

Original Research Article

Role of neoadjuvant chemotherapy in downstaging locally advanced breast carcinoma, selection of surgical procedure and its outcome

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ABSTRACT

Background: In clinical practice all cases of locally advanced breast carcinoma (LABC) warrant chemotherapy followed by multimodality care. Neoadjuvant chemotherapy (NACT) has been the mainstay in the management of LABC. The main aim of NACT is to downstage and prevent systemic micrometastasis early.

Methods: This was a prospective study conducted on 36 diagnosed cases of stage III locally advanced breast cancer coming to the Dept. of Surgery, Dr. D. Y. Patil Medical College and hospital, Pune for a period of 2 years from 2017-2019. The effectiveness of neoadjuvant chemotherapy was assessed based on clinical, pathological and radiological response.

Results: Among 36 LABC cases, maximum number of patients fell in the 41-50 years (41.6%) and presented in the Infiltrating ductal carcinoma group with a clinical stage IIIA disease. The response to NACT showed that a total of 12 patients (33.3%) showed complete clinical response and 30 patients were downstaged after neoadjuvant chemotherapy which was statistically significant. Only 4 out of the total 12 complete clinical responders went for Breast conservative surgery. Seroma formation was found to be the most common post-operative complication.

Conclusions: LABC subjected to neoadjuvant chemotherapy based on taxanes/Anthracyclines show good clinical and radiological response. Patients preferred modified radical mastectomy due to the lack of awareness and low socioeconomic strata. The type of surgery did not increase the chance of recurrence in the follow up period.

Keywords: Breast conservation surgery, Locally advanced breast cancer, Neoadjuvant chemotherapy

INTRODUCTION

In 2018, the number of new cases diagnosed with breast cancer was 2.1 million with approximately estimates to 1 in 4 cancer cases in women. Most of the countries (154/185) report breast cancer to be the commonest malignancy and the leading cause of cancer related death. In terms of mortality, breast cancer rates show less variability.

Among Indian women, breast cancer is the commonest cancer overall accounting for 1,62,468 new cases and

87,090 deaths in 2018. Locally advanced breast cancer constitutes 10-20% of all the breast cancer in the United States whereas it is 30-60% in India.¹

LABC and IBC refers to a heterogenous group of breast cancer that present with extensive disease in the breast or regional lymph nodes, without evidence of distant metastasis.

LABC includes operable disease (Stage T3 N1), inoperable disease (Stage T4 N2-3) and IBC which is clinical stage (T4d N0-3, also inoperable).

Subdividing patients into these 3 broad group facilitates clinical management. However, in clinical practice nearly all cases of LABC and IBC will warrant chemotherapy followed by multimodality care.

Some women with LABC may be candidates for Breast conservation surgery following neoadjuvant chemotherapy. Locoregional control following BCS approach appears to be excellent except in patients with one or more of the features including clinical N2-3 disease, lymphovascular invasion, residual primary pathological size >2 cm and multifocal disease.

Patients presenting with IBC cannot be taken for breast conservation surgery even after complete resolution and is an absolute contraindication for BCS.²

Neoadjuvant chemotherapy (NACT) has been the mainstay in the management of LABC. The main aim of NACT is to downstage and prevent systemic micrometastasis early. The effectiveness of NACT depend on the drug/drug combination used.³ Studies show that pathologic complete response is a crucial factor in long term survival.⁴ Factors which effects complete pathological response to neoadjuvant chemotherapy are age, size of the tumour, pre/peri/post-menopausal status, chemotherapy given, number of chemotherapy cycles, IHC status, lympho-vascular and perineural invasion.⁵ A lot of trials have been done reporting effectiveness of anthracycline -based chemotherapy regimens over conventional regimens.⁶ In one of the clinical study conducted in India for evaluation of efficacy of NACT for LABC, revealed more effectiveness of taxane-based chemotherapy as compared to anthracycline-based chemotherapy.⁷ Taxanes (docetaxel or paclitaxel) have been found to be more effective than anthracyclines and have been added in the chemotherapy regimen to get better pathological response.⁸⁻¹⁰

Aims and objectives of the following study were assessment of effectiveness of neoadjuvant chemotherapy to downstage locally advanced breast cancer based on clinical and radiological findings, selection of surgical procedure according to response to neoadjuvant chemotherapy and to assess the pathological response and to assess the surgical outcome of the procedure.

