

Effects of neoadjuvant chemotherapy on the surgical outcome of locally advanced breast cancer

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ABSTRACT

Background: Results of surgery and radiotherapy in the treatment of locally advanced breast cancer (LABC) used to be uniformly poor. Turning point in the treatment of LABC came when neo-adjuvant chemotherapy (NACT) was integrated in its management. This study reviews the long-term outcome of patients who were treated with NACT when it was first introduced in the authors' center.

Methods: This observational study included the initial cohort with LABC, enlisted for NACT during the period of January 2003 to December 2006 and a follow-up of 5 years at the Christian Medical College Hospital, Ludhiana. The protocol followed was neo-adjuvant chemotherapy (NACT) followed by surgery and adjuvant radiotherapy with or without chemotherapy and hormonal replacement.

Results: Among the 24 patients who received NACT, 20 patients (83.33%) completed treatment with modified radical mastectomy followed by adjuvant therapy. All of them responded to NACT thereby making the tumor resectable. Among them 4/20 (20%) patients developed locoregional recurrence and similar number developed distant metastasis

Conclusion: Patients with locally advanced breast cancer tolerated NACT well without any increase in surgical morbidity. Chemotherapy response was characterized by clinical down staging in all the patients thereby making the tumor surgically resectable. Although NACT was advantageous in initial resection, it was not shown to be advantageous in overall survival long-term follow-up.

Key words: Breast cancer, locally advanced carcinoma, neo-adjuvant chemotherapy, Neoplasia, local recurrence

Abbreviations: *AJCC* - American Joint Committee on Cancer; *ER* - Estrogen receptor; *FAC* - Fluorouracil + Adriamycin + Cytosine; *Her-2 neu* - Human epidermal growth factor receptor type-2 (neural source prototype);

LABC – Locally advanced breast cancer; *MRM* – Modified radical mastectomy;

NACT – Neo-adjuvant chemotherapy, *PR* - Progesterone receptor; *SD* - Standard deviation

Introduction

Locally advanced breast cancer comprises of a heterogeneous group of patients including neglected slow

growing tumors at one end of the spectrum and biologically aggressive disease at the other end. [1] In India LABC accounts for 50% of all cases.[2] LABC is characterized by a large primary tumor and/or extensive locoregional lymphadenopathy. It includes patients with T3 (>5 cm) or T4 tumors (chest wall fixation or skin ulceration and/or satellitosis) and N2/N3 disease (matted axillary and/or ipsilateral supraclavicular lymph node metastases). [3]

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Results of surgery and radiation therapy alone were uniformly poor in LABC [4]. However, multimodality approach has been shown to improve survival in patients

with metastatic disease limited to the supraclavicular nodes.[3,5] Historically, LABC was treated with radical mastectomy [6], until Haagensen and Stout showed that clinical features such as skin ulceration, *peau d'orange* and tumor fixity were associated with increased morbidity and poor outcome.[7] Radiation therapy either as primary treatment or as adjuvant therapy offered better locoregional control. However, it was disadvantaged by inherent debilitating morbidity and minimal impact on overall survival. [8,9] NACT, refers to preoperative chemotherapy given in addition to surgery or radiation (local therapies). NACT significantly improved the outcome of LABC, and was integrated into its management.[10] At the Christian Medical College Hospital, Ludhiana multimodality treatment for LABC was incorporated as a standard of treatment since 2003. This study reviews the 5-year outcome in this earliest cohort of patients.

Methods

This retrospective observational included all patients with LABC who were enrolled for NACT during the period of January 2003 and December 2006 at the Christian Medical College Hospital, Ludhiana. Male breast cancer, metastatic disease, Paget's disease of the breast, inflammatory breast cancer and treatment defaulters were excluded from the study. The multidisciplinary management team included general surgeons, oncologists and radiation oncologists. The protocol followed was initial neo-adjuvant chemotherapy (NACT), subsequent surgery followed by adjuvant radiotherapy with or without chemotherapy and hormonal replacement (depending on the hormonal receptor status).

