn't suffer from delayed wound healing had poor cosmetic outcome, 7 had fair cosmetic outcome, 8 had good cosmetic outcome & 10 had excellent outcome, the total patients who had good & excellent cosmetic outcome was 33% for both groups while figure 2 shows the cosmetic outcome for the patients who had operations after 4 weeks chemotherapy with regard to delayed wound healing we found that 2 patients had delayed wound healing but their cosmetic outcome was Fair, 2 had good cosmetic outcome & 1 Excellent cosmetic outcome while 1 out of 28 patients who didn't suffer from delayed wound healing had poor cosmetic outcome, 9 had fair cosmetic outcome, 11 had good cosmetic outcome & 4 had excellent outcome, the total patients who had fair & Good cosmetic outcome was 36.7% & 43.3% respectively for both groups.

	Patients		Total	Chi-square test	p-value	significance
	neoadjuvant chemotherapy within 3 weeks	neoadjuvant chemotherapy within 4 weeks				
Family History	no	20	26	46	3.3	NS
	Yes	10	4	14	54	
Total		30	30	60		

Table 3: Representing the number of patients having family history of cancer breast in both groups.

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

In our study we found that patients having positive family history of cancer breast was 10 in the first group and 4 in the second group with total of 14 (23.3%) patient in the whole sample having family history of cancer breast, the difference between the two groups was statistically non-significant.

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 (Bonilla et al., 2017).

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 (Yoo et al., 2017).

60 patients in our study underwent conservative breast surgery after neoadjuvant chemotherapy

We divided the study sample into two groups: 30 female patients who underwent conservative breast surgery after neoadjuvant chemotherapy within 3 weeks from the last chemotherapy session (Group A) and 30 female patients who underwent conservative breast 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 years 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. who claimed that the peak incidence of breast carcinoma is between 40 -59 years old (Zeeneldin et al., 2013).

In our study we found that patients having positive family history of cancer breast was 10 in the first group and 4 in the second group with total of 14 (23.3%) patient in the whole sample having family history of cancer breast, Unfortunately BRCA gene test, which is related to significantly positive family history, was not available in our hospitals during this study.

The difference between the two groups was statistically non-significant.

For the cosmetic outcome

The total patients who had good & excellent cosmetic outcome was 33% for both in Group A while it was 43.3 % & 16.7 % respectively in group B. which is 76.3 % was good in all study sample while it was 49.7% for excellent cosmetic out come. in contrast with *Denewer et al.* (2012), who reported (64%)

as excellent and (30%) as good Of the patients, 5–14% have a poor cosmetic outcome following OPS. Our results are very similar to the published literature in this aspect. This 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. (2019)* (26.1%). (*Crown A, Rocha FG, Grumley JW (2019):* Oncoplastic Central Partial Mastectomy and Neareolar Reduction Mammoplasty with Immediate Nipple Reconstruction: An Initial Report of a Novel Option for Breast Conservation in Patients with Subareolar Tumors.

In our study, there was no local recurrence during our period of follow up for 12 months, due to the limitation of our study period and available resources the follow up was only 12 months; but *Niinikoski et al. (2019)* reported local recurrence rate as 2.3% during a median of 75 months follow-up. Also we found in *Romics et al. (2018)*, reported a 2.7% recurrence during a median of 30 months follow-up and *Clough et al. (2018)*, 2.2% during a median of 55 months follow-up.

There are too few studies, all retrospective, addressing time interval after completion of neoadjuvant chemotherapy for breast cancer. in 2014, gabordi et al, presented 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 NAC show greater reductions in final Ki-67, a marker of proliferative activity, which was associated with decreased recurrence rates (Farazmand et al., 2017).

A total of 1101 patients were identified. Median time to surgery was 33 (range 8–159) days; 335 patients (30.4 %) 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 (range 3–178) months. The 5-year overall survival (OS) estimates were 79, 87, and 81 % in patients who underwent surgery ≤ 4 , 4–6, and > 6 weeks after neoadjuvant chemotherapy, respectively ($p = 0.03$). The three groups did not differ in 5-year recurrence-free survival (RFS) or locoregional recurrence-free survival (LRFS). In multivariable analysis, compared with an interval of ≤ 4 weeks, patients who underwent surgery at 4–6 or > 6 weeks had equivalent OS, LRFS, and RFS; a sensitivity analysis suggested worse OS in patients who underwent surgery at > 8 weeks (Sanford et al., 2016).

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 ≥ 8 weeks. Median OS and median DFS have not yet been reached. Of the 17% of patients that had surgery after ≥ 8 weeks, 12.9% had pathological complete response (pCR), while among those that received surgery 4-7 weeks and < 4 weeks after neoadjuvant chemotherapy, 26% and 21% had pCR, respectively ($p = 0.02$) (Suleman et al., 2020).

The study has many limitations, mainly the small number of cohort. This is a feature of most of OPS studies where randomised trial data are still lacking. The other limitation of our study is the very simplified cosmetic outcome scale. This is due 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 divided into 2 groups, the first one was including patients who did operation after 3 weeks from ending the neoadjuvant chemotherapy & the second group included those who did operation after 4 weeks we followed up them and analyzed different variables like intraoperative blood loss, operative time, delayed wound healing & seroma formation. All of these variables were statistically non-significant so there is no difference of doing operations after neoadjuvant chemotherapy either within 3 or 4 weeks as it doesn't affect in the outcome clinically or statistically.

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