METHODS

It is a prospective study conducted on the patients in the Department of General surgery at Dr. D.Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune, from August 2017 to September 2019 for the duration of two years. Sample size includes 36 with 15% error.

Inclusion criteria

Patients with 30-70 years of age with locally advanced breast carcinoma on trucut biopsy and clinical staging were selected.

Exclusion criteria

Patients with inflammatory breast carcinoma and immunocompromised patients were excluded from the study.

All female patients who came to the OPD underwent thorough physical examination and investigations as per the proforma and categorised as Stage III disease. Specific investigations were done which included sonomammography of both the breasts, CECT thorax, abdomen and pelvis and bone scan. All patients after clinical and radiological examination were categorised as Stage IIIA, Stage IIIB and Stage IIIC and based on Core-cut biopsy report and Er,Pr/Her2neu status, patients were subjected to Neoadjuvant chemotherapy.

Chemotherapy included

CAF regimen

FU 500 mg/m², Adriamycin 50 mg/m² and Cyclophosphamide 500 mg/m². 3 cycles were given with a 21 day interval between cycles.

TAC regimen

This included Paclitaxel 75 mg/m², Adriamycin 50 mg/m² and cyclophosphamide 500 mg/m². Three cycles were given with a 21-day interval between cycles.

Clinical and radiological reassessment were done after 3 cycles and were classified as: Complete response (CR) - defined as complete clinical disappearance of palpable tumour at the primary site, Partial response (PR)-More than 50% reduction in primary tumor size, Static disease (SD)-Less than 50% reduction or upto 25 % increase in tumour size and progressive disease (PD)-25 % increase in primary tumour size.¹¹

Static disease and progressive disease were categorised as non-responders and radiological response were categorised as Complete responders and non-responders.

Clinical TNM staging was done after 3 cycles of the neoadjuvant chemotherapy and compared to TNM staging before neoadjuvant chemotherapy and results tabulated.

Patients who showed complete clinical response were given an option of breast conservation surgery and Modified radical mastectomy. Patients who did not prefer BCS in the complete response category and all partially responding patients underwent modified radical mastectomy.

An informed and written consent was taken prior to surgery and the specimen was sent for Histopathological examination and further pathological response assessed and tabulated.

Pathological response

Only focal invasive tumour residuals in removed breast tissue, only in situ tumour residuals in removed breast tissue, no invasive or in -situ tumour cells (PCR) and no malignant tumour cells in breast and lymph node (PCR breast and lymph nodes).¹¹

Immediate post-operative complications were assessed which included surgical site infection, skin necrosis and seroma formation. Post-surgery, patients were given Taxane based chemotherapy. All patients were given radiotherapy after completion of the 3 cycles of adjuvant chemotherapy. 50 Gy in 25 daily fractions were given in 5 weeks that is 2 Gy per day for 5 days and continued for 5 weeks.

All patients who showed positivity for hormonal receptors by Immuno histochemistry received hormonal therapy. A total of 15 patients received Tamoxifen as hormonal therapy and 10 patients received Aromatase inhibitors.

Trastuzumab (Herceptin) was advised for all the Her2neu positive patients but due to the economical constraints none of the patients were given trastuzumab.

The patients were followed up for 18 months. Patients were reviewed after chemotherapy and radiotherapy. Follow up included 3 months- clinical examination, 6 months -clinical, if symptomatic -metastatic work up, 12 months-Mammography, radiological examination and metastatic work up and 18 months - clinical examination, radiological examination and metastatic work-up.

Statistical analysis

Approval was taken from the Ethical Committee before start of the study and written and informed Consent was obtained from all patients. The patients were informed regarding the purpose, procedures, risks and benefits of the study. Data analysis was done using the SPSS version 17 for window using appropriate test of significance like t test, chi-square test, proportion test etc. A probability value of 0.05 was accepted as the level of statistical significance.

