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Breast conservation treatment in women with locally advanced breast cancer — Experience from a single centre

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KEYWORDS
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Abstract *Introduction:* In absence of randomized evidence to support safety of conservative surgery (BCT) in locally advanced breast cancer (LABC), we analyzed a cohort of 664 women with LABC treated during January 1998 to December 2002 at Tata Memorial Hospital, Mumbai, India.
Materials and methods: All were treated with a multimodality regimen comprising of neoadjuvant chemotherapy (NACT) followed by surgery (modified radical mastectomy or BCT) and adjuvant radiotherapy and hormone therapy. The outcome was evaluated to assess safety of BCT.
Results: 71% (469/664) women responded to NACT (22% clinical CR and 49% PR) and 28.3% (188/664) underwent BCT. Positive lumpectomy margins were reported in

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8.5%, with gross presence of tumor at the margins in 2.3% requiring a revision surgery. At a median follow-up of 30 months, local relapse rate was 8% after BCT and 10.7% after mastectomy. The 3-year local DFS was better post-conservation than after mastectomy (87% vs 78%, $P = 0.02$). The disease-free survival (DFS) was also superior after BCT, 72% vs 52% ($P < 0.001$) at 3 years and 62% vs 37% ($P < 0.001$) at 5 years respectively. On multivariate analysis, presence of lymphatic vascular emboli (LVE) was the major significant predictor of local recurrence ($P < 0.001$, HR 2.52, 95% CI 1.52–4.18). DFS was better after BCT [($P < 0.001$, HR 2.0 (95% CI 1.38–2.91)]; shorter DFS was noted in LVE positive (HR 1.54, $P = 0.007$) and larger residual disease after NACT (HR 1.13, $P = 0.001$).
Conclusion: BCT is technically feasible and safe post neo-adjuvant chemotherapy in women with LABC with no detriment in outcome.

Introduction

In spite of increasing awareness, locally advanced breast cancer (LABC) still remains an important problem in developing countries accounting for nearly 30% of all breast cancer cases at presentation. Virtually all evidence regarding management of these patients has been derived from results of phase II studies or from retrospective reviews of single institution experiences. It is well known that women with LABC carry an increased risk of local recurrence after primary treatment and have a poorer overall survival, as compared to early breast cancer.

Multimodality treatment has now become the established approach to patient management in locally advanced breast cancer.[1] Neoadjuvant chemotherapy in conjunction with surgery and radiation therapy[2,3] is the treatment of choice for patients with locally advanced breast cancer. Neoadjuvant chemotherapy downstages tumors effectively, making breast conservation acceptable.[4,5] Another advantage of neoadjuvant therapy is the in vivo assessment of tumor sensitivity to chemotherapy, which allows optimization of available therapeutic agents. One disadvantage of neoadjuvant chemotherapy is that preoperative treatment causes an alteration of prognostic information regarding lymph node status prior to systemic treatment. But it has been shown that improved pathological response at the primary site and axillary nodes correlates directly with improved outcome.[6–8] Although the optimal chemotherapy regimen has not been established, doxorubicin-containing regimens are considered superior to non-doxorubicin-containing regimens and have been the standard of care in many centers.[9] Currently, early results of neoadjuvant trials with taxanes (NSABP B27, Aberdeen Trial) have shown better response rates compared to anthracyclines.[10] Presently at our institute, neoadjuvant anthracycline-based chemotherapy for women with LABC has been the standard protocol since 1998 with taxanes being used only in selective cases.

Breast conservation surgery followed by radiotherapy is established as a safe and standard treatment in early breast cancer. But can we extrapolate these results and offer selected patients with locally advanced breast cancer (LABC) breast conservation after down staging with chemotherapy without compromising their final outcome? In other words, how safe is conservative surgery in these patients?

