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Evaluation of locoregional recurrence in patients with early breast carcinoma post-breast-conserving surgery with and without the use of preoperative chemotherapy

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ABSTRACT

The effects of neoadjuvant chemotherapy in increasing the rate of conservative breast therapy and associated with reducing morbidity and better cosmetic has been fully acknowledged. Now, there are commonly used neoadjuvant chemotherapy for operable early breast carcinomas patients. Currently, neoadjuvant chemotherapy is used for locally advanced breast carcinoma, inflammatory breast cancer, and down staging of the large tumour to allow for breast conservative therapy. A prospective study performed in the department of surgery in Al-Sadder Medical City/Najaf city/Iraq, from the month of October 2015 to the 1st of October 2018, where 48 patients presented with a breast cancer diagnosis by clinical examination, Mammography, breast ultrasound, chest x-ray, bone scan, serum CEA, CA15_3 level, the initial diagnosis of breast cancer made by core needle biopsy. Breast saving surgery consisted of wide local excision with a safe margin with standard level I, II lymph node of axilla dissection. The resected specimen and lymph node was sentd for histopathological examination; the size, width, length & height dimension were recorded and the resection margin was recorded positive if close to 2mm and negative if >2mm tumourtumor-free margin. The A 48 patients enrolled in this study with a mean age at diagnosis of 44.6 ± 8.4 years. 34 patients received neoadjuvant chemotherapy, Locoregional recurrence reported in 4 patients (28.6%) not received neoadjuvant chemotherapy (P. value < 0.001), the higher relapse rate was reported significantly in the cases aged more than 50 years compared to those aged 50 years or below (P. value = 0.05, significant). Neoadjuvant chemotherapy decreases the incidence of locoregional recurrence of early breast carcinoma after breast-conserving surgery.

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INTRODUCTION

Neoadjuvant chemotherapy (NAC) is the giving of systemic treatment before the excision of a tumor surgically. NAC primary was fashioned to be utilized in locally advanced patients to transform non-operable tumors into operable one. As this idea of preface, the significance of NAC in raising the preservation surgery rate with decreased morbidity and better cosmetics. Meantime, there have been interesting about to control the tumor locally

over the down-staging of the neoplasm and the postponementd of surgery, inpatient resistant to NAC (Kuerer *et al.*, 1999; Smith and Lipton, 2001). Yet, the study on a randomized trial comparing the competence of NAC with adjuvant chemotherapy in operable patients with breast carcinoma has shown equal results. The study was set up on 5500 desirable women for these analyses. It also stated that NAC prevents mastectomy in twenty-five percent of the patients. In contrast, less than five percent of the patients who were a primary nominee for preservation treatment need an excision of the breast because of disease progression whilst taking NAC (Mieog *et al.*, 2007a; Kaufmann *et al.*, 2003). NAC at present is usually used for early operable early patients with breast carcinoma. Currently, NAC is utilized for locally advanced carcinoma of the breast, inflammatory breast cancer, and down-staging of big tumors to permit for breast preservation treatment (Rouzier, 2005; Mauri *et al.*, 2005). The usage for NAC at present expanded to clinically node-negative breast cancer patients with inappropriateunappropriated tumor profiles, in whom adjuvant systemic treatment is foretold (Vugts *et al.*, 2016; Shin *et al.*, 2013) . Various benefits of the utilityze of NAC . It shows a single chance for the assessment of management responds with full pathologic response doing as a replacement marker of existence and for more prompt evaluation of the effectiveness of new therapeutic factors and early stopping of inefficient therapy. Also, in case of reluctance to therapy, adjusting the dose and/or alteration of other drug conserve patients from a load of side effects and toxicity. Moreover, NAC tailored to each individualized patient (Sahoo *et al.*, 2012; Fisher *et al.*, 2002). Response to NAC can be evaluated by clinical checking, breast imaging investigations, and, lastly, pathologic examination of post-treatment specimens. A clinical checkup is done by evaluation of the size of the tumor by palpation. This job is harder in tumors that have reacted to treatment, as it is defying to palpate the real tumor against the therapy-induced changes (Pierga *et al.*, 2003; Mieog *et al.*, 2007b). The breast imaging form such as ultrasound and mammography are not deemed sufficient for quantitative evaluation of variation in size of the tumor imaging. However, more modern apparatus such as MRI (magnetic resonance imaging) and PET (positron emission tomography) have been shown to supply a better evaluation of tumor reply to NAC and better portend reply to treatment (Keune *et al.*, 2010; Partridge *et al.*, 2005). The gross examination was the gateway to the input the location and the size and of the neoplasm before the treatment is critical. Sample radiography will help with the identity of clips or microcalcifications. Correlated with entire responsed to treatments, it is impossible to recognize any grossly visible lesions. The identity of the neoplasm mattress and surrounding tissue helps select the right tissue sectioning area. So, pains should be made to assess the surgical margins since the tumor mattress are usually seen as a non-descriptive area of irregular rubbery fibrous tissue that may also contain ill-defined areas of residual tumor. The tumor size mattress should also be documented. The important margin assessment in case the residual neoplasm is later found by microscopic examination. (Sahoo and Lester, 2009; Liu *et al.*, 2010). The microscopic evaluation, it is remarkable microscopically to detect the prior biopsy alterations recognized by stromal fibrosis, macrophage, lymphocytes, and, sometimes, a multinucleated giant cell response. In the lack of this feedback, the tolerance of specimen mistakes in the lumpectomy sample should be so deemed. Likely, understanding of the tumor mattress is fundamental. Neoplasm mattress are distinguished by chronic inflammatory penetrate, necrosis, stromal fibrosis, calcifications, and histiocytic (Londero *et al.*, 2004; Sahoo *et al.*, 2012). The series of alterations after treatments is known as full respond “no residual tumor identified”; partial response (residual tumor is seen singly or in the cluster), and non-response “no change identified; at some times, it is rough to set between reactive/inflammatory atypia and residual neoplastic cells”. Alterations in non-tumor tissue of the breast contain nuclear enlargement, cytoplasmic and basement membranes sclerosis may similar to a residual neoplasm. In such a situation, immunostaining for epithelial markers such as cytokeratin-1/AE-3 or CK7 and CD68 for histiocytic and myoepthelial markers are suitable diagnostic assistants (Chen *et al.*, 2008; Sahoo and Lester, 2009). The perfect pathologic restrain includes the disappearanceing of all axillary lymph nodes and invasive carcinoma in the breast after the accomplishment of treatments.