RESULTS

The maximum number of patients fall in the 41 -50 years (41.6%). Maximum number of patients were in Stage IIIA (80.6%). Out of the 36 patients, 30 patients had a histopathology report of IDC (83.3%).

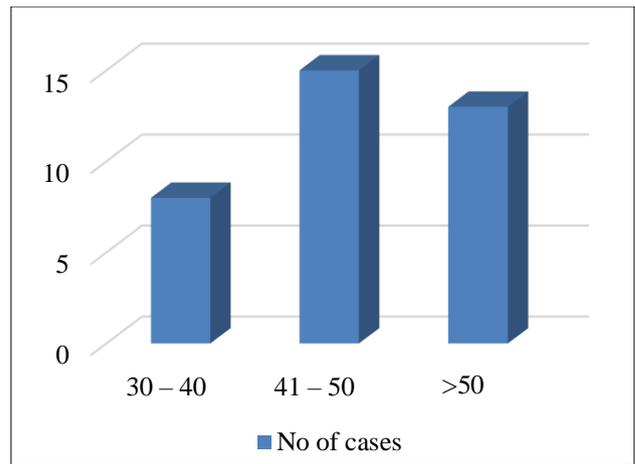


Figure 1: Age wise distribution of cases in study group.

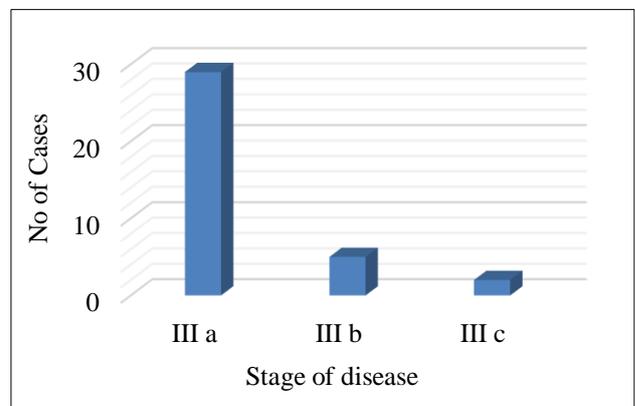


Figure 2: Stage of disease wise distribution of cases.

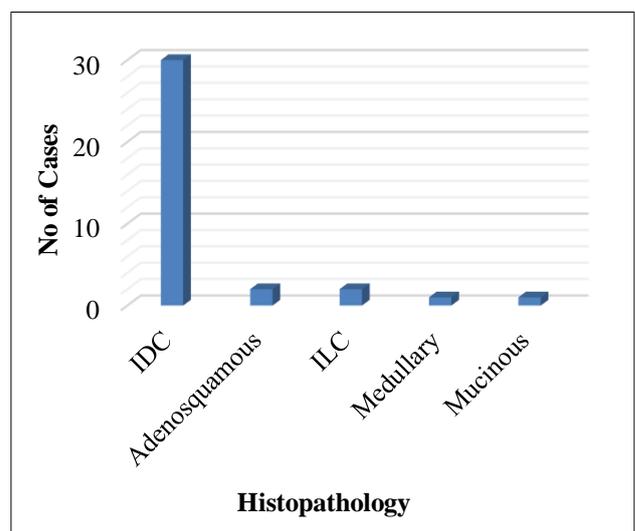


Figure 3: The histological type of the malignancy.

Maximum patients in ER/PR+ve / Her2neu-ve group (21 patients).

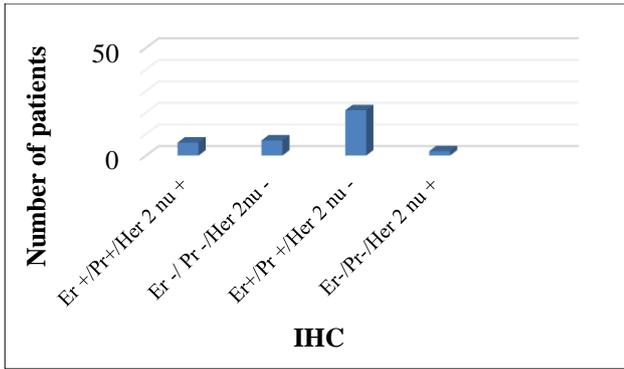


Figure 4: The IHC status of the patients.

