

Feasibility of breast conservation surgery in locally advanced breast cancer downstaged by neoadjuvant chemotherapy: A study in mastectomy specimens using simulation lumpectomy

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Abstract

BACKGROUND: The response of locally advanced breast cancer (LABC) to neoadjuvant chemotherapy (NACT) offers these patients previously treated by mastectomy, the chance for breast conservation. **AIM:** This study aims to assess the feasibility of lumpectomy in patients with LABC treated by NACT, with residual tumor ≤ 5 cm. **SETTINGS, DESIGN:** Single group prospective study from August 2001 to June 2003 in a teaching hospital. **MATERIALS AND METHODS:** Thirty patients with LABC whose tumors reduced with NACT to ≤ 5 cm were included. Simulation lumpectomy was performed on the mastectomy specimens to achieve 1 to 2 cm clearance from tumor and hence margin negativity. Multiple sections of the inked margin were studied. **STATISTICAL ANALYSIS:** Margin positivity was correlated with patient factors. Chi square test and Fisher's exact test used as appropriate. P value ≤ 0.05 was considered significant. **RESULTS AND CONCLUSIONS:** After three cycles of NACT, 4 patients (13%) had complete clinical response including 2 with complete pathological response. Twenty-two (73%) showed partial response and 4, no response. Fourteen out of thirty (47%) had tumor involvement of margins. Tumors with post-chemotherapy size >4 cm were margin positive in 10/13 (77%). Tumors with post-chemotherapy size >3 cm were margin positive in 13/24 (54%). Tumors with post-chemotherapy size ≤ 3 cm were margin negative in 5/6 (83%). Pre-chemotherapy tumor size and post-chemotherapy tumor size were significantly associated with margin positivity ($P=0.003$). Tumors in the subareolar location had significantly higher incidence of residual tumor in the nipple areola complex. ($P=0.04$). Margin positivity of lumpectomy on downstaged tumors can be reduced by removing the nipple areola complex in subareolar tumors and by limiting breast conservation to tumors with post-chemotherapy size ≤ 3 cm.

Key Words: Breast conservation surgery, locally advanced breast cancer, neoadjuvant chemotherapy, downstaging, lumpectomy

Introduction

The standard treatment of locally advanced breast cancer (LABC) is neoadjuvant chemotherapy (NACT). It has a high rate of success, causing complete clinical response

in some patients and reducing the size of the tumor in many patients.^[1]

Patients with LABC previously treated by total mastectomy with level II axillary clearance could now

be offered the chance for breast conservation surgery.^[1]

It is known that the risk of recurrence is related to margin status and within the limits of esthetics, there is consensus that wider margins are always better if achievable.^[2]

This study is planned with the purpose of demonstrating the feasibility of breast conservation surgery (lumpectomy) by achieving negative surgical margins in simulation lumpectomies performed on the mastectomy specimens of patients with LABC treated by NACT and mastectomy.

Materials and Methods

This single group prospective study, conducted between August 2001 and June 2003 included patients of LABC with tumor size greater than five cm and whose treatment plan was neoadjuvant chemotherapy followed by total mastectomy.

Patients unfit for chemotherapy, those requiring preoperative radiation, patients with skin ulceration, those with previous incisional biopsy of the primary tumor and male patients were excluded.

The workup included fine needle aspiration cytology from the primary tumor and palpable axillary lymph nodes, complete blood count with peripheral smear, routine biochemistry and liver function tests, chest X-ray, ultrasound of abdomen and electrocardiogram.

For clinical staging, size of the primary tumor was measured over the two longest perpendicular diameters and the product calculated. The number and groups of palpable axillary nodes were noted.

Informed consent was obtained, explaining the nature of disease, treatment options, advantages and side-effects of chemotherapy and need for surgery after chemotherapy. All patients received three cycles of Adriamycin-based chemotherapy intravenously at three weekly intervals (Cyclophosphamide 500 mg/m², Adriamycin 50 mg/m², 5-FU 500 mg/m², Vincristine 1.2 mg/m²; CAFV on Day 1 and 5-FU on Day 8). Patients were assessed for side-effects and response of the primary tumor and axilla before every cycle. All postmenopausal patients received Tamoxifen 10 mg twice daily.

