Response to neoadjuvant chemotherapy in operable breast carcinoma and conversion of modified radical mastectomy to breast conservation surgery, long term results: an Indian perspective

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INTRODUCTION

Breast cancer brings with itself an added fear of disfigurement and psychological trauma that leads to personality devastation, the breast ever since being considered the ultimate symbol of femininity. Despite extensive research, its etiology and treatment are still not fully understood. Clinicians world over are in constant search of insight into the behaviour of this disease so that they are able to provide better chances of cure, survival and personality preservation.

Breast cancer incidence is showing rising trend in India for last two decades competing with cancer cervix and interchanging places for the top position in all the registries of ICMR among women.¹ Thus it becomes all the more important how the disease is dealt with because small improvements in treatment strategy may translate...
into huge benefits in terms of well-being of breast cancer patients in India.

**METHODS**

The study included 25 female FNAC proved T1-T3, No-N1, M0 breast cancer patients who reported in the department during one year w.e.f. 1.09.06 to 31.08.07. General prerequisites for inclusion in the study were Hb >10 gm%, TLC > 4000, Platelet count > 100000, renal and liver function tests within normal limits, Karnofsky performance status >50 and age below 70 years. Patients who had breast cancer along with pregnancy and the patients who did not match the above inclusion criteria were not included in the study. Patients were evaluated by thorough clinical history and detailed clinical examination. Mammography of bilateral breasts and ultrasound of the diseased breast was carried out. The tumour size was measured clinically and ultrasonographically before administration of first cycle and clinically before administration of each subsequent cycle. The tumour size was finally assessed both clinically and ultrasonographically two weeks after completion of last cycle of neoadjuvant chemotherapy. The product of two greatest perpendicular diameters was used to quantify the size of the tumour. Two to four cycles of CAF based neoadjuvant chemotherapy were administered to all the patients three weeks apart on day one only as per schedule each time ensuring proper hydration and by giving antiemetics and symptomatic treatment. Neoadjuvant chemotherapy was administered as under:

- **Inj. Cyclophosphamide** - 600 mg/m2 I/V infusion on day 1
- **Inj. Doxorubicin** - 50 mg/m2 I/V bolus on day 1
- **Inj. 5-Fluouracil** - 600 mg/m2 I/V infusion on day 1

During treatment patients were monitored for toxicity and response to neoadjuvant chemotherapy.

In the absence of clinical evidence of tumour in the breast, the response to therapy was categorised as clinically complete response (cCR). When the clinical size of the tumour decreased by 50% or more, the response was judged to be partial (cPR). When there was an increase of more than 50 % in the original size of the tumour after a minimum of two cycles of NACT, the patient was considered to have progressive disease (cP). Patients whose response criteria did not meet the definitions of either cCR, cPR or cP were considered to have clinically stable disease.

Depending upon the response to NACT, appropriate surgery was performed in each case, which was either breast conservation surgery (BCS) or modified radical mastectomy (MRM).

The former was either in the form of quadrantectomy or wide local excision combined with axillary dissection through a separate incision. None of the patients who had undergone BCS showed evidence of histologically positive margins. Modified radical mastectomy was performed in those patients who were not fit for BCS or had clinically progressive (cP) or clinically stable disease (cS) disease after at least 2 cycles of NACT.

Patients who had large tumour in a small breast, tumour size more than 4 cm, multicentric disease, were not taken for BCS.

The BCS or MRM were carried out under general anaesthesia. The palpable lesions were localised sonographically before surgery and non-palpable lesions were localised prior to surgery by insertion of a hook wire under ultrasound guidance. An appropriate sized skin incision was made and deepened and dissection was continued towards wire. The specimen having been excised was immediately oriented before submitting to detailed histopathological examination using sutures. In this study, one suture for anterior margin, two for medial margin and three for inferior margin were used.

Histopathological examination of the surgically removed specimens was done for resection margins and for axillary lymph nodes. In patients showing clinically complete response (cCR), histopathological examination was done to know the extent of pathological response (pCR or pinv).

Radiotherapy was delivered to intact breasts after breast conservation surgery as:

50 Gray /5 weeks in 25 fractions by tangential portals by Cobalt-60 teletherapy ± boost of 10 Gray/5 fraction covering tumour bed. Radiotherapy was delivered to chest wall and draining area after modified radical mastectomy.