Observations were made in 3 phases: In phase-1 diagnosis of LABC was established and chemotherapy was initiated. All the patients were clinically staged by triple assessment (clinical examination, imaging and cyto/histopathology) and a Tru-cut biopsy for ER/PR and Her-2 neu status. NACT consisted of anthracycline based regimens, the most commonly used being FAC regimen. The number of chemo-cycles was decided for individual patients on the basis of clinical response. In phase-2 response to chemotherapy and disease progression were assessed prior to mastectomy. Chemoresponse was graded as complete (impalpable tumor), partial (>50% size reduction) or no response (<50% size reduction). All patients were counseled regarding the options of breast conservation surgery versus MRM. Majority of them opted for MRM and none opted for breast conservation. In phase-3 final disease-staging was done according to tumor size, histopathological subtype and operation findings. Post-operative adjuvant treatment was

administered (chemo-radiotherapy) along with hormonal therapy (tamoxifen) depending on the receptor status. Patients were followed-up for 5 years. Patients were evaluated for short-term outcomes such as wound healing, delay in adjuvant therapy and absence of macroscopic disease. Relapse-free or disease-free survival time was calculated between the time of primary tumor diagnosis and the time of detecting locoregional recurrence, distant metastasis or death. The results obtained were analyzed statistically using the Student's 't' test, 'z' test, ANOVA and Pearson's coefficient of correlation 'r'. P value less than 0.05 was considered as statistically significant.

Results

There were 24 patients with LABC during the study period. There were 4 defaulters post-NACT who refused consent for surgical operation and/or adjuvant therapy and failed to follow up. Mean age of the patients was 51.63 ± 9.67 SD (range 28-70 years). Table-1 summarizes the pre-treatment tumor attributes. Left sided lesions and menopausal age group were significantly more common than right sided lesions and peri-menopausal age. Twenty patients (83%) were educated whereas 4 (17%) were uneducated (p<0.05). The mean duration of symptoms was 12.98 months ± 9.06 SD. Awareness of breast cancer in the study group was extremely low as indicated by the educational status of patients and the duration of symptoms. Majority of patients (79%) were unaware of breast cancer and only 5 patients (21%) had some knowledge of the disease (p < 0.01). Majority of patients (62%) in spite of being educated were unaware of the disease. Cancer awareness had no effect on the duration of symptoms as 80% of them had symptoms for more than 6 months.

Table 1: Tumor Attributes at diagnosis

Parameters	n (24)	%	P Value
Pre-treatment tumor staging			<0.01
III a	5	21	
III b	19	79	
Size (cm)			> 0.10
4-6	6	25	
6-10	18	75	
Side of lesion			<0.01
Right	9	37	
Left	15	63	
Menstrual status			<0.01
Menopausal	17	70	
Peri-menopausal	7	29	

In all age groups >4 cycles of NACT was administered. Complete response was seen in 45% and partial response in 54% of patients ($p>0.10$) - which remained unaffected by hormone receptor status (Table-2). Complete response was significantly less frequent in stage IIIB tumors and ($n=5$) and in lesions >4-6 cm. Most of the patients ($n=21$) irrespective of tumor size-stage or nodal status received FAC based NACT. MRM was opted by 17 patients (81%) in FAC group and 3 patients (100%) in non FAC group. Four patients in FAC group (19.05%) defaulted from further treatment and did not follow-up thereafter. Following NACT with FAC complete and partial response was noted in 10 and 11 patients respectively; but the difference was not statistically significant. Among the 12 patients (60%) with clinically impalpable nodes at the end of NACT, 4 were found to have histologically positive nodes in surgical specimen.

In those who underwent mastectomy following NACT, histopathological residual tumor was seen in all excised breast specimen. Microscopic nodal disease was present in 10 patients in FAC group and 2 in non-FAC group. Histopathological nodal negative disease was noted in 40%. All the patients received radiotherapy after surgery. NACT did not affect short-term surgical outcome such as wound healing, and skin loss. (Table 3) Delayed healing was noted in 10 patients (50%), due to which adjuvant

chemotherapy was delayed by 2 weeks.

Histopathological examination showed residual tumor was present in all the patients at primary site but, positive nodal disease was seen in 12 patients (60%) only. Thus in 8 patients (40%) there was complete regression of nodal disease in axilla after NACT. However, during initial evaluation only the primary tumor was biopsied and the lymph nodes even when enlarged were not subjected to histopathological examination. Histopathologically 17 patients (85%) had infiltrating ductal carcinoma and 3 (15%) had invasive lobular carcinoma. Following surgery all patients received adjuvant external beam radiotherapy with a dose of 50 Gy to chest wall and 50 Gy to axilla along with adjuvant chemotherapy. No additional significant complications were noted. Fourteen patients received Tamoxifen therapy depending on receptor status. All patients were followed up for 60 months.