It shows the number of clinical responders after NACT which showed that 12 (33.33%) patients were complete responders whereas 18 (50%) patients were partial responders and 6 (16.67%) patients were non-responders.

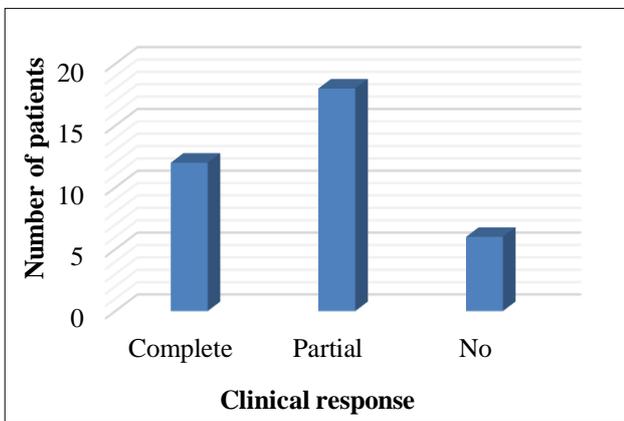


Figure 5A: The clinical response of patients to neoadjuvant chemotherapy.

30 patients out of 36 patients showed downstaging which is statistically significant, p value <0.05. Chi-square: 10.35, p value: 0.005.

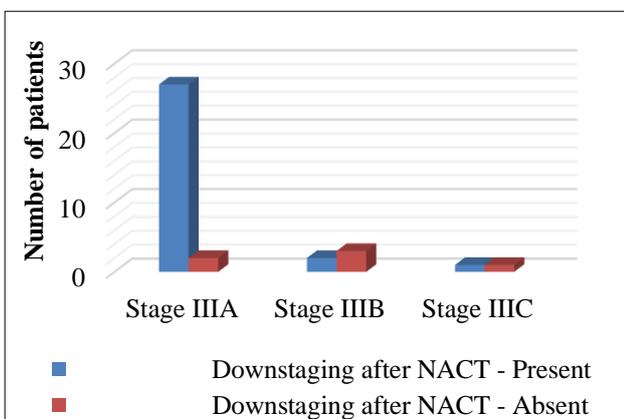


Figure 5B: The number of patients downstage after NACT.

Out of the 12 patients (33.3%) who had clinical complete response, only 6 showed a radiological response (30%). Chi-square = 0.45, p=0.80.

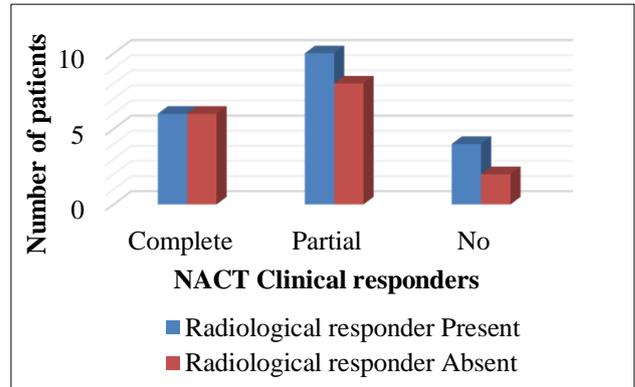


Figure 5C: Correlation between the clinical response in patients and association with radiological response.

(30 cases) were operated and 6 cases (16.6%) were non responders.

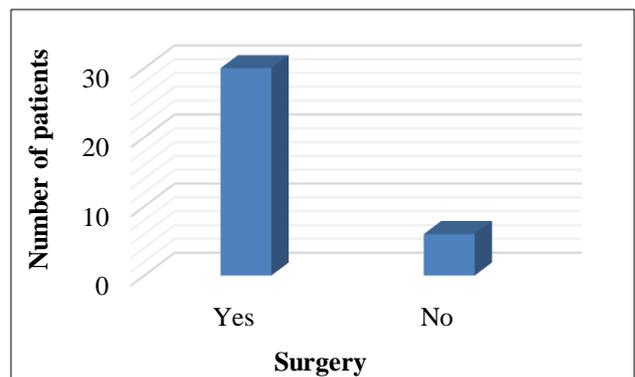


Figure 6A: Number of patients who were operated in the case study.

