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## The Efficacy of Primary Surgery Compared to Post Chemotherapy Surgery for Patients with Locally Advanced Breast Cancer

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### Abstract

**Purpose:** to compare primary surgery and surgery after neoadjuvant chemotherapy (NCT) in locally advanced breast cancer (LABC) patients for whom loco-regional & systemic treatment in the form of chemotherapy and radiotherapy were performed. **Patients and methods:** Between 2008 & 2011, 112 patients with LABC were treated at KAAH & OC-Jeddah-KSA. Of whom 42 were treated by NCT followed by surgery either mastectomy or conservative surgery, then adjuvant chemotherapy and radiotherapy. The rest patients (70) were treated by primary surgery (mastectomy or conservative resection) followed by adjuvant chemotherapy and radiotherapy. All patients received adjuvant antiestrogen. Patients were followed for a median duration of 33 months. Disease-free survival (DFS) and overall survival (OAS) were studied for all patients, compared between both groups and related to extent of surgery and menopausal status.

**Results:** median age was 46.5 years for all patients. 48 years, and 46 years for NCT and primary surgery groups respectively. Median DFS was 15 months for all patients, 16 & 15 months for NCT and primary surgery groups. Median OAS was 24 months for all patients, 22 & 24 months for NCT and primary surgery groups. Difference in DFS & OAS were highly significant in favor of postmenopausal patients ( $p = 0.05$  for DFS &  $p = 0.03$  for OAS) while in primary surgery group the differences between pre and postmenopausal patients in DFS & OAS were statistically insignificant ( $p = 0.4$ ). NCT followed by surgery group patients showed significant improvement in DFS & OAS in patients performed conservative surgery while in primary surgery group the difference was insignificant. The results of neoadjuvant chemotherapy showed (14.3%) complete clinical remission (33.3%) showed more than 50% primary tumor regression, while the rest of patients (52.4%) showed less than 50% reduction of the primary tumor. The incidence of metastases was 56.5% for all patients, 49.4% for NCT group and 61.1% for primary surgery group. Freedom of disease was seen in 28.6% in NCT group and 37.1% for primary surgery group and local recurrence was noticed in 23.8% in NCT group Vs 2.9% in the primary surgery group.

**Conclusion:** Surgery post-neoadjuvant chemotherapy neither prolongs DFS nor OAS in comparison with primary surgery followed by adjuvant chemotherapy. However, it permits more conservative surgery to be performed in LABC patients, but many of these patients could not achieve complete pathological remission leading to increased incidence of local failure. Postmenopausal patients fared much better than premenopausal patients regarding DFS & OAS. Earlier surgical interference with modified radical mastectomy for those who showed minimal response to NCT (after 2 courses) is highly recommended. Alternatively, aggressive treatment with

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newer chemotherapeutic drugs or increasing dose intensity plus growth factor support may be warranted for younger patients to improve the outcome of conservative surgery.

**Keywords:** primary surgery, neoadjuvant chemotherapy, locally advanced breast cancer, mastectomy and conservative surgery.

## 1. Introduction

Locally advanced breast carcinoma (LABC) comprises a heterogeneous group of tumors ranging from relatively large primary tumors (stage T4) to small breast tumors presenting with extensive nodal metastases (involvement of ipsilateral, infraclavicular, supraclavicular, or internal mammary nodes). It remains a clinical challenge as the majority of patients with this diagnosis develop distant metastases despite appropriate therapy (Singletary et al., 2002), inflammatory carcinomas also included in locally advanced breast carcinoma (Cristofanilli et al., 2003). It is defined by 1992 American Joint Committee (AJC) staging criteria as stage IIIa and IIIb disease (Taylor et al., 1997). Despite the awareness of physician and public of the importance of screening and early detection, 10-20% of women with breast cancer have locally advanced disease at diagnosis in industrialized countries (14% in the United States) while in developing countries it might constitute up to 50% of incident cases (Hortobagyi et al., 1995). In populations that receive regular screening mammography, the percentage of patients with the locally advanced disease is less than 5% (Seidman et al., 1987). The treatment for patients with locally advanced breast cancer is typically a combination of systemic chemotherapy, surgery, and radiotherapy. There is a consensus that all patients with the technically resectable disease should have radical mastectomy (Taylor et al., 1997). Earlier results of radical mastectomy alone were associated with a 53% local failure rate and a zero % 5-year disease free survival (Harris et al., 1992). Similarly radiation therapy alone for these patients resulted in poor 3-year survival (10–25%) with significant risk for disease recurrence and death, as well as the complications of soft tissue, ribs, heart and lung injury, also brachial plexopathy, lymphedema, chest wall fibrosis, skin ulceration, and skin necrosis (Harris et al., 1992). The combination of surgery and radiotherapy although decrease incidence of local failure, a high frequency of distant metastasis were seen after either treatment approaches. The introduction of multimodality treatment with the addition of chemotherapy has resulted in improvement of disease-free survival particularly in stage IIIA (Taylor et al., 1997, Harris et al., 1992).