PATIENT AND METHODS

A prospective study performed in the department of surgery in Al-Sadder Mmedical Ccity, Najaf city, from October 1, 2015, to October 1, 2018, where 48 patients presented breast cancer with the clinical checkup. Mammography, breast ultrasound, CXR, bone scan, serum CEA CA15_3 level, the initial breast cancer diagnosis made by core needle biopsy. All enrolled patients were undergoing breast-conserving surgery(BCS) with lymph node axillary dissection followed by radiotherapy with systemic adjuvant therapy, but not all patients with

Table 1: Age distribution of studied group

	Neo adjuvant chemotherapy		Non-Neo Adjuvant chemotherapy	
Size	No.	%	No.	%
T1	4	11.8%	4	28.6%
T2	30	88.2%	10	71.4%
	34	100 %	14	100%

P. value= 0.322 (not significant)

Table 2: Descriptive statistics of lymph nodes status in patient received Neo adjuvant chemotherapy or not

	Neo adjuvant chemotherapy		Non-Neo adjuvant chemotherapy	
LN	No.	%	No.	%
N0	18	52.9%	4	28.6%
N1	16	47.1%	10	71.4%
Total	34	100%	14	100%

P. value = 0.221 (not significant)

Table 3: Descriptive Statistics of hormones status in patients received Neo adjuvant chemotherapy or not

	Neo adjuvant chemotherapy		Non-Neo adjuvant chemotherapy	
Hormones receptors	No.	%	No.	%
ER+ve,PR+ve,HER2+ve	8	23.5%	6	42.9%
ER+ve, PR+ve,HER2-ve	22	64.7%	8	57.1%
Triple -ve	4	11.8%	0	0
Total	34	100%	14	100%

P. value = 0.222 (not significant)

Table 4: Distribution of Locoregional recurrence among the studied group

	Neo adjuvant chemotherapy		Non-Neo adjuvant chemotherapy	
Locoregional recurrence	No.	%	No.	%
No	34	100 %	10	71.4 %
Yes	0	0	4	28.6 %
Total	34	100 %	14	100 %

P. value <0.001 (significant)

Table 5: Relationship Locoregional recurrence regarding age

		Relapse			
		Yes (n=6)		No (n=42)	
		No.	Row N %	No	Row N%
Age (Year)	= < 50	1	2.5	39	92.5
	> 50	3	37.5	5	62.5

Fisher´s Exact test =9.44, P. value 0.0119 (significant)

Table 6: Descriptive Statistics of grade in patients received Neo adjuvant chemotherapy or not