Safety of BCT in early breast cancer has been proven in large randomized trials. No such randomized clinical trial has been published in LABC. An EORTC randomized trial carried out previously in 410 women with LABC had concluded that a multimodality treatment including CT and HT had the greatest therapeutic benefit but did not address the issue of surgical intervention.[11] A number of observational studies in locally advanced breast cancer cases are available in literature but the sample sizes are either small,[12–17] or have included a mixed prognosis group comprising of patients with stages I to III of breast cancer who have received neoadjuvant chemotherapy.[13] Presently a large randomized trial is being conducted by EORTC in patients with locally advanced breast cancer and results are still awaited. In absence of such level I evidence, we have critically looked retrospectively at a cohort of patients with locally advanced T3–T4 disease to evaluate the safety of breast conservation therapy in this subset having a known poorer prognosis, with the ultimate aim to achieve a better quality of life without compromising on disease control.

Patients and methods

We analyzed 664 women with locally advanced breast cancer who presented at the Breast Clinic at our institute during January 1998 to December 2002. The median follow up in these women was 30 months (range 3–72 months). The clinical diagnosis of locally advanced disease was based on presence of any of the following features of locally advanced disease: skin involvement (peau d'orange, ulceration, skin infiltration, satellite nodules), matted or fixed axillary lymph nodes, ipsilateral supraclavicular or internal mammary lymph nodes, fixity to chest wall, arm oedema, and no evidence of distant metastasis. All patients underwent an initial incision biopsy for tissue diagnosis, receptor study and quadrant localization. A mammography was performed for a baseline documentation of tumour size and for a later comparison following chemotherapy for response assessment and feasibility for breast conservation. Metastatic work up was mandatory to confirm absence of distant metastasis and included chest radiography, ultrasound/CT scan of abdomen, liver function test, bone scan, and relevant skeletal survey.

All patients underwent a standard multi modality treatment protocol comprising of neo-adjuvant chemotherapy (2–6 cycles) till maximum clinical response was achieved. This was followed by surgery, completion of remaining chemotherapy (if any) and sequential RT (chest wall & SCF). The standard chemotherapy schedule consisted of a total of 6-cycles of 3-weekly dose of Cyclophosphamide 500 mg/m^2, Anthracycline (Adriamycin 50 mg/m^2 or Epirubicin 90 mg/m^2), and 5-Fluorouracil 500 mg/m^2. Tamoxifen 20 mg/day was added after chemotherapy if the tumor was ER and or PR positive.

Clinical response was documented using the UICC criteria based on primary tumor response and defined as follows: complete response (CR) defined as complete clinical disappearance of palpable tumor at primary site, partial response (PR) (>50% reduction in primary tumor size), static disease (SD) (<50% reduction or up to 25% increase in tumor size), progressive disease (PD) (>25% increase in primary tumor size).

Based on clinical response, 3–4 weeks after the last chemotherapy, the patients either underwent a breast conservation surgery (wide excision of residual tumor along with a surrounding gross 1–1.5 cm margin of normal tissue in all cases accompanied by a complete axillary clearance) or, a modified radical mastectomy if found unsuitable for or unwilling for BCT. No attempt was made to excise the preoperative volume of disease during conservation surgery. All the gross positive margins, and focal positive margins, in presence of extensive intraductal component (EIC), were subjected to margin revision to attain a free pathological margin prior to the starting of adjuvant radiotherapy treatment.

Pathological response was stated as complete if no tumor was found at primary site or in the axillary nodes. Postoperative sequential radiotherapy was administered (with a Linear Accelerator with bi-tangential portals) to the breast or chest wall to a maximum dose of 50 Gy in 25 fractionated doses over 5 weeks. A tumor bed boost of 15–20 Gy was administered after BCT. Supraclavicular radiation was given to a dose of 50 Gy in 25 fractions to supraclavicular fossa (SCF) in all patients. In case of pathological positive supraclavicular nodes an additional boost of 10 Gy is administered to SCF.

After completing the primary treatment, all patients were followed up at 6 monthly intervals for 5 years and annually thereafter. Mammography was performed annually after BCT on all patients.

Disease free survival (DFS) was defined as the interval between date of surgery, and the date of first recurrence. Survival curves were calculated using the Kaplan–Meier method and compared by Log rank test. Cox regression was used to evaluate possible predictors in the time to event outcomes of loco regional DFS. All statistical analysis was carried out using SPSS 11.5 statistical package program.