Neoadjuvant chemotherapy (NCT) was developed in 1970 and is used before local treatment in LABC to downstage the primary tumor to make subsequent surgery easier, hoping to eliminate occult distant metastasis to prolong survival (Wang et al., 1996). The natural history of this disease has been changed dramatically by the introduction of these combined modality therapies with 5-year survival rate of 35–60% commonly are reported (Hortobagyi et al., 1995). Despite the theoretical and experimental data indicating the survival superiority of neoadjuvant chemotherapy over postoperative adjuvant chemotherapy, the role of neoadjuvant in staging remains unclear (Wang et al., 1996), and there are few studies that compare this approach to postoperative treatment (Taylor et al., 1997, Cunningham et al., 1998). The purpose of this study is to compare the disease-free survival (DFS) and overall survival (OAS) of patients with LABC treated with NCT, surgery and radiotherapy to patients treated by primary surgery followed by adjuvant chemotherapy and radiotherapy and to study the prognostic impact of menopausal status and extent of surgical resection on these survival parameters.

## 2. Material and Methods

Eligible patients for this study are those with technically resectable non-inflammatory locally advanced cancer breast (stage III A & B). 112 patients with previous criteria were treated at King Abdul Aziz Hospital and Oncology Center-Jeddah-Kingdom of Saudi Arabia between May 1998 and April 2002 and between June 2007 and May 2011. These patients were treated by multimodality therapy and have been classified into two groups according to whether they were initially treated by neoadjuvant chemotherapy or by surgery. The first group (NCT) included 42 patients who were primarily treated with neoadjuvant chemotherapy followed by surgery after biopsy proven carcinoma and staging work-up at the oncology center. Those patients received FAC regimen (5 fluorouracil, doxorubicin and cyclophosphamide), then followed by surgery in the form modified radical mastectomy or conservative resection and axillary clearance. All patients received postoperative radiotherapy to chest wall or breast and lymphatic drainage site. Adjuvant hormone

therapy (antiestrogen) was given to all patients regardless of the hormone receptor status plus adjuvant 4 courses of chemotherapy (postoperatively). The second group (Primary surgery) included 70 patients who were referred to the oncology center for adjuvant postoperative management. Those patients have been staged and defined as locally advanced cancer breast (IIIA & IIIB) by surgical and pathology teams. Patients were operated either by modified radical mastectomy or by conservative surgery and axillary clearance. Those patients have been staged and defined as locally advanced cancer breast (IIIA & IIIB) by surgical and pathology teams. Patients were operated either by modified radical mastectomy or by conservative surgery and axillary clearance. For those patients staging work up was performed, including full blood picture, biochemical profile, chest X-ray (CXR), abdominal ultrasonography, bone scan and study of left ventricular ejection fraction by MUGA scan (the later performed for patients who were planned to receive anthracycline).

These second group patients were treated by triple modality i.e. surgery followed by adjuvant chemotherapy (6 courses of CMF or FAC) followed by postoperative radiotherapy to chest wall or breast and peripheral lymphatic. All patients received hormone therapy (antiestrogen) regardless of the hormone receptor status.