Only 4 (13.3%) patients opted for BCS whereas the rest 26 (86.6%) cases preferred MRM as the operative procedure of choice.

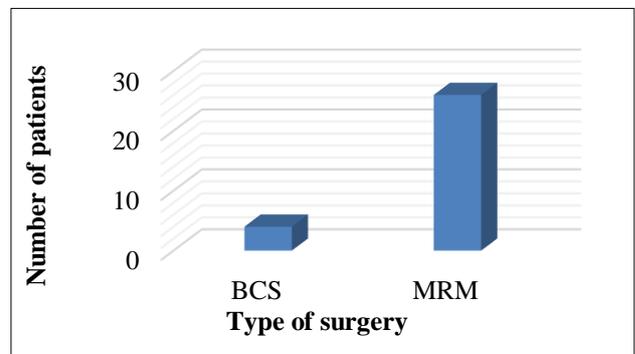


Figure 6B: Operative procedure wise distribution of cases in study group.

Out of a total of 36 patients, only 12 patients had post-operative complications and maximum cases had seroma (7) formation.

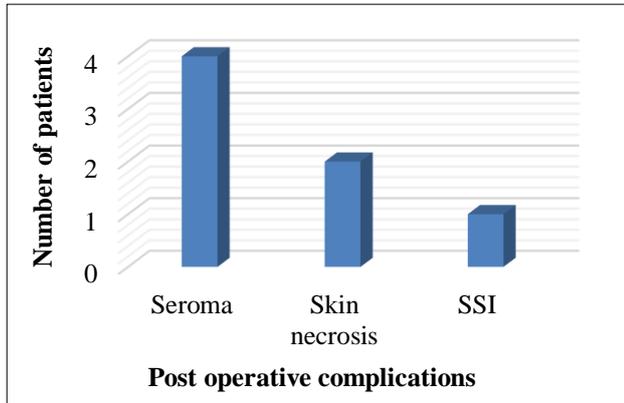


Figure 7: Types of post-operative complications.

The histopathological examination of the 30 specimens, 23 patients showed residual disease (76.6%). Complete pathological response was seen in only 7 patients (19.4%).

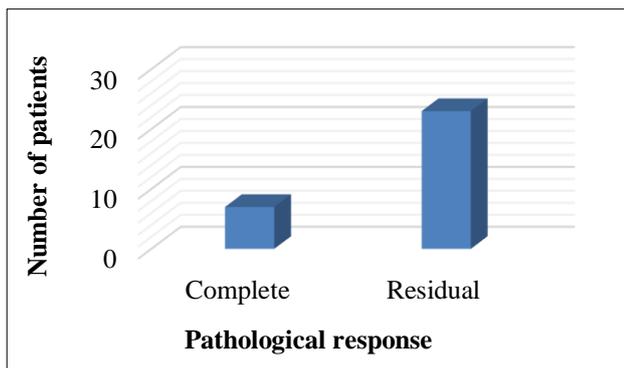


Figure 8A: Pathological response wise distribution of cases in study group.

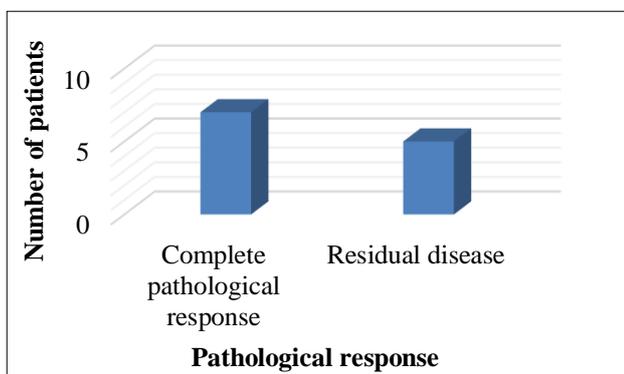


Figure 8B: Number of patients with complete clinical response showing pathological response.