Results

Between January 1998 and December 2002, 664 patients with locally advanced breast cancer underwent treatment at the Breast Clinic. Age of patients ranged from 22 to 81 years (mean age 47.6 years), with 54% women in the pre and perimenopausal age group. The mean tumor size at presentation was 7.4 cm (range 3–20 cm). At presentation, 82.8% had T4 tumors and T1–3 tumors in 17.2%. Supraclavicular lymph node was found at presentation in 15%; locally advanced signs such as peau d'orange in 36%, ulceration or skin infiltration in 26%, satellite nodules in 1% and more than one sign of locally advanced status in 22% cases. The tumor was positive for estrogen receptors in 24.7% and progesterone receptors in 31.5% cases; 37% were ER and or PgR positive. The median follow up was for 30 months (range 3–72 months) (Table 1).

Table 1 Patient demographics and Pathological features ($N = 664$)

Factors	*N*	All	BCT	MRM
Mean age (in years)	664	47.6 (22−81)	45	46
Mean clinical *t* size (cm)	642	7.4 (3−20)	6	8.3
Mean pathological *t* size (cm)	539	3.5	1.5	4.1
		No. (%)	No. (%)	No. (%)
Menopausal status	664			
Pre & Perimenopausal		359 (54.1)	83 (44.1)	222 (46.6)
Postmenopausal		305 (45.9)	105 (55.9)	254 (53.4)
ER Positive	664	164 (24.7)	43 (22.9)	121 (25.4)
PR Positive	664	209 (31.5)	63 (33.5)	146 (30.7)
EIC Positive	608	68 (11.6)	8 (4.8)	60 (13.6)
LVI Positive	608	185 (27.9)	37 (21.6)	148 (33.9)
T stage				
T1−3	664	114 (17.2)	56 (30.9)	56 (11.8)
T4		550 (82.8)	130 (69.1)	420 (88.2)
Post NACT LN status				
N −ve	658	214 (32.5)	88 (47.1)	126 (26.8)
N + ve		444 (67.5)	99 (52.9)	345 (73.2)
Post NACT LN status				
N 0	658	214 (32.5)	88 (47.1)	126 (26.8)
1−3		197 (30.0)	55 (29.6)	142 (30.6)
4−10		177 (26.9)	31 (16.7)	129 (27.8)
>10		70 (10.6)	13 (7)	74 (15.5)
NACT responders (CR + PR)	664	467 (70.3%)	165 (92.7%)	302 (67.1%)
NACT non-responders (SD + PD)		161 (24.3%)	13 (7.3%)	148 (32.9%)
Not noted		36 (5.4%)		

Neoadjuvant anthracycline-based chemotherapy was completed in 93.2% patients; 4.8% received CMF and 2% received taxanes. A clinically complete response was documented in 21.7% and partial response in 48.6% (responders 70.3%); static or progressive disease was registered in 24.3%. Response to neo-adjuvant chemotherapy was not documented in 5.4% cases. A pathological CR, on the other hand, was seen in only 8% of all cases. Post chemotherapy, 32% patients were LN negative and nearly an equal proportion (30%) had 1−3 LN positive for residual metastasis; 4−10 positive LN in 27%, and >10 positive LN in 10.6%.

Surgical intervention and histopathological features

The mean clinical tumor size was 7.4 cm (range 3−20 cm) at presentation, and post neo-adjuvant chemotherapy the pathological tumor size was reduced to 3.5 cm resulting in a breast conservation rate of 28.3%. The mean tumor size in women who had breast conservation was 1.5 cm as compared to 4.1 cm in those who had a mastectomy. A total of 188 (28.3%) women underwent conservation surgery and the remaining 476 (71.7%) underwent mastectomy. Following conservative surgery, a gross positive margin was reported in 2.3% cases and focal positive margin in 6.5%. The margin was negative in the remaining 91.2% cases. Multicentricity in the form of extensive intraductal carcinoma (EIC) was detected in 11.6% (65/664) and lymphovascular emboli were seen in 27.9% (185/664) cases.