### Main outcome measures

All the patients have been followed up regularly for either recurrence, disease-free interval or death, this continued for two years minimum and five years maximum (median 33 months) Check up in the form of CXR, abdominal ultrasound six monthly and bone scan yearly or whenever clinically indicated. Comparative analysis of the two groups regarding disease-free survival (DFS) and overall survival (OAS) was done. The incidence of disease progression as well as the type of progression was studied for all patients and for both groups separately with statistical evaluation of the results. The prognostic significance of extent of surgery and menopausal status were studied and correlated to DFS, OAS and disease progression with statistical evaluation of the results in both groups.

The chemotherapy: consist of FAC regimen (5-Fu 500 mg/m<sup>2</sup>/D1 cyclophosphamide 500 mg/m<sup>2</sup>/D1 doxorubicin 50 mg/m<sup>2</sup>/D1. This course was repeated every three weeks. (Patients with ejection fraction less than 50%, doxorubicin was replaced by mitoxantrone 12 mg/m<sup>2</sup>). The hormonal treatment was Anti-estrogen (Tamoxifen) 20 mg/day orally was prescribed for all patients and continued all over treatment period and is planned to be taken for 5 years. The postoperative irradiation used for the treatment of all patients by the linear accelerator to a dose of 5040 cGy/28 fractions for chest wall with an electron beam and peripheral lymphatics (with photon beam). Patients with intact breast received their treatment with the above-mentioned dose with photon beam and the primary site was boosted to 6000–6500 cGy total dose with an electron beam.

Statistical evaluation: Fisher's exact test was used for comparative statistical significance.

### 3. Results

The median age for the whole group was 46.5 years and the mean age was 46.19±14.69 years (range 23-75) and the peak age was in the third fourth decade which represents 50% of all patients (Table 1). No difference was noticed in the median age between neoadjuvant chemotherapy group (NCT) and surgery or adjuvant group (surgery) 48 and 46 years respectively (Table 2)

Premenopausal patients constitute 62.5% of whole patients while 37.5% were postmenopausal. In both studied groups (NCT) and (surgery) 57% and 56% were premenopausal while 43% and 35% were postmenopausal respectively (Table 2). Analysis of survival parameters revealed that the median disease-free survival (DFS) for all patients was 15 months and the median overall survival (OAS) was 24 months and there was no difference in (DFC) in (NCT followed by surgery) group and the primary surgery group (16 months and 15 months) as well as the OAS (22 months and 24 months in NCT and the primary surgery group respectively (Tables 3, 4). The influence of menopausal status revealed a highly significant improved differences in DFS and OAS for postmenopause versus premenopause for all patients with DFS 12 months for menopause versus 24 menopause (p=0.01). Similarly, OAS was 18 months in premenopause versus 27 months for postmenopause (p=0.01) (Table 3).

These differences were also noted in NCT followed by surgery group where DFS was 10.5 months for pre menopause and 29 months for post menopause with ( $p=0.05$ ) and OAS was 15.5 months and 35 months for pre and post menopause respectively ( $p=0.03$ ). In the primary surgery group this difference in DFS and OAS for pre and post menopause was statistically insignificant ( $p=0.04$ ) (Table 4). Although the noticed improvement of DFS in NCT followed by surgery group versus the primary surgery group in postmenopausal patients (median 29 months versus 19.5 months), but the difference was statistically insignificant ( $p=0.06$ ). Similarly, the OAS was 35 months in NCT group versus 24 months in the primary surgery group in postmenopausal patients and also the difference was statistically insignificant ( $p=0.5$ ) (Table 4). Relating the survival data to the extent of surgery performed revealed that the median DFS was 12 months for patients performed modified radical mastectomy (MRM) and 20 months for those patients performed conservative surgery, but the difference was statistically insignificant ( $p=0.03$ ). Similarly, the OAS was 24 and 29 months for those performed MRM and conservative surgery respectively with statistically insignificant difference between both groups ( $p=0.06$ ). However, when survival parameters and extent of surgery were studied within each treatment group, it revealed a statistically insignificant difference in the surgery group for DFS ( $p=0.8$ ) and OAS ( $p=0.7$ ) for those performing MRM and conservative surgery (Table 5). But in the NCT followed by surgery group, there was statistically significant difference for DFS ( $P=0.02$ ) and OAS ( $p=0.02$ ) in favor of patients performing conservative surgery. It was also noted in patients performed MRM that there was a statistically significant difference in favor of the primary surgery group versus NCT followed by surgery group regarding DFS (15 Vs. 8 months,  $p=0.02$ ) and OAS (24 Vs 15.5 months,  $p=0.02$ ) (Table 5). The effect of primary chemotherapy in (NCT followed by surgery) group revealed that 6 patients (14.3%) showed complete clinical remission, 14 patients (33.3%) showed more than 50% regression of the primary tumor while 22 patients (52.4%) showed less than 50% regression of the primary tumor. There was no pathological complete remission among patients who achieved complete clinical remission, however, pathologically free margin was achieved for all patients performed post chemotherapy conservative excision.

