



A STUDY ON THE TREATMENT OUTCOME OF VARIOUS MANAGEMENT REGIMENS FOR LOCALLY ADVANCED CARCINOMA BREAST CANCER

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ABSTRACT **Background-** Breast cancer is the commonest malignant disease among women in the Western world accounting for 1/5th (18%) of all cancers in women. Every year about one million women and several thousand men are diagnosed with breast cancer worldwide.

Methods and materials- The study was carried out in the Departments of General Surgery and Radiotherapy, Patna Medical college & Hospital, Patna between Sep 2012 and Oct 2014

Results- The median age was 45 years. Infiltrating ductal carcinoma was found in 86% cases. Modified radical mastectomy was the commonest surgery done post NACT (87.2%). Hormonal therapy showed relapse free survival in 81 percent cases. 82 percent relapse free survival was noted in patients whose treatment regimen was a combination of NACT, surgery and radiotherapy.

Conclusion- Early confirmation of diagnosis, staging and metastatic work up is important. The whole treatment regimen is a multidisciplinary approach consisting of surgeon, pathologist, oncologist and radiation oncologist. All cases should be treated aggressively.

KEYWORDS : Mastectomy, Locally advanced breast cancer, Radiotherapy, Chemotherapy

INTRODUCTION

In India, breast cancer is the commonest cancer in urban women and second only to carcinoma cervix in rural women with 75,000 new cases occurring every year as per the cancer registries in the country. It is the most common cause of death in middle aged women. Breast cancer is categorized into early and advanced breast cancer for the management purpose. Advanced breast cancer is either locally advanced or metastatic disease. Locally advanced breast cancer is a very common clinical scenario especially in developing countries (30-60%) possibly due to various factors like lack of education and poor socio-economic status.

Diagnosis of breast carcinoma is best done by a combination of clinical examination, breast imaging (Mammography/USG/MRI), and tissue examination (FNAC/Trucut Biopsy), called as triple examination. The treatment of locally advanced breast cancer requires a combination of systemic chemotherapy, surgery, and radiotherapy to optimize the chance of cure. The earliest therapy for locally advanced breast cancer was radical mastectomy. Patients who were treated with primary radiotherapy also had a high risk for disease recurrence and death. The first reports of the use of induction chemotherapy for locally advanced disease were published in the 1970s. Since then, the use of systemic chemotherapy has become standard and has substantially improved the prognosis of locally advanced breast cancer.

The benefit of adjuvant chemotherapy for the treatment of breast cancer has been clearly established, although most trials have not been specifically focused on patients with locally advanced disease. Initially, Bonadonna et al. demonstrated a survival benefit for women with node-positive breast cancer treated with CMF chemotherapy.

Neoadjuvant chemotherapy was pioneered in the setting of locally advanced breast cancer. The administration of systemic chemotherapy prior to definitive local therapy is advantageous for women with locally advanced disease, since induction chemotherapy can render inoperable tumors (stage T4, N2, or N3) resectable and can increase rates of breast-conserving therapy. For women with HER-2 positive metastatic breast cancer, treatment with trastuzumab in combination with chemotherapy can improve survival. Therefore, the potential use of trastuzumab in the adjuvant and neoadjuvant settings has generated much interest. After patients complete neoadjuvant chemotherapy, they should proceed with definitive local therapy. The traditional approach has been to treat women with locally advanced tumors with modified radical mastectomy. An alternate approach to breast conservation has been the use of primary radiation therapy in place of surgery, as most studies that have compared primary radiation therapy with primary surgical therapy have shown equivalent outcomes.

MATERIAL AND METHODS

The study was carried out in the Departments of General Surgery and

Radiotherapy, Patna Medical college & Hospital, Patna between September 2012 and October 2014. Ethical approval from the Institutional Ethics Committee was obtained before the commencement of this study.

86 cases of locally advanced breast carcinoma who were candidates for neoadjuvant chemotherapy (NACT) & Surgery were included i.e. stage III A, IIIB, IIIC (according to American Joint Committee on Cancer guidelines, 2010) in the study.

Patients having any of the following characteristics were not included in the study:

1. Early stage breast carcinoma [i.e., stage 0, stage 1, and stage 2]
2. Metastatic disease [stage 4]
3. SGOT/SGPT > 1.5 times normal
4. Serum total bilirubin > 1.5
5. TC < 3500
6. Platelet count < 75000
7. Pregnancy/lactation
8. Comorbidities rendering patients unfit for chemotherapy or surgery.
9. Progressive disease (as per the RECIST criteria).

RESULTS-

The median age was 45 years, mean was 47.7 years and the range was 35-80 years.