Postoperative chemotherapy was delivered as 4 cycles of CAF based adjuvant chemotherapy 3 weeks apart in all cases. Patients who had clinically stable (cS) or clinically progressive (cP) disease after NACT were administered taxane group of drugs.

**RESULTS**

None of the patients was below 20 years of age in the present study. Only 1 (4%) patient was in the 21-30 years age group whereas 5 (20%), 10 (40%) and 9 (36%) patients were in the age groups of 31-40, 41-50 and 51-60 years. Maximum no. of patients was in the age group of 41-50 years. All the 25 patients were female. Eleven patients (44%) were premenopausal and 14 (56%) were postmenopausal. None of the patients had bilateral disease. The disease was multicentric in 1 patient. The lump was situated in 14 (56%) in upper outer quadrant, 5 (20%) in upper inner, 2 (8%) in lower outer, 3 (12%) in lower inner and 1 (4%) in central quadrants of the breast respectively. Clinically complete response was observed.
in 1 (4%) after 2 cycles of NACT. All other patients i.e. 24 (96%) received 3 cycles of NACT and none of the patients received 4th cycle of NACT. The lump became non-palpable in 3 (12%) patient following NACT whereas it was so in none of the patients in pre-NACT group. None of the patients had tumour size of <10cm2 in pre-NACT group while 10 (40%) patients had a tumour size of <10cm2 in the post - NACT group. Tumour size was between 10.1-20 cm2 and 20.1-30 cm2 in 4 (16%) and in 10 (40%) patients respectively in pre-NACT group whereas this size was present in 10 (40%) and 2 (8%) patients respectively in the post NACT group. Clinical size of the tumour>30cm2 was found in none of the patients in post NACT group while sizes between 30.1-40, 40.1-50 and 50.1-60cm2 were seen in 8 (32%), 2 (8%) and in 1 (4%) patients respectively in pre-NACT group.

Ultrasound did not detect any lump in 3 (12%) patients in post-NACT group.

Whereas none of the patients had this in pre-NACT group. Lump size was <10 cm2 in 5 (20%) patients in pre-NACT group and it was so in 17 (68%) patients in post-NACT group. Tumour size was between 10.1 - 20cm2 in 18 (72%) patients in pre-NACT group and 5 (20%) patients in the post-NACT group. No patient had tumour size between 31-40 cm2 in post-NACT group while 2 (8%) patients had this size in pre-NACT group. Tumour size between 20.1-30cm2 was seen in none of the patients in either pre-NACT or post NACT group.

Table 1: Clinical tumour size in cm (T) pre - NACT and post - NACT (n = 25).

<table>
<thead>
<tr>
<th>T</th>
<th>Pre - NACT (%)</th>
<th>Post - NACT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TO</td>
<td>0 (0)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>T1</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>T2</td>
<td>5 (20)</td>
<td>19 (76)</td>
</tr>
<tr>
<td>T3</td>
<td>20 (80)</td>
<td>3 (12)</td>
</tr>
</tbody>
</table>

Table 2: Pre - NACT and Post - NACT axillary lymph node status (n = 25).

<table>
<thead>
<tr>
<th>Axillary lymph node status</th>
<th>Pre - NACT (%)</th>
<th>Post NACT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>5 (20)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>N1</td>
<td>20 (80)</td>
<td>13 (52)</td>
</tr>
</tbody>
</table>

Clinically complete response (cCR) following NACT was observed in 3 (12%) patients while clinically partial response (cPR) was observed in 18(72%) patients. Disease was found to be clinically stable (cS) IN 3 (12%) patients while it was clinically progressive in 1 (4%) patient.

Pathologically complete response was observed in all three patients who had cCR (12%).

Table 3: Overall comparison of pre - NACT and post - NACT TNM stage breast tumour (n = 25).