Regarding treatment results, the incidence of metastatic disease was 55.4% for all patients, 47.6% in NCT followed by surgery group and 60% in the primary surgery group with statistically borderline significant difference between both groups ( $p=0.07$ ). Freedom of disease was achieved in 33.9% of all patients, 28.6% for NCT followed by surgery group and 37.1% for the primary surgery group with statistically borderline significant difference between both groups ( $p=0.08$ ). As for local recurrence, only 2/70 of patients in the primary-surgery group (2.9%) experienced local recurrence versus 10/42 patients (23.8%) in NCT followed by surgery group. Statistical analysis could not be estimated for this category due to the presence of only two patients in the primary-surgery group (Table 6).

**Table 1.** Age group distribution in locally advanced cancer breast

	Age groups	No.	%
1	20 -< 30	12	10.7
2	30 -< 40	28	25
3	40 -< 50	30	26.8
4	50 -< 60	14	12.5
5	60 -< 70	14	12.5
6	> 70	16	14.3
Total		112	100

**Table 2.** Patients characteristic in both groups

Patients characteristic	Neoadjuvant followed by surgery	Primary surgery
<b>Number</b>	42	70
Age (median)	48	46
<b>Menopause:</b>		
Premenop-	24	46
Postmenop	18	70
<b>Tumour status:</b>		
T2		12
T3	30	34
T4	12	20
Tx		4
<b>Nodal status:</b>		
N1	36	38
N2	6	24
Nx		8
<b>Surgical procedures:</b>		
Mod. Rad. Mas.	20	62
Conservative surgery	22	8

**Table 3.** Survival parameters in correlation with menopausal status

	No.	Dis. Free survival (median)	Overall survival (median)
Premenopause	70	12*	18**
Postmenopause	42	24*	27**
Total	112	15	24

\* $p=0.01$

\*\* $p=0.01$

**Table 4.** survival parameters (median values) in correlation to menopausal status in both studied groups

	Neoadjuvant group			Surgery group		
	No.	DFS	OAS	No	DFS	OAS
Premenopausal	24	10.5*	15.5 <sup>a</sup>	46	12 <sup>1</sup>	20 <sup>2</sup>



Postmenopausal	18	<sup>b</sup> 29*	35 <sup>a</sup>	24	<sup>b</sup> 19.5 <sup>1</sup>	24 <sup>2</sup>
Total		16	22	35	15	24

\* $p=0.05$  <sup>2</sup> $p=0.4$  <sup>a</sup> $p=0.03$  <sup>b</sup> $p=0.6$  <sup>1</sup> $p=0.4$  <sup>c</sup> $p=0.5$

**Table 5.** Survival parameters (median values) in correlation to the extent of surgery in the studied groups

	All patients			Neoadjuvant followed by surgery group			Primary surgery group		
	No.	DFS	OAS	No.	DFS	OAS	No.	DFS	OAS
Modified radical mastectomy	82	12	24	20	<sup>1</sup> 8 <sub>a</sub>	<sup>b</sup> 15.5 <sup>2</sup>	62	<sup>3</sup> 15 <sup>a</sup>	<sup>b</sup> 24 <sup>+</sup>
Conservative surgery + axillary clearance	30	20	29	22	<sup>1</sup> 16	35 <sup>2</sup>	8	<sup>3</sup> 15	19 <sup>+</sup>
Total	56	15	24	21	16	22	35	15	24