The location of the lump in 86 patients. Most of the patients had large tumors involving more than one quadrant of the breast.

The histological character of the tumor. Majority of patients (86%) were reported to have infiltrating ductal carcinoma and 14% have infiltrating lobular carcinoma on histopathological examination. 53.5% tumors were high grade (grade III and grade IV), and remaining were of low grade (either grade I or grade II).

The hormonal and her-2 receptor status of the tumor. 50% tumors were hormone receptor positive (ER+/PR+/both+). 36 (56.2%) tumors had overexpression (3+) of HER-2. In this study 14% triple negative (ER-, PR- and HER-2-) tumor was found.

The stage of the tumor at the time of presentation. Vast majority of cases (79.1%) were categorized as T4. 44 (51.2%) cases had T4b lesion while 6 (7%) patients had T4c lesion at presentation.

Mean pre NACT (Neo-adjuvant chemotherapy) tumor size was 6.97 cm, while mean post NACT tumor size was 2.99 cm, and this difference was found to be statistically significant ($p < 0.001$). Out of 62 patients with either T4a or T4b disease 14 were downstaged to T3,

24 to T2, 11 to T1 and 5 to T0, while 8 patient remained T4 (there was significant reduction in size of the lump but skin or chest wall was involved even after 4 cycles of NACT).

The nodal stage of patients at the time of presentation. 89.5% (77 out of 86) patients in this study presented with palpable axillary lymphadenopathy.

The chemotherapy regimen used for NACT. Two types of regimen used (Anthracyclin based regimen and Taxane based regimen). Majority of patients (65.1%) received Taxane based regimen and the remaining patients received anthracyclin based regimen.

The response to neoadjuvant chemotherapy. 10 (11.6%) cases included in this study had clinical complete response with disappearance of all target lesions, while 73 (84.8%) had partial response.

3 weeks after completion of neoadjuvant chemotherapy, surgery was done in all patients. Modified radical mastectomy was done in majority of patient (87.2%). Breast conserving surgery was done in 8 patients (9.4%). 3 patients had fixed axillary node even after neoadjuvant chemotherapy, in that mastectomy with partial nodal clearance was done.

The postoperative complication in patients after surgery. Majority of patients had uneventful recovery. Most common complication was found to be seroma in MRM (17.3%) as well as BCT (12.5%) group. Wound infection was found to be more common in patients undergone breast conserving surgery (12.5%). Flap necrosis was noticed only in patients undergone modified radical mastectomy.

The disease recurrence during the study period. 18 patients developed disease recurrence, in which 9 patients (10.4%) developed local recurrence and 12 patients (14%) developed distant metastasis where as 3 patients was common in both groups.

On assessing the effect of response to NACT (Neoadjuvant chemotherapy) on relapse free survival, 90% of patients with complete clinical response to NACT had relapse free survival. In patients with partial response to NACT, 78% of patients had relapse free survival. In the other hand, only 66.7% patients had relapse free survival in no response to NACT group.

On comparing the relapse free survival in patients who received hormonal therapy or not, 81.2% patients had relapse free survival who was on hormonal therapy. Whereas relapse free survival was only 68.7% in patients who didn't received hormonal therapy.

On comparing the relapse free survival with different management regimen, relapse free survival was 87.5% with the regimen containing surgery, Neoadjuvant chemotherapy, postoperative radiotherapy and Hormonal Therapy. Only 55.6% relapse free survival was noticed in patients who received the regimen containing only surgery and Neoadjuvant chemotherapy.

DISCUSSION

This study included 86 patients of locally advanced breast carcinoma, who received 3-6 cycles of Neo adjuvant Chemotherapy (NACT) followed by Surgery (Modified Radical Mastectomy in 75 patients and Breast Conservation Surgery in 8 patients). 69 out of 86 patients received Radiation to the chest wall and Axilla (5000 cGy for a duration of 4-6 weeks) 3-4 weeks after surgery. Hormonal therapy in the form of Tamoxifen or Letrozole were given to all hormonal receptor positive patients (32 out of 86) postoperatively. All the patients were followed up during the study period and outcome in the form of local recurrence, Distant metastasis, Disease free survival and improvement in quality of life were noticed in different group of patients received different management regimens.

Patient characteristics :-

31 of the 86 patients (36%) included in our study were premenopausal which is comparable to other studies (34.1%, Tehard et al, 2004).

The mean age of the study population in this study was 47.7 years and 63.3% patients were in the 3rd or 4th decade of their life. In an Indian study (Raina et al, 2005) the mean age of presentation of breast cancer in India was found to be less than 50 years, which is lower than that in the developed countries (median age of 52 years, Petit et al, 2004).