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Pre NACT</th>
<th>Post NACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>TONOMO</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>T1NOMO</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T1N1MO</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T2NOMO</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>T2N1MO</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>T3NOMO</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>T3N1MO</td>
<td>19</td>
<td>1</td>
</tr>
</tbody>
</table>

Following NACT tumour versus breast volume ratio was found to be adequate in 22 (88%) patients while it was found inadequate in 3 (12%) patients. Breast conservation surgery was possible in 16 (64%) patients while modified radical mastectomy had to be done in 9(36%) patients following NACT. Breast conservation surgery was done in all the 3 patients showing cCR while it was possible in only 13 out of total 18 patients who had shown cPR as in one of these patient’s mammography revealed multicentricity of the disease while in 3 patients the tumour versus breast volume ratio was inadequate and in one patient, the size of the residual tumour following cPR after NACT was more than 4 cm. So, in these 5 patients MRM was done. MRM was also carried out in all the 3 patients showing clinically stable disease (cS) and in one patient showing clinically progressive disease (cP). One IBTR was noted at four years and one at six years of follow up. None of the patients with pathologically complete response developed locoregional recurrence or distant metastasis. Of total 25 patients, six (24%) developed distant metastasis at different intervals of time and three died subsequently. Two patients who had IBTR developed distant metastasis later.

DISCUSSION

The youngest patient in the present study was 27 years old whereas majority of the patients were in the 5th or 6th decades of their life. Carcinoma breast is rare below the age of 20 years but the incidence increases steadily thereafter so that by the age of 90 years nearly 20% of women are affected.2 A woman aged 50 years has an 11% lifetime risk of developing breast cancer and a woman aged 70 years has a 7% lifetime risk of developing breast cancer.3

Carcinoma breast is more common in postmenopausal women than in the premenopausal, same was the observation in the present study.4

The size of breast lumps was clinically measurable in all the 25 (100%) patients before NACT. The masses appeared larger in size on palpation than on ultrasound due to desmoplastic stromal reaction of the tumour as in other studies.5-7
The tumour was found to be confined to either of the breasts in all the 25 (100%) patients. Bilateral lesions were found in none of the patients though in literature cancer may appear in both breasts simultaneously in 1-2% cases. This may be due to small no. of patients in our study.

On mammography, the tumour was found to be multicentric in 1 (4%) patients only, Iglehart DJ et al reported an incidence of 33% of multicentric disease in ipsilateral breast while Bland KI reported an incidence of 37%. This may again be attributed to small sample size in our study and 10-15% patients may be missed by mammography. The tumour was located in the upper outer quadrant in 14 (56%) patients, 5 (20%) in upper inner quadrant, lower outer quadrant in 2 (8%) and lower inner quadrant in 3 (12%) patients. The tumour was centrally located in 1 (4%). The reported incidence of location of primary tumour in breast has been 60%, 12%, 6%, 10% and 12% respectively for upper outer, upper inner, lower outer, lower inner and central tumours. The higher frequency in upper outer quadrant is attributed to greater amount of breast tissue in that quadrant.

The magnitude of clinical and pathological response of primary breast tumour to NACT in the present series showed cCR, cPR, cS, cP and pCR of 12%, 72%, 12%, 4% and 12% respectively. All three patients showing cCR also showed pCR (12%). The response rate of NACT in operable breast cancer in NSABP-B18 series showed reduction in tumour size in 80% patients with a cCR, cPR, cS, cP and of 36%, 44%, 17% and 3% respectively. 26% of women with a cCR had a pCR whereas in the present study all the patients showing cCR had pCR. In the study by Smith I.E. an overall response rate of 98% and a cCR of 66% was observed following administration of infusional neoadjuvant chemotherapy. An overall objective response rate of 49% with a cCR, cPR, cS and eP of 6.6%, 42.3%, 39.7% and 1.4% respectively was observed in the study by Jose A et al while it was 60.8% with a cCR, cPR, cS and eP of 20.2%, 40.6%, 37.9% and 1.3% respectively in the series of Calais G et al. An overall response rate of 88% to preoperative chemotherapy in operable breast cancer was reported by Cholet P et al in his study of 50 patients from 1991-1996. The cCR, cPR and cS were 51%, 37% and 12% respectively. The pCR observed after NACT was 22%. In NSABP-B 18 trial clinically complete remission (cCR) was inversely related to primary tumour size (57% in tumour < 2 cm in largest diameter but only 17% in tumour > 5 cm). This finding was endorsed in study by Kuerer et al. In the present study, however, this relationship was not observed as all the patients who had cCR had T2 disease. Our results are comparable to the results observed in many trials. In present study, after NACT, the no. of patients with clinically palpable axillary nodes reduced from 20 (80%) to 13 (52%). These findings clearly reflect the effectiveness of NACT on axillary nodes apart from primary tumour. There was significant down staging of axillary nodal status in the NSABP-B 18 trial. Powel et al reported a randomised study in which clinical involvement of axillary nodes was documented in 14% of women allocated to primary surgery and in 22% of patients allocated to primary chemotherapy. After chemotherapy only 3% of patients were having clinically involved axillary nodes.