Follow up and survival analysis

Follow up data was available in 664 patients. Median follow up was for 30 months (range 3−72) for surviving patients, with a relatively longer median follow up of 32 months in breast conservation group as against 25 months in mastectomy group. In total, there was evidence of recurrent disease in 186 out of 664 patients (28%) with local recurrences in 66 patients (9.9%). The 3-year and 5-year disease free survival for the entire cohort was 54% and 38% respectively (Fig. 1).

The respective 3 and 5-year disease-free survival was 72% and 62% for the conservation group. In the mastectomy group, the 3 and 5-year disease-free survival was significantly lower, being 52% and 37% respectively ($P < 0.001$) (Fig. 2). The local disease-free survival at 3 years was better

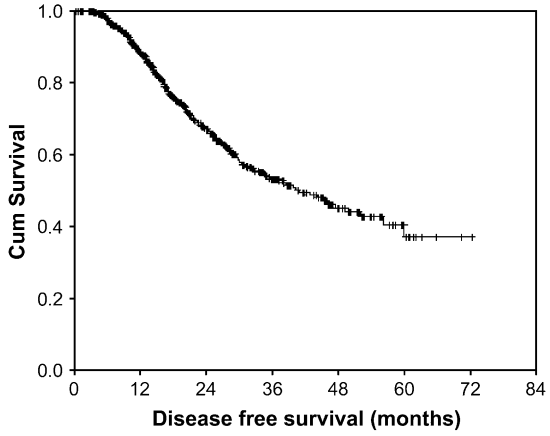

Figure 1 Disease-free Survival in all patients with locally advanced breast cancer treated at Tata Memorial Hospital from 1998–2002 ($N = 664$).

after conservation than mastectomy (88% vs 78%, $P = 0.02$) (Fig. 3).

Fifteen cases (8%) developed LR (IBTR) following breast conservation as compared to 51 patients (10.7%) who developed chest wall recurrence after mastectomy ($P = 0.02$, log rank 5.38). Distant recurrences were also fewer in conservation group with 11.1% patients presenting with distant recurrence as compared to 25.6% patients after mastectomy ($P < 0.0001$, log rank 22.44) (Table 2).

Predictors of local recurrence

When correlated with prior treatment and post-chemotherapy histopathological features, presence of LVE ($P < 0.001$), more extensive surgery

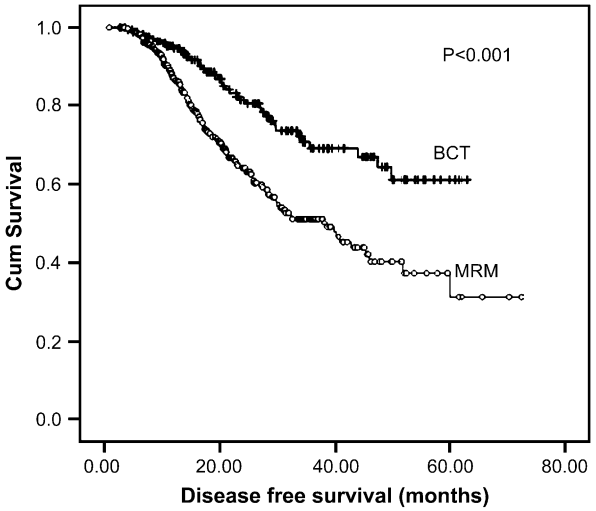

Figure 2 Kaplan–Meier Analysis plot of Disease-free survival comparison between conservation group ($n = 188$) and mastectomy group ($n = 476$).

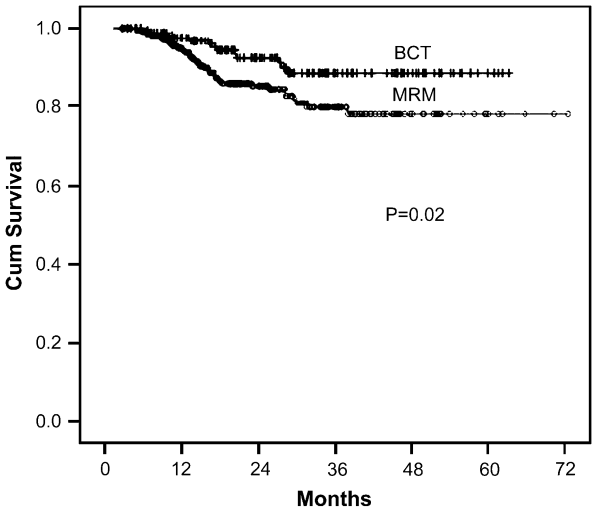

Figure 3 Kaplan–Meier Analysis plot of Local Disease-free survival comparison between conservation group ($n = 188$) and mastectomy group ($n = 476$).