Location of the Lump :-

The site specific incidence of breast cancer in our study was 23.2%, 55.8%, 10.5%, 4.6% and 5.8% in the central region, upper outer, upper inner, lower inner and lower outer quadrants respectively. The site specific incidence of breast cancer varies between different studies. In one study from England and Wales which included 212,677 breast cancer patients, 11.2% tumors were located in the central portion of the breast, 52.5% in the upper outer quadrant, 14.6% in the upper inner quadrant, 6.4 % in the lower inner quadrant, 9.8% in the lower outer quadrant (Darbre PD, 2005).

Histological Character of Tumor :-

In our study 74 patients (86%) had infiltrating duct carcinoma whereas in most populations infiltrating ductal carcinoma covers about 70% of all diagnoses (Gamel et al, 1996; Northridge et al, 1997). In a recent Indian study on 148 patients of locally advanced breast carcinoma 82.4% cases was of invasive ductal carcinoma (Tapesh Bhattacharyya et al 2014).

Hormonal receptor status of tumor :-

In our study 21.9% patients were ER +ve, 36.9% were PR +ve while 50% patients were hormone receptor -ve. The hormone receptor positivity was low (50%) in our study which is consistent with the findings of earlier studies on Indian patients. As suggested by previous Indian studies the hormone receptor expression in breast cancers in India is low (Redkar et al, 1992; Desai et al, 2000).

Tumor stage before and after NACT :-

The mean tumor size at presentation in this study was 6.9 cm which is greater as compared to other similar studies (Breslin et al, 2000 [5.0 cm]; Chintamani et al, 2011 [6.31 cm]).

Nodal stage before and after NACT :-

89.5% patients included in our study had palpable axillary lymphadenopathy, but advanced axillary disease (N2a or higher) was present in only 39.5% cases. In a similar Indian study on 30 patients 56.7% cases had N2 axilla and rest had N1 axilla (Chintamani et al, 2011).

Neo adjuvant chemotherapy Regimen :-

In our study, 65.1% received combination of anthracyclin and taxane based neo adjuvant chemotherapy (TAC – Docetaxel, Adriamycin, Cyclophosphamide) and 34.9% patients received only anthracyclin based neo adjuvant chemotherapy (CAF – Cyclophosphamide, Adriamycin, 5 – Fluorouracil). Majority of patients received anthracyclin and taxane based chemotherapy as an institutional protocol and due to increasing popularity of taxanes. Taxane was found to give better response rate in comparison to anthracyclin in selected patients as reports in some small series (Hortobagyi et al 1998). But in our study difference in response of two regimens were not noticed.

Response to Neo adjuvant chemotherapy :-

In our study 28 patients underwent definitive surgical treatment after 4 cycles and 48 patients after 3 cycles of NACT. Only 10 patients received 6 cycles of NACT. None of the patients had a pathological complete response (pCR), while complete clinical response, partial response and No response was observed respectively in 11.6%, 84.8% and 3.5% cases. Patients with a progressive disease were excluded from this study. In clinical trials of neoadjuvant chemotherapy the rate of pathological complete response (pCR) has ranged from 6-26% (Rastogi et al, 2008; Bear et al, 2003; Dieras et al, 2004 and von Minckwitz et al, 2001).

Surgery and postoperative complications :-

75 out of 86 patients undergone modified radical mastectomy and only 8 patients were treated with Breast conservation surgery. 3 patients undergone mastectomy with partial nodal clearance due to fixity of axillary nodes with major vessels. This is explained by the more advanced disease at presentation in this study as well as the patient preference. 13 out of 75 patients (17.3%) undergone modified radical mastectomy developed seroma in postoperative period where as 1 out of 8 patients (12.5%) in breast conservation group. This is comparable to a study of 359 patients, in which postoperative seroma occurred in 19.9% of patients undergoing MRM and in 9.2% of patients undergoing breast conserving surgery (Gonzalez et al 2003).

Association of relapse free survival with different management regimens :-

4 Patients out of 9 had disease recurrence who undergone NACT and

surgery only. The relapse free survival in this group is 55.6%. It is comparable to similar study of 91 patients, in which relapse free survival was 54.9% (Perloff et al 1998).

SUMMARY AND CONCLUSION

The present study "Treatment outcome of various management regimens for locally advanced breast carcinoma" has been carried out in department of surgery, PMCH, between September 2012 to October 2014.