Patients were reassessed 21 days after the completion of the third cycle by clinical examination, and ultrasound in patients with complete clinical response. Those whose

residual tumor was >5 cm were excluded. Those with residual tumor ≤ 5 cm in longest diameter underwent total mastectomy with level II axillary clearance.

A simulation lumpectomy was performed on the mastectomy specimens with a margin of 1-2 cm around the palpable tumor. The lumpectomy specimen obtained was marked for orientation of the pathologist, coated with India ink for staining of margins and immersed in formalin for fixation.

Samples were taken from the superior, lateral, inferior and medial margins of the transversely cut central section and from the residual central tumor. The superior and inferior hemispheres were now sectioned in the sagittal plane and margins closest to the tumor were studied. Samples of all quadrants of the breast, any suspicious areas on gross examination and the nipple areola complex were obtained to exclude multicentricity. Examination of axillary fat pad and nodes was done.

Histopathological examination was done for margin involvement by the tumor and described as positive or negative based on the presence or absence of invasive or intraductal carcinoma at the surface of the margin. Samples from the quadrants were studied for any residual invasive carcinoma or insitu carcinoma changes. The nipple areola complex was studied for tumor infiltration. Axillary lymph nodes were examined for metastasis.

Margin positivity was correlated with factors such as age (<50 years), menopausal status, site of tumor, pre-chemotherapy tumor size, clinical response, and post-chemotherapy tumor size.

Statistical Analysis-Chi square test, Fisher's exact test and student's t test were used as appropriate. A *P* value of less than or equal to 0.05 was considered statistically significant. The Statistical Package for Social Sciences (SPSS, Chicago, Illinois, USA) software version 10.0 was utilized for data analysis.

The study protocol was approved by the hospital's ethics committee.

Results

Forty patients were initially included in the study. Only 36 completed three cycles of chemotherapy. Of these 6 patients showed no response, their tumors did not reduce to a size ≤5 cm and they were not considered for the rest of the study.

The patients' age ranged from 30-72 years (mean= 48 years) and all were multiparous. Thirteen patients (43%) were premenopausal and 17 patients (57%) were postmenopausal. Tumors were right-sided in 16 and left-sided in 14. Upper outer quadrant tumors predominated, 18/30. Five patients had central quadrant tumors. Sixty per cent patients presented within 4 months of onset of symptoms (lump in breast). No tumor was fixed to the pectoralis major or the chest wall. There was no detectable distant metastasis. Twenty-one out of thirty (70%) had T3 tumors whereas 9/30 had T4 tumors. Axillary nodal status was N1 in 28 patients (93%) and N2 in 2 patients (7%). Twenty-one patients had Stage IIIa disease and 9 had Stage IIIb disease. The size of the primary tumor ranged from 5-9 cm (mean=7.1 cm). Axillary nodes ranging from 1-3 in number were palpable in all. All patients tolerated chemotherapy without major complications, alopecia and vomiting being the commonest side-effects.

Of 30 patients 4 (13%) had complete clinical response, 22 (73%) had partial response and 4 (13%) no response. Complete pathological response was seen in 2/4 of the patients with complete clinical response.

There was a significant association between pre-chemotherapy tumor size and histopathological margin status ($P=0.003$) (Table 1) and a significant difference in mean tumor size in patients with positive histopathological margin (7.5 ± 0.76 cm) and negative histopathological margin (6.63 ± 1.02 cm) by students 't' test ($P=0.01$). The size of the tumor decreased in response to chemotherapy in all the patients. Mean post-chemotherapy tumor size was 3.8 cm.

There was a significant association between post-chemotherapy tumor size and histopathological margin status ($P=0.003$) (Table 1).