(mastectomy with axillary clearance) ($P = 0.02$), and hormone insensitive tumor ($P < 0.05$) were associated with a higher local recurrence rates in a univariate analysis. In Cox regression multivariate model, however, the presence of LVE ($P < 0.001$, HR 2.52, 95% CI 1.52–4.18) correlated significantly with a higher risk for local recurrence. A higher local relapse rate was also observed after mastectomy [$P = 0.031$, HR 1.98, (95% CI 1.06–3.69)]; an important observation was that the risk of local failure increased with increasing post NACT residual tumor size ($P < 0.001$, HR 1.22, 95% CI 1.09–1.36). However, menopausal status, type of chemotherapy, receptor status, degree of pathological response to NACT, post chemotherapy nodal disease and presence of EIC did not predict increased risk for local relapse (Tables 3 and 6).

Predictors of any recurrence

Independently as well as on multivariate analysis, type of surgery performed was the strongest predictor of any recurrence ($P < 0.001$, HR 2.00, CI = 1.38–2.91) favoring breast conservation treatment; followed by presence of LVE ($P = 0.007$, HR 1.54, CI = 1.12–2.12). Increasing size of residual

Table 2 Recurrence pattern

Recurrences	BCT $N = 188$ patients	Mastectomy $N = 476$ patients	Total $N = 664$ patients
Local	15 (8.0%)	51 (10.7%)	66 (9.9%)
Regional	10 (5.3%)	37 (7.7%)	47 (7.0%)
Distant	21 (11.1%)	122 (25.6%)	143 (21.5%)

Table 3 Predictors of local recurrences in women with LABC-Univariate analysis

Factors	Log Rank	*P* value
LVE (+ve vs −ve)	16.6	<0.001
Type of Surgery (MRM vs BCT)	5.38	0.02
ER status (−ve vs +ve)	4.04	0.04
PgR status (−ve vs +ve)	3.72	0.05
Age (<35 years vs >35 years)	3.31	0.07
Response to NACT (Non-responder vs Responders)	3.19	0.07
Residual axillary LN status (N+ vs N0)	3.09	0.08
Pathological response (RD vs CR)	0.92	0.34
EIC (−ve vs +ve)	1.65	0.20
Menopausal status (Pre vs Post)	1.49	0.22
Clinical T stage (T4 vs T1−3)	0.06	0.81

tumor post NACT correlated with increased risk of disease recurrence ($P = 0.001$, HR 1.13, 95% CI 1.05−1.22). Premenopausal status, residual disease in axillary nodes, and age less than 35 years independently predicted a higher risk for relapse but were not found to be significant on multivariate analysis; clinical stage at presentation and hormone responsiveness of primary tumor also did not correlate with a higher risk for relapse (Tables 4 and 6).

Predictors of distant recurrence

The most significant factor correlating with distant metastasis was the type of surgery performed with more recurrences reported in mastectomy group ($P < 0.0001$, log rank 22.44). The other factors independently correlating with higher risk for distant metastasis were larger tumor at presentation, residual nodal disease after NACT, young age, presence of LVE, premenopausal status, and ER negative tumors (Table 5). On multivariate analysis

Table 4 Factors predicting any recurrence by univariate analysis

Factors	Log Rank	*P* value
Type of Surgery (MRM vs BCT)	17.76	<0.001
LVE (+ve vs −ve)	12.9	<0.001
Residual nodal axillary status (N+ vs N0)	9.44	0.002
Menopausal status (Pre vs Post)	4.67	0.03
Age (<35 years vs >35 yrs)	5.37	0.02
PgR status (−ve vs +ve)	3.88	0.05
Clinical T stage (T4 vs T1−3)	2.69	0.10
Pathological response (RD vs CR)	1.98	0.16
ER status (−ve vs +ve)	1.99	0.16
EIC (+ve vs −ve)	0.06	0.81