- 86 cases of LABC patients were selected for the study.
- All the above cases were of stage IIIA, IIIB and IIIC according to AJCC classification of breast cancer.
- The clinical diagnosis was proved histologically by FNAC and Trucut biopsy and only histologically proved cases were included in the study.
- All histological proven cases, in case of metastatic workup, if found to have distant metastasis were excluded from the study.
- The median age was 45 years and one third of patients were premenopausal, and majority were multiparous.
- Location of the breast lump was maximum (55.8%) in upper outer quadrant and minimum (4.6%) in lower inner quadrant.
- Infiltrating ductal carcinoma was found in 86% cases whereas infiltrating lobular carcinoma was in 14%.
- 54% cases were of high grade in histological grade and remaining were of low grade.
- Hormone receptor status of tumor was done in 64 cases only, who agreed for this test. ER, PR positive and negative tumors were found to be in equal numbers, whereas Her-2 overexpression were positive in 56% cases. 14% tumors were triple negative.
- At the time of presentation 79.1% cases were in tumor stage T4 which came down to 11.6% in the same stage after neoadjuvant chemotherapy (NACT). The remaining cases were downstaged to tumor stage T0 to T3.
- Around 50% of cases had palpable mobile axillary nodes, whereas only 7% had N3 and 32% had N2 stage. In a very small number (10%) only, there were no palpable lymph nodes.
- After NACT there was appreciable fall in the number, size and fixity of the lymph nodes. All N3 nodes were either downstaged to N2 and majority to N1 (55%). In 40% of cases palpable nodes in the axilla becomes impalpable after NACT.
- Thus chemotherapy downstaged both the tumor size and the lymph nodes to an appreciable extent in my study so much so all the 28% cases, which were found to be inoperable on the basis of tumor / axillary node fixity were subsequently made operable with NACT.
- In chemotherapeutic regimen it was found that CAF (Cyclophosphamide, Adriamycin, 5-fluorouracil) regimen was used only in 35% cases, whereas as TAC (Docetaxel, Adriamycin, Cyclophosphamide) regimen was used in 65% cases. This change in the regimen in the present days was found to be more effective and less toxic. However the chemotherapeutic cycle varied from 3 to 6 cycles in individual cases depending on size and fixity of tumor and the node. In 56% of cases NACT was used for 3 cycles only.
- Unfortunately in 84% cases there was only partial response to NACT that is to say there was diminution in the size and fixity of tumor and nodes. Complete disappearance of tumor and nodes were found to be in 12% cases only. This means that NACT is not a therapeutic substitute to surgery, but an intermediate management to facilitate a curative surgery.
- Modifies radical mastectomy (MRM) was the commonest surgery done post NACT (87.2%). All patients going for surgery were properly counseled regarding various options and outcome of surgery. Only 9.4% patients offered Breast conserving surgery (BCS). So, in our setup with existing family and social condition, and level of education, breast conserving surgery still not become popular.
- All patients going for modified radical mastectomy (MRM) were satisfied and had the feeling that cancer is finally out with her removed breast.
- Unfortunately this feeling had the drawback that 19% of the operated patients (post MRM) didn't turn up for radiotherapy.
- 75% of patients (who undergone MRM) had uneventful recovery and remaining patients had minor complication like seroma, wound infection and flap necrosis.
- All patients postoperatively were subjected to complete their chemotherapy regimen says 2 to 4 cycles and subsequently radiotherapy. The dose and duration of radiotherapy was fixed by

radiation oncologist, but as stated above there was a fall out of 19 percent cases for radiotherapy.

- On follow up it was found that 35% cases, who didn't had postoperative radiotherapy developed local recurrence within one year of surgery. This indicates that all LABC patients should have postoperative chemotherapy and radiotherapy for increased disease free survival.
- Hormonal therapy was given in 32 cases and fortunately a disease free survival/ relapse free survival was noticed in 81 percent cases.
- Relapse free survival was noticed with different treatment regimen in patients and 82 percent relapse free survival were noted in patients whose treatment regimen was a combination of NACT, surgery and radiotherapy. Also in patients whose regimen was a combination of NACT, surgery, radiotherapy and hormonal therapy, 87 percent patients had relapse free survival.

CONCLUSION

In conclusion, LABC is a common surgical problem in our place. Because of illiteracy, poverty and family & social stigma the cases are reported late to a good hospital. Early confirmation of diagnosis, staging and metastatic work up sorts out cases of locally advanced breast carcinoma (LABC), who can be offered relapse free survival in majority of cases with adequate treatment. The whole treatment regimen is a multidisciplinary approach consisting of surgeon, pathologist, oncologist and radiation oncologist. Once diagnosed as LABC, all cases should be treated aggressively by NACT followed by surgery and further followed by remaining chemotherapy. Radiotherapy after completion of chemotherapeutic regimen is an integral part of treatment for loco-regional control. Few cases who are hormone receptor positive has been found to have added advantage in terms of morbidity, mortality and quality of life.

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