In tumors with post-chemotherapy tumor size >4 cm, 10/13 (77%) were margin positive and 3/13 (23%) were margin negative whereas in tumors with post-chemotherapy size >3 cm, 13/24 (54%) were margin positive and 11/24 (46%) were margin negative. In tumors with post-chemotherapy size <3 cm, 1/6 (17%) were margin positive and 5/6 (83%) were margin negative.

Clinical examination of the axilla revealed a complete response in 10/30 (33%) and an incomplete response in 20/30 (67%). Pathological examination showed metastasis in 20/29 (69%) and no metastasis in 9/29 (31%).

All patients underwent total mastectomy and 29

Table 1: Analysis of patient and tumor characteristics associated with histopathological margin status

Characteristics		Margin status		P value
		Positive	Negative	
Age (Years)	<50	8	9	0.961
	≥ 50	6	7	
Menopausal status	Premenopausal	6	7	0.961
	Postmenopausal	8	9	
Tumor location	Subareolar	4	1	0.419
	Other quadrants	10	15	
T stage	T3	10	11	0.873
	T4	4	5	
AJCC stage	IIIa	10	11	0.873
	IIIb	4	5	
Clinical response	Complete	1	3	0.35
	Incomplete	13	13	
Pre-chemotherapy Tumor size (cm)	5.1-7.0	5	14	0.003
	7.1-9.0	9	2	
Post-chemotherapy Tumor size (cm)	>4	10	3	0.0036
	≤ 4	4	13	
Post-chemotherapy Tumor size (cm)	>3	13	11	0.17
	≤ 3	1	5	
Axillary lymph node metastasis	Positive	11	9	0.28
	Negative	3	6	

underwent level II axillary clearance. One patient did not undergo axillary clearance due to fibrosis of axilla. Simulation lumpectomy margins were free from tumor on gross examination. In 4/30 cases the skin overlying the tumor showing fixity had to be removed with 1 cm margin. Skin margins were not involved on histopathological examination. The nipple areola complex was sacrificed in one case since the areolar skin appeared to be involved by the tumor. There was no visible or palpable residual tumor in any of the mastectomy specimens.

Histopathological examination of the margins showed positive margins in 14/30 (47%) and negative margins in 16/30 (53%). Of the 14 patients who had peripheral margin involvement, 10 had single peripheral margin involved. Seven were partial responders, 2 were in the no response category and one was in the complete response category. A clearance of 1 to 2 cm was achieved in 7/10 of these cases. Four patients had two peripheral margins involved and all were in the partial response category. A clearance margin of 1 to 2 cm was achieved in three of these cases.

Tumor histology was infiltrating ductal carcinoma in 29/30 and infiltrating lobular carcinoma in one. In 2

patients with complete pathological response, the lumpectomy specimen did not reveal any tumor. The remaining breast tissue in the mastectomy specimen did not show any invasive carcinoma or any ductal carcinoma in situ (DCIS).

The nipple areola was positive in 6/30 (20%). Of these 3 were subareolar tumors, 3/6 (50%). There was a significant association between tumor location and histopathological status of the nipple areola complex (Table 2) ($P=0.04$ by Fischer's exact test).

Discussion

The overall objective response of the primary tumor was 87% with a complete clinical response of 13%. Machiavelli et al^[3] in their study of 148 patients with LABC recorded objective response in 71%. Primary tumor response was assessed by clinical examination. Herrada et al^[4] demonstrated that physical examination correlated best with pathological findings in the measurement of primary tumor.

There was a significant association between pre-chemotherapy tumor size, post-chemotherapy tumor size and histopathological margin status. Tumor size was found to be associated with positive surgical margins by Peterson et al,^[5] Park et al^[6] and Tartter et al^[7] by univariate analysis. Tartter et al^[7] and Luu et al^[8] demonstrated by multivariate analysis also, that tumor size showed a significant correlation with surgical margins.

In tumors with post-chemotherapy size >4 cm, 10/13 (77%) were margin positive, and 13/24 (54%) were margin positive in tumors with post-chemotherapy size >3 cm. In tumors with post-chemotherapy size <3 cm 1/6(17%) were margin positive and 5/6(83%) were margin negative.