	Neo adjuvant chemotherapy		Non-Neo adjuvant chemotherapy	
Grade	No.	%	No.	%
I	8	23.5 %	2	14.3 %
II	24	70.6 %	10	71.4 %
III	2	5.9 %	2	14.3 %
Total	34	100 %	14	100 %

P. value= 0.535 (not significant)

Table 7: Results of Binary Regression analysis

Variable in the equation	Odd ratio	P.value
Age at diagnosis (older than 50)	1.05	0.06
Tumor size (=>5 cm)	1.09	0.043
TNM staging (advanced)	0.63	<0.001
Grade (advanced)	0.59	<0.001
Adjuvant Radiotherapy (Yes)	1.00	0.38
Adjuvant chemotherapy (Yes)	0.96	0.42
Hormonal Therapy (Yes)	1.00	0.95

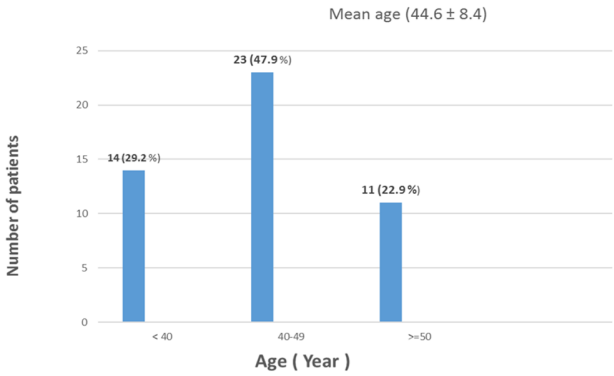

Figure 1: Age distribution of studied group

neoadjuvant systemic therapy. The patients split into two groups of patients, the first group received NAC and another group did not received NAC. Before surgery, all patients with NAC received 2 cycles of chemotherapy. The tumor response to NAC was monitored by clinical examination, ultrasound, and mammography, after chemotherapy. Several regimens of chemotherapy were used the most popular was ACT (doxorubicin, cyclophosphamide, Taxol), FEC (5-fluorouracil, epirubicin, cyclophosphamide) if patient HER2 positive added to above regimens (trastuzumab).

The patient involved in the study,

Early breast cancer

Patient excluded from the study was ineligible for breast conservative surgery those with,

1. Multicentric tumor

2. Medial tumor

Breast conservative surgery consisted of wide local excision with a safe margin with standard level I, II axillary lymph node dissections. The resected specimen and lymph node had to undergo histopathological examination. Examination of the size, width, length, height dimension was recorded and the resection margin was recorded positive if close to 2mm and negative if 2mm tumor-free margin. ER, PR& HER2 receptors were evaluated. Pathological examination of level I, II axillary lymph node dissected to determine if positive or negative. All patients received postoperative radiotherapy within 30-40 days post-operative the whole breast and chest wall were treating patients with axillary lymph nodes positive given radiation to the axillary and supraclavicular area. Adjuvant chemotherapy at least six monthly cycles werewas given post-surgery (CMF). Hormonal therapy using tamoxifen 20mg /day was given for hormone-positive receptor patient for2-5 years.

Follow up

The patient was followed by a 6-month interval for 3 years; the patients were evaluated by clinical examination and radiological evaluation and if any suspicions of recurrent confirm by core needle biopsy. Locoregional recurrence was defined by ipsilateral breast axillary, internal mammary supraclavicular and infraclavicular lymph node.

Statistical analysis

Data were entered and resolved using the statisti-

cal package for social sciences (SPSS) version 25. Descriptive statistics presented as standard deviation, mean, frequencies, and percentages. We used A chi-square test to evaluate the relevance between categorical variables, Fisher's exact test used when chi-square was inapplicable. Binary regression analysis used to assess the relevance between relapse and other variables with adjustment for confounders. The level of significance of $\leq$ 0.05 was deemed significant.