Table 5 Factors predicting distant recurrence by univariate analysis

Factors	Log rank	*P* value
Type of Surgery (MRM vs BCT)	22.44	<0.0001
Clinical T stage (T4 vs T1−3)	7.46	0.006
Residual nodal axillary status (N+ vs N0)	6.10	0.01
Age (<35 years vs >35 years)	5.17	0.023
LVE (+ve vs −ve)	5.40	0.02
Menopausal status (Pre vs Post)	5.09	0.02
ER status (−ve vs +ve)	4.51	0.03
Pathological response (RD vs CR)	1.60	0.20
PgR status (−ve vs +ve)	1.60	0.19

of factors influencing distant recurrences, mastectomy group had higher risk (HR 3.04, CI 1.59−5.85), followed by presence of LVE (HR 1.57, CI 1.05−2.35). A larger residual tumor at the primary site, a younger age, and ER negative tumors also correlated with poorer prognosis (Table 6).

Discussion

Safety of breast conservation therapy in early stage breast cancers is well supported by large

Table 6 Significant predictors of recurrence by Cox regression analysis

Factors	*P* value	HR (95% CI)
Local recurrence		
LVE (+ve vs −ve)	<0.001	2.52 (1.52−4.18)
Pathological *t* size	<0.001	1.22 (1.09−1.36)
Type of Surgery (MRM vs BCT)	0.03	1.98 (1.06−3.69)
Any recurrence		
Type of Surgery (MRM vs BCT)	<0.001	2.00 (1.38−2.91)
Pathological *t* size	0.001	1.13 (1.05−1.22)
LVE (+ve vs −ve)	0.007	1.54 (1.13−2.12)
Distant recurrence		
Type of Surgery (MRM vs BCT)	0.01	3.04 (1.59−5.85)
LVE (+ve vs −ve)	0.03	1.57 (1.05−2.35)
Pathological *t* size	0.03	1.10 (1.01−1.20)
Estrogen receptor (−ve vs +ve)	0.04	1.71 (1.01−2.90)
Age (<35 years vs >35 years)	0.048	1.70 (1.00−2.86)

prospective randomized trials that have compared mastectomy with breast conservation surgery and radiation therapy for T1−2 tumors. Larger tumors were excluded in these trials from a conservative approach to surgery fearing poor local control and cosmesis. No adequately powered randomized control trial is available in LABC to address the issue of safety of BCT in these patients. Most of available evidence is from observational cohort studies. An EORTC randomized trial carried out previously in 410 women with LABC had concluded that a multimodality treatment including CT and HT had the greatest therapeutic benefit but did not address the issue of surgical intervention.[11]

The most clearly established advantage of NACT is in its ability to allow more BCT (22−45%) to be performed in patients who were initially ineligible.[12−14] The cohort of patients of LABC included in this series had a mean clinical tumor size of 7.4 cm (range 3−20 cm), treated by a multimodality approach and examined for the feasibility and safety of breast conservation surgery. We could achieve breast conservation in 28.3% women post neoadjuvant chemotherapy.

Women undergoing BCT had a superior 3-year DFS as compared to after mastectomy (72% in BCT vs 52% after mastectomy, $P < 0.001$) with a lower LR (8%). Similar outcomes have been reported in other studies of locally advanced tumors post NACT.[15,16] Reports in literature of studies evaluating local recurrence after NACT and BCT have shown conflicting results. While some single institution studies have reported a low local recurrence rate of 2−10%, others have reported a much higher incidence up to 16−28%.[12,13,18,19] It is worth noting that some of the studies that reported higher rates of local recurrences after NACT included large percentages of patients for whom radiation therapy was the only loco regional treatment administered,[12,20] without an attempt to resect the primary tumor site and some studies even included patients with inflammatory carcinomas as well. A large percentage of patients who attain a clinical CR have residual disease detected at surgical resection. In our series, also although we had a complete clinical response of 22.9%, a pathological complete response was documented in only 8.0%. Therefore surgery remains an important component of BCT for all patients treated with NACT.