Forrest et al demonstrated that NACT allowed the primary tumour response to serve as in vivo chemosensitivity test. NACT also guides about adjuvant chemotherapy after loco-regional treatment. In the present study four patients who did not show response to NACT were subsequently given adjuvant chemotherapy with taxane group of drugs.

Breast conservation surgery rate noted in the present study was 64% (16 out of 25). In the late 1980s’, the use of NACT improved the rate of breast conservation upto 98% of patients with large operable breast cancer. Endorsed later in other studies. According to Smith IE 62% patients had breast conservation surgery following neoadjuvant infusional chemotherapy for large early breast cancers. In the present study only 3 (12%) patients had a primary tumour size < 4cm thus qualifying for BCS at presentation while remaining 22 (88%) patients were candidates for MRM. BCS could be performed in total 16 (64%) out of 25 patients after NACT. Thus, NACT greatly increased (by 52%) the breast conservation surgery from 12% to 64% in the present study and thus had been successful in achieving the primary goal of NACT. While breast conservation surgery was feasible in 48.7% of patients in the study of Calais G et al. In the series of Bonadonna G et al following preoperative chemotherapy 85% patients could be subjected to breast conservation surgery. This was reported in other studies later.

Figure 1: Breast conservation surgery of a sub-areolar tumour after neo adjuvant chemotherapy.

Primary tumour was located in either of four quadrants of breast in 15 women in whom BCS was carried out while it was centrally located in one case. Central tumours can be removed from under the nipple if these are not superficial, by a standard wide excision preserving the overlying nipple skin. If the lesion is superficial and is
tethering or inverting the nipple, then it is usually necessary to remove the nipple and / or areolar complex.\textsuperscript{24}

\begin{center}
\textbf{Figure 2: Complete pathological response after neoadjuvant chemotherapy.}
\end{center}

Tumour size assessed by methods adopted by authors correlated directly in patients who achieved cCR and pCR with the residual pathological tumour size but were moderately useful in other cases as reported earlier.\textsuperscript{24}

One patient (6.25\%) had IBTR at four years and another one (12.50\%) at six years of follow up, this was seen in patients with large tumour pre-NACT clinically and ultrasonographically.\textsuperscript{26} Being a small study and maximum no. of patients taken for BCS who could be allowed this surgery, IBTR rates may differ though comparable as imaging modalities could not differentiate patchy cyto reduction.\textsuperscript{27} The fact that none of the patients with pCR developed locoregional recurrence or distant metastasis during these years of follow up underscores its importance in improved survival. Though, a small study, yet there is conclusive evidence that in carefully selected patients BCS is a fairly good alternative.\textsuperscript{15,26,27} Six patients in entire group (24\%) developed distant metastasis at different intervals during ten years of follow up that is comparable to other studies.\textsuperscript{13,27} Two of these were the patients who had developed IBTR. IBTR is considered a strong predictor of distant metastasis in some studies.\textsuperscript{27} As selection criteria for BCS improve with better imaging modalities available for judging the response of neoadjuvant chemotherapy, more no. of patients can be brought under purview of BCS with less risk of recurrence and better acceptance by surgeons and patients as well.

**CONCLUSION**

As is evident from the study, though small in size that neoadjuvant chemotherapy in operable breast cancer is feasible in our setup and has been very effective in reducing the size of primary tumour as well as down staging the axillary nodal status and that more no. of patients can be offered breast conservation surgery.

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**Ethical approval:** The study was approved by the institutional ethics committee

**REFERENCES**