Four patients developed loco-regional recurrence during follow-up period. (Table 4) Local relapse was not affected by disease stage at diagnosis, nodal status, pre-treatment tumor size, hormone receptor status, chemoresponse or post-NACT tumor size. However, local recurrences were significantly less common among post-menopausal women. In the patients with locoregional relapse the mean duration of disease-free survival was 21 ± 11.5 months and the same for patients with distant metastasis

Table 2: Comparison of chemotherapy response and different tumor attributes

	No. of cycles (mean)	Clinical response At cycle (mean)	Complete Response (n)	Partial Response (n)	P Value
Age groups (yrs)					
< 40	3.67	3	0	3	>0.10
40-49	4.5	3.25	1	3	>0.10
50-59	4.36	2.82	7	4	>0.10
60-69	4.8	3.6	2	3	>0.10
>70	4	2	1	0	>0.10
Receptor status					
ER+	4.39	2.94	8	10	>0.10
ER-	4.33	3.33	3	3	>0.10
her-2 neu +	4.4	3.2	3	2	>0.10
Pretreatment Clinical staging					
IIIA	4	2.6	4	1	<0.05
IIIB	4.47	3.16	7	12	>0.10
Pretreatment tumor size					
4-6	4	2.67	4	2	>0.10
6-10	4.5	3.17	7	11	<0.01

Table 3: Correlation between the type of neo - adjuvant chemotherapy (NACT) and short-term outcome

n=20	FAC (n = 17)	Others* (n = 3)	P value
Histopathology of surgical specimen following NACT			
Residual tumor present	17	3	>0.10
Nodal disease present	10	2	>0.10
Nodal disease not present	7	1	>0.10
Need for Radiotherapy	17	3	>0.10
Drain removal (mean days)	6.3 ± 3.1	7 ± 2.7	>0.10
Suture removal (mean days)	14.8 ± 5.0	21.7 ± 8.5	>0.10
Delay in healing	7	3	>0.10
Skin loss	0	0	-

* Others include CMF, PC and FEC regimen in one each
 FAC-Fluorouracil +Adriamycin+Cytosin;
 CMF- Cyclophosphamide + Methotrexate + Fluorouracil ;
 FEC - Fluorouracil + Epirubicin + Cyclophosphamide;
 PC - Paclitaxel + Carboplatin

was 37.5 ± 11.2 months.

Distant metastasis was seen in 20% of tumors initial tumor size of 6-10 cm. although a high percentage of locoregional recurrence (15%) and distant metastasis (20%) was noted in patients with stage IIIB disease and also in patients with tumor size 6-10 cm, the difference was not statistically significant. Recurrences were frequently seen in chest wall (n=3), axilla (n=1), lungs (n=3), liver (n=2) and brain (n=2).

Of the 4 patients with distant metastasis, 1 patient had an isolated lung metastasis along with a local chest wall recurrence, 1 patient had a simultaneous pulmonary and liver secondary, 1 patient had malignant plural effusion and cerebral metastasis simultaneously, and 1 patient had simultaneous liver and cerebral metastasis. All these patients were alive at their last follow-up, except for the patient with liver and cerebral metastasis who died during the follow up period.

DISCUSSION

Breast cancer is one of the commonest causes of cancer related death in middle aged women of developed countries and its incidence is increasing in developing countries as well. After uterine cervix, breast is the second most common site of cancer among Indian women. Annually 75,000 new cases of breast cancer are diagnosed in India [11]. Multimodality treatment of breast cancer prolonged the survival of patients with

metastatic disease limited to supraclavicular nodes. This necessitated revision of the (AJCC) staging system which in its 6th edition included isolated supraclavicular metastases in the stage III or LABC disease category. Data from the American College of Surgeons reveals that approximately 6% of breast cancers in the United States present as stage III with 5-year survival approximately 50%, compared with 87% for stage I disease. [3, 12 ,13]