<sup>a</sup> $p=0.02$  <sup>b</sup> $p=0.02$  <sup>1</sup> $p=0.02$  <sup>3</sup> $p=0.8$  <sup>+</sup> $p=0.7$

**Table 6.** Results of treatment in correlation to the treatment strategy adopted for locally advanced cancer breast

Patient status	All patients		Neoadjuvant group		Surgery group	
	No.	%	No.	%	No.	%
Free	38	33.9	12	28.6*	26	37.1*
Local recurrence.	-	-	-	-	-	-
Metast. Dis.	12	10.7	10	23.8	2	2.9
Metast. Dis.	62	55.4	20	47.6**	42	60**
Total	56	100	21	100	35	100

\* $p=0.08$  \*\* $p=0.07$

### 3. Discussion

Locally advanced breast carcinoma is associated with a poor prognosis; with single treatment modality, i.e. surgery, and/or radiotherapy, results has been consistently dismal (Karlesson et al., 1998). The appropriate management of locally advanced breast cancer is controversial, the trends towards a more effective means of improving response rates and survival have shifted to earlier aggressive treatment and the strength in the management of LABC lies in the team approach to multimodality care (Singletary et al., 1995). The sequence of treatment in those patients still has to be optimized since despite the theoretical and experimental data indicating the survival superiority of neoadjuvant followed by surgery over primary surgery with adjuvant chemotherapy. The role of neoadjuvant chemotherapy in the treatment of breast cancer remains unclear although downstaging of the primary tumor is confirmed (Wang et al., 1996). In the present study which

aimed at comparison of patients treated with neoadjuvant chemotherapy followed by surgery and those treated by primary surgery followed by adjuvant chemotherapy, analysis of data revealed that the median age was 46.5 years and the mean was 47.19±14.69 years. This median age was also reported from a similar study performed in KFSH-Riyadh study (Ibrahim et al., 1999). This mean age is not different from the overall age incidence for breast cancer in Saudi Arabia, which reported mean age at diagnosis to be 48.3 years (Cancer Incidence SA, 1999). Premenopausal patients comprise 62.5% of all patients and 37.5% postmenopausal, this incidence was similar to that reported by KFSH-Riyadh (Ibrahim et al., 1999).

Analysis of survival data revealed that the median DFS in our patients was 16 months, a similar figure (17 months) was reported in a similar study (Eisten et al., 1998). No difference in DFS and OAS was noticed in patients treated by NCT followed by surgery or by primary surgery, this finding has been documented by Fisher (Fisher et al., 1998), who compared preoperative with postoperative therapy in operable breast cancer patients including LABC cases and found no difference in DFS and OAS between pre and postoperative chemotherapy. Cunningham (Cunningham et al., 1998) and Kuerer (Kuerer et al., 1999) also found no significant difference in DFS and OAS between NCT and postoperative adjuvant treatment.

This significance of menopausal status in this study showed that DFS and OAS were significantly better in older age group (postmenopause). This finding has been studied by Crowe (Crowe et al., 1994) who found that younger patients had more estrogen receptor negative tumors and a greater number of positive lymph nodes and he concluded that younger patients as a group has more aggressive and advanced cancer compared to older patients, but it should not be used alone for management decision. This was reported also by Newman (Newman et al., 1998) who confirmed that younger women tend to present with more locally advanced breast cancer and their tumors may have different response to treatment, compared to older patients and hence this significant difference in survival is a reflection of the aggressive nature of the disease in younger age group.

The second finding concerning age in our results was noticed by inspecting the insignificant difference in DFS and OAS for pre and postmenopausal patients in the primary surgery group and also postmenopausal patients in either group. This finding could suggest the possibility that younger age group might benefit from earlier surgical interference in premenopausal patients especially those who initially showed minimal response to chemotherapy (after 2 courses). Although, the DFS and OAS were more or less similar in both groups; however earlier surgery for premenopausal patients may abolish this significant difference in survival between pre and post menopause for patients treated with neoadjuvant chemotherapy.