RESULTS AND DISCUSSION

48 patients had registered in this study with a mean age at diagnosis of 44.6 $\pm$ 8.4 (Range: 31 – 66) years, moreover, 37 patients (77.1%) aged below 50 years, (Figure 1). The total patients registered in this research were divided into 34 patients who received NAC, 4 patients (11.8%) tumor size were T1 and 30 patients (88.2%) tumor size were T2, other 14 patients had not received NAC 4 patients (28.6%) tumor size were T1 and 10 patients (71.4%) tumor size were T2 the P. Value = 0.322 (not significant), (Table 1). With regard to lymph node status, 18 patients (52.9%) lymph node status were N0 and 16 patients (47.1%) lymph node status were N1 in the NAC group, while 4 patients (28.6%) lymph node status were N0 and 10 patients (47.1%) lymph node status was N1 in the non-NAC group with P. Value = 0.322 (not significant), (Table 2). For the hormonal status of the studied group, each of ER-positive, PR positive and HER2 positive reported in 8 (23.5%) in patients received NAC while 6 patients (42.9%) in patients did not receive NAC, each of ER-positive, PR positive and HER2 negative reported in 22 (64.7%) in patients received NAC while 8 patients (57.1%), where triple negative 4 (11.8%) in patients received NAC and 0 (0.0%) in patients did not receive NAC (Table 3). Loco regional recurrence reported in 4 patients (28.6%) did not receive NAC P. Value < 0.001 (significant) As in (Table 4), higher relapse rate was reported significantly in the cases aged more than 50 years compared to those aged 50 years or below, 37.5% vs. 7.5%, respectively, (P. Value = 0.05, significant) (Table 5enrolled). More analysis was done early in the relationship between locoregional recurrence and grade, where statistically not significant results of this analysis are seen in (Table 6). Further assessment was done for the correlation between locoregional recurrence and other variables in addition to mode of treatment using the bivariate regression analysis, which was used to control any confounding effect and inter-correlation between these variables which may affect the significance of correlation between relapse and adjuvant therapy, however, the correlation still insignificant after modulation for other significant variables; age, tumor size, TNM staging, and grades, P>0.05) (Table 7).

Locoregional recurrence (LRR) after BCS is a well-known independent risk factor associated with unfavorable long-period results. Debate occurs regarding the predicted effect of an LRR post long incident-free period (van Laar *et al.*, 2013; Gosset *et al.*, 2016). Our research tries to assess the benefit of neoadjuvant treatment before surgery on the recurrence of breast cancer among a group of Iraqi patients, therefore an overall of 48 patients registered in our research. The majority of the patients in the studied group aged 50 years or more, which indicated the higher breast cancer incidence among this age group, which is similar to previous epidemiological studies regarding the distribution of age of patients with breast carcinoma. (Rottenberg *et al.*, 2018; Agarwal *et al.*, 2018). The present study found a higher recurrence rate among patients aged 50 years or older, compared to younger age groups, 37.5% Vs. 7.5%, respectively, Conversely, Shin et al. From the Republic of Korea, reported in 2018 that the younger age $\leq$ 40 years were associated with worse recurrence. (Sweeting *et al.*, 2011; Shin *et al.*, 2018). It is recognized that NAC can effectively downstage the main neoplasm. For patients with huge neoplasms permitting breast excision at the first diagnosis, the utilize of NAC has been seen to decrease the size of the main neoplasm and make a possible breast conserving surgery (Kuerer *et al.*, 2001; Vlastos *et al.*, 2000). The NSABP-B18 trial demonstrated higher locoregional recurrence following surgery in the -NAC BCS group parallel with the NAC –breast excision group (Wolmark *et al.*, 2001). Three studies backed the idea that BCS after in NAC patients with big initial breast neoplasm could be a logical therapy choice if the tumor size decreased to $\leq$ 4 cm after NAC regardless of the primary size of the tumor. But, patients who exhibit no restraint to NAC submitting BCS had a significantly higher local relapse rate contrast to breast excision patients. But, because of significant variation in the state of the lymph nodes, grading, and size of the tumor between the two groups, the outcome has to be seen with caution (Parmar *et al.*, 2006; Shin *et al.*, 2013). Several studies explained that BCS after NAC is a logical choice for female who respond to NAC. But, our research has various restrictions. First of all, it was a retrospective research, and that may become favorable in the data analyzed. Secondly, the local recurrence rate was weak and the follow-up of some researches (Parmar *et al.*, 2006; Cho *et al.*, 2013) were so short. This may have been a cause of why these researches

drop to detect a variation in local recurrence rates among groups. More studies and researches must be done with proper recording of recurrence established on stage and 10-year follow-up post-surgery, which would then permit the doctors to better counsel patients about breast-conserving surgery-NAC for locoregional recurrence post BCS.

CONCLUSIONS

Utilization of neoadjuvant chemotherapy in this research was accompanied with neoplasm plus axillary down staging, which increased the number of cases undergoing breast conservation, so Neo adjuvant chemotherapy reduces the incidence of locoregional recurrence of early breast carcinoma after breast conserving surgery. Many multi-centre researches studies with a prolonged follow-up are required to compare the total and disease-free survival advantage of this management modality.

Ethical approval

The ethical committee of the, Faculty of Medicine, Jabir Ibn Hayyan Medical University

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Conflict of interest statement

All authors stat they don't have any conflict of interest.

Declarations

Ethical consent has been taken from all patients.

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