At the same time, a few series that included patients who were treated both with surgery and radiation have also reported higher LR rates. For example, in the Institute Bergonie series, 28% experienced a LR.[2] Differences in surgical approaches may also have contributed to the difference in outcomes. In addition to grade, size of tumor, LVI and EIC, local recurrence may be related to residual disease within the breast, which may be assessed by examining the excision margin. Therefore, a careful pathological assessment after surgery is essential to ensure free resection margins.[21] Eleven percent of the patients from the Institute Curie series[18] had positive margins (and reported a LR of 27%) as against our gross margin positive rate of 2.3%. In our institute, all patients with gross positive margins were managed under a standard protocol ensuring negative margins (by undergoing a re-excision or treated with an additional radiotherapy boost).

Conservative surgery was found to be associated with a lower local recurrences than following mastectomy (HR 1.98, CI 1.06−3.69, $P = 0.03$). Similar findings were seen in the study reported from North Carolina[14] and some other studies.[15] This probably does not really represent a true impact of extent of surgery, rather the inherent selection bias that discriminates between women who were responders (hence, offered breast conservation) and those who were non-responders (and therefore underwent mastectomy). The projected 3-year local disease free survival outcome in our series was better post conservation (88%) than after mastectomy (78%) confirming the safety of BCT.

Subset analysis of induction chemotherapy trials reveals a statistically significant improvement in survival for patients found to have a complete pathological response at the time of definitive surgery.[22] In our series, the degree of pathological response to chemotherapy, particularly a complete pathological response did not predict the likelihood of developing a local recurrence (Table 3). However, a significant relationship may be overlooked here by virtue of the fact that there are only a small number of patients who had a pathological CR (8.0%) and thus it is possible that there are not enough events within the subgroup to allow a significant relationship to be shown.

The presence of residual nodal metastasis did represent a risk factor for disease recurrence especially distant recurrence. This observation is in concordance with the observations made by McIntosh,[16] Buchholz[19] and others,[7] that nodal involvement after primary chemotherapy retains its significance and predicts an increased risk of developing recurrent disease. This finding is perhaps unsurprising, as it has been clearly demonstrated in patients who have treatments not involving NACT, that axillary lymph node involvement is itself an adverse prognostic factor. Residual axillary nodal metastasis persisting after neo-adjuvant

chemotherapy continues to remain an important prognostic factor.

Larger clinical tumor size has been found to be a statistically significant factor-influencing outcome in some studies. Jacquilat et al.[20] Ahern et al. from West mead hospital,[23] Australia and Buchholz et al.[19] found greater clinical T stage and advanced disease at presentation to be associated with a greater risk of recurrence. Larger tumor size at presentation did not correlate with increased local relapses in our cohort of patients, but did correspond to a higher risk for distant relapse. However, post NACT, larger residual tumor in the primary site correlated directly with an increasing risk for disease recurrence locally (HR 1.22. CI 1.09—1.36, $P < 0.001$) as well as at distant site (HR 1.10, CI 1.01—1.20, $P = 0.03$).

Conclusion

Breast conservation can safely be offered to women with locally advanced breast cancers who respond to neo-adjuvant chemotherapy. Surgery remains an essential part of treatment even in good responders. Obtaining a clear surgical excision margin is essential for reducing local recurrences and should be consolidated with postoperative radiotherapy. Prognosis is determined by post NACT residual nodal disease, residual tumor in the breast, and presence of LVI. Responders self-select themselves out as a subgroup with better clinical outcome. The current use of taxanes in the neo-adjuvant setting promises a higher pathological CR as compared to anthracyclines and may possibly eventually translate into an overall better outcome.

The identification of prognostic factors presents an opportunity to investigate and identify markers that may allow optimal prediction of response to adjuvant radiation and chemotherapy or both, and hopefully lead to future strategies for the improved management of both locally advanced as well as early breast cancers.

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