Considering the extent of the surgery, the insignificant difference in survival parameters (DFS and OAS) for all patients and also for patients in primary surgery group could be explained by the fact that the main problem in patients with LABC is the distant failure regardless the locoregional control of the disease (Taylor et al., 1997; Harris et al., 1997). For this reason, recent trials and utilizing aggressive chemotherapy with newer agents like Taxol (Philiph et al., 2000; Esteva et al., 2000) or by increasing dose intensity in conjunction with growth factors to increase the response of the tumors to primary chemotherapy which may improve the survival and this is reported in southwest oncology group phase II trials (Ellis et al., 2000).

On the other hand, in NCT followed by surgery group, there was the discrepancy in the results since there was the significant difference in survival parameters (DFS and OAS) favoring patients who performed conservative surgery. However, this finding could be explained by the fact that patients who performed conservative surgery were those who showed excellent response to primary chemotherapy and they achieved better results than those who showed minimal response to chemotherapy and consequently performed modified radical mastectomy did. These results were also reported by Schwartz (Schwartz et al., 1994) who showed in their series of patients treated by neoadjuvant chemotherapy a five-year disease-free survival 56% for those having mastectomy and 77% for those having breast conservation and five years overall survival was 67% for those performed mastectomy and 80% for those having breast conservation. Recent trials currently are using aggressive chemotherapy to achieve a higher remission clinically and pathologically in order to improve DFS and OAS (Philiph et al., 2000; Esteva et al., 2000; Ellis et al., 2000). Worth mentioning that those responsive patients to primary chemotherapy who underwent conservative surgery might

be responsive also to the adjuvant chemotherapy postoperatively and that is why they showed improved survival parameters in comparison with all other subsets of patients.

Regarding treatment results, freedom of disease was noticed in 37.1% of primary surgery group Vs 28.6% in NCT followed by surgery group with the borderline significant ( $p=0.08$ ). This could be explained by the presence of only one patient with local recurrence in the primary surgery group Vs 5 in the NCT followed by surgery group and this is the consequence of a large number of patients performed conservative surgery in the NCT group (22 patients) versus only eight patients in the primary surgery group. This finding was reported by Taylor (Taylor et al., 1997) who found that mastectomy substantially decreased locoregional recurrence but distant metastases were a major component of failure. This was noticed in this work, where there is 60% incidence of metastatic disease in the primary surgery group Vs 47.6% in NCT followed by surgery group with the borderline significant difference ( $p=0.07$ ). This could be explained by the fact that most LABC patients would be already harbouring micrometastases at their initial diagnosis, that should be primarily treated by chemotherapy as it was suggested that chemotherapy may modulate the host environment to prevent tumor cell migration (Murthy et al., 1999).

#### 4. Conclusion

The results of this study showed that primary surgery followed by postoperative therapy is comparable to neoadjuvant therapy followed by surgery in LABC regarding disease-free survival, overall survival, distant failure and disease control. However, local recurrence was higher in NCT followed by surgery group because of the favorability of conservative resection in both patients and surgeons side once they got tumor shrinkage, but we have to give attention to what was reported about this situation by Kent (Kent et al., 1995) who found that chemotherapy is useful in reducing tumor size to allow surgical resection but does not sterilize the breast of cancer and they caution against the use of any surgery less than total mastectomy in partially responsive tumor if optimal local control is to be achieved in locally advanced breast cancer. Secondly, the post menopause (older age) patients fared much better than younger age regarding survival parameters particularly with NCT followed by surgery group. So, we recommend that younger patients who deserve neoadjuvant chemotherapy have to be treated aggressively by surgery not less than mastectomy. The other alternative is the use of a newer chemotherapeutic agents or increasing dose intensity of chemotherapy to obtain a higher clinical and pathological remission so that conservative surgery could be performed with optimal local control and reducing distant failure (Green et al., 2005; Ellis et al., 2006; Von et al., 2005; William et al., 2011). Neo adjuvant chemotherapy will also provide a useful biological model to assess the effects of systemic treatment on the primary tumor and regional metastases, in addition to hoping to reduce distant failure.

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