Therefore a smaller post-chemotherapy size is found to give lesser margin positivity. The previous recommendation for breast conservation surgery was for tumors up to 4 cm or those with residual tumor size < 5 cm.^[9] Cosmetic results are more acceptable with

smaller tumors.^[10-12] Cosmetic outcome could not be evaluated in our study since surgery was done on specimens.

Various authors have studied patient and tumor characteristics associated with positive surgical margins in patients with invasive ductal carcinoma treated with primary breast conservation therapy.^[5-8,13-15] Those which were significant included younger age, DCIS, extensive intraductal component, positive family history, lymphovascular invasion, axillary node positivity status and large tumor size.

In this study age, menopausal status, quadrant location, T stage, AJCC stage, clinical response to NACT and axillary lymph node status were not found to be significantly associated with histopathological margin positivity.

Margin positivity may be either due to technical error in dissection or due to the response of the tumor to chemotherapy, leaving behind islands of tumor cells while it shrinks. This phenomenon was explained by Hunt et al^[11] and Moneer et al^[16] as due to irregular tumor angiogenesis or tumor polyclonality, resulting in cell populations with varying exposure and susceptibility to the cytotoxic agents.

Holland et al^[17] in their classical pathologic study estimated that if conservative surgery was done with a 2-cm margin, infiltrating disease would be left behind in 12% and ca in situ in 25%. With a 3-cm margin these values were 8% and 9% and with 4 cm the values were 5% and 5%. Since a 1-2 cm margin was given in our study, the almost 50% positivity of the margins has been contributed to, at least in part, by the process of tumor segmentation.

In our study, the rest of the breast tissue of the mastectomy specimen did not show any evidence of invasive carcinoma or ductal carcinoma in situ in spite of sampling from all quadrants, any suspicious areas and the nipple areola complex. Moneer et al^[16] had 9 no response cases and tumor multifocality was observed in only 1 case (11%) whereas 20/29(70%) of the partial response cases had tumor foci in the vicinity of the main lesion. This was statistically highly significant.

Veronesi et al^[18] in their study of 226 patients found histological multifocality in the primary in 37 patients (16%). In 22 (60%) of these cases, pre-chemotherapy mammography showed a carcinoma associated with microcalcifications. Multifocality was observed more frequently in larger tumors, probably because the

Table 2: Correlation of histopathological status of the nipple areola complex with tumor location

Tumor location	Nipple areola		
	Positive	Negative	Total
Subareolar	3	2	5
Other quadrants	3	22	25
Total	6	24	30

tumors had not been uniformly destroyed by chemotherapy.

The nipple areola complex was positive for tumor in 6/30 (20%). Of these 3 were central quadrant tumors. There was a significant association between tumor location and the histopathological status of the nipple and areola. Gajdos et al^[19] in their study of 95 patients with subareolar cancer showed that subareolar cancers can be successfully treated with breast conservation surgery provided adjuvant radiotherapy is always given, and that clinical involvement of the nipple areola complex is associated with high risk of local failure when treated with breast conservation without radiation therapy.

Since 3/5 of the central quadrant tumors were showing nipple areola complex involvement, it might be recommended that the nipple and areola be removed in cases of breast conservation in subareolar tumors.

In conclusion, the following methods may be adopted to reduce margin positivity in breast conservation surgery performed on locally advanced breast cancer downstaged with neoadjuvant chemotherapy.

1. Removal of the nipple areola complex in subareolar tumors.
2. Limiting breast conservation surgery to tumors with a post-chemotherapy size less than 3 cm.

In patients showing partial response and/or those with a larger tumor size at presentation, wider margins may be useful during lumpectomy for removing tumor foci left behind due to tumor segmentation.

The question also arises whether additional cycles of NACT and/or use of taxanes will improve the response and thereby lessen the margin positivity.

Further studies with larger numbers, incorporating use of radiological methods for tumor measurement and marking and cytological methods for intraoperative margin assessment will be required to make recommendations for breast conservation surgery in locally advanced breast cancer downstaged with neoadjuvant chemotherapy.

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