Preoperative chemotherapy protocols (also known as neoadjuvant or induction chemotherapy) significantly improved the outcome of LABC. NACT is now considered as the standard of care for patients with bulky lesion of the breast and/or axillary disease. Comparable operative morbidity has been demonstrated in LABC patients treated with mastectomy and those who received NACT; the latter actually had lower rate of postoperative wound complications. Similar studies reported that NACT neither adversely affects surgical complication rates nor delays postoperative treatment. Most patients can be taken up for surgery within 3 to 4 weeks after the last chemotherapy cycle, when the absolute neutrophil and platelet counts are greater than 1500 and 100,000, respectively.[14,15] Whether NACT improves survival in LABC remains controversial. Several prospective trials have shown that delay in surgery consequent to NACT does not compromise surgical outcome when compared to the surgery first regime, followed by adjuvant chemo-radiotherapy. It has been shown that NACT does not worsen survival but it improves resectability.

Table 4: Correlation between tumor characteristics, chemoresponse and locoregional relapse

Clinical characteristics	Locoregional Relapse		P value
	Present (n = 4)	Absent (n = 16)	
Patient age			
Age (Mean ± SD)	41.5 ± 10.7	53.4 ± 7.8	
Post-menopausal	1	13	
Peri-menopausal	3	3	< 0.05
Receptor status			
ER negative	0	6	> 0.10
ER positive	4	10	
pre-treatment staging			
Stage IIIA	1	4	
Stage IIIB	3	12	> 0.10
Pre-treatment tumor size			
4-6 cm	2	4	
6-10 cm	2	12	> 0.10
Pre-treatment nodal status			
N 1	1	6	
N 2	2	9	
N 3	1	1	> 0.10
Chemotherapy response			
Complete response	1	7	
Partial response	3	9	> 0.10
Post-treatment tumor size			
< 2 cm	1	0	
2-5 cm	3	12	
> 5 cm	0	4	> 0.10

Approximately 80% of patients exhibit significant shrinkage of primary tumor while only 2% to 3% have disease progression.[16,17] In our study, complete clinical response in relation to age was found to increase with increasing age followed by a sharp decline in clinical response after the age of 70 years.

ER positive receptor status was ascertained in 18 patients in whom 6 were ER negative (25%), 16 (67%) were PR positive and 8 patients were PR negative (33%). It was found that 15 patients with Stage III B (62%) disease and 14 patients with tumor size of 6-10 cm (59%) had ER positive tumors. This suggests that ER positivity is more often associated with large tumors. Her-2 neu receptor was assayed in only 5 patients in the latter half of the present study and was found to be positive in all 5. The mean number of chemotherapy cycles to a clinical

response was 4.4. Colleoni et.al and Daidone et.al have demonstrated a superior clinical response for ER negative compared with ER positive tumors. This was related to a higher rate of tumor cell proliferation in ER negative tumor. [18,19]. However we could not find any correlation between receptor status and chemoresponse.

Among the 12 patients who had complete post-NACT clinical response in axilla, we found complete histopathological response in 4 patients (20%) and positive nodal status in 8 (40%). Kuerer et al in their study observed post-NACT complete clinical response of axillary disease was 31% while a complete pathological response was 22% [20].

All patients received neo adjuvant chemotherapy, 21 (87%) received FAC regimen while 3 patients had received other regimens (CMF, Paclitaxel + Carboplatin,

FEC in one each). All patients responded to chemotherapy and none had progression of disease during the treatment period. Myelosuppression was seen in 10 patients (41.7%). Alopecia was documented in all the patients. Delayed wound healing was seen in 10 patients (50%) in the form of seroma formation with wound dehiscence and minimal superficial flap necrosis. However, in all the patients, skin could be approximated primarily during surgery without mobilization of any flap or requirement of skin graft. In view of advanced stage of disease at presentation, and small cohort of patients, it is difficult to comment upon the impact of NACT treatment schedule on overall survival or biological behavior of disease, with 20% patients having local recurrence and similar number with distant metastasis.

Conclusions

Although chemoresponse was variable NACT was useful in all patients in downsizing the tumor prior to surgery thus making them resectable. NACT did not adversely interfere with subsequent surgical or adjuvant therapy in these patients. However NACT does not appear to affect overall survival as evident from local recurrence and distal metastasis in 40% of patients.

Conflicts of Interest : Nil

Ethics : Compliance with ethical principles declared

Funding : Self funded

Guarantor: Dr. Parvez David Haque will act as guarantor of this article on behalf of all co-authors

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