Out of a total of 30 patients, 4 (13.3%) patients developed local metastasis in which 2 (6.6%) developed at 12 months and 2(6.6%) developed at 18 months.

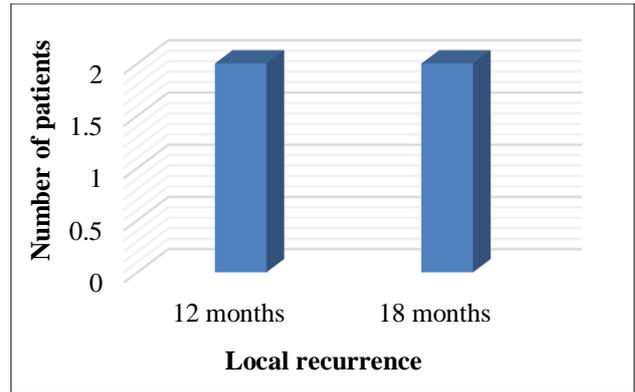


Figure 9A: Number of patients having local recurrence.

A total of 34 patients, 5 (14.7%) patients developed distant metastasis in which 2 (5.8%) developed at 12 months and 3 (8.8 %) developed at 18 months. Out of the 6 patients who showed no response after neoadjuvant chemotherapy, 2 patients defaulted and rest 4 went for palliative chemotherapy.

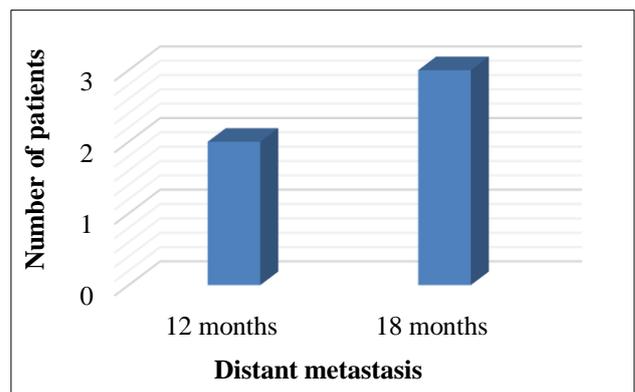


Figure 9B: Number of patients showing distant metastasis.

DISCUSSION

This study was a prospective study assessing the role of neoadjuvant chemotherapy in downstaging locally advanced breast carcinoma and selection of surgical procedure and its outcome. A total of 36 patients who were diagnosed with LABC were included in the study and the clinical and radiological response was assessed after neoadjuvant chemotherapy. Patients with clinical response were offered breast conservation surgery. Patients were followed up for 18 months post adjuvant chemotherapy and clinical and radiological recurrence assessed.

Age wise distribution

The maximum number of patients with LABC fall in the age group of 40-50 years (41.6%) whereas only 13 patients presented after 50 years (36.1%).

In a study conducted by Parmar et al on-breast conservation treatment in women with locally advanced breast cancer-experience from a single centre the maximum number of patients fell in pre-menopausal category with a mean age at presentation of 47.6 years.¹¹

Stage of the disease

Out of the total of 36 patients who presented with LABC, maximum number of patients were in Stage IIIA (80.6%). In a study conducted by Gedam et al, clinical presentation and management of locally advanced breast carcinoma majority of patients were in stage IIIA (55.6%) followed by stage IIIB (37.7%).¹²

In a study Cance et al on long-Term outcome of neoadjuvant therapy for locally advanced breast carcinoma effective clinical downstaging allows breast preservation and predicts outstanding local control and survival, fifty-one (82%) of the patients were clinical stage III at diagnosis, with 34 stage IIIA and 17 stage IIIB.¹³

Histopathology

A total of 30 patients had a histopathology report of IDC (83.3%) and 2 patients presented with adenosquamous, 1 patient with mucinous carcinoma and 3 patients with lobular carcinoma. In a study conducted by Mukherjee et al on the correlation of clinic-pathological and radiologic parameters of response to neoadjuvant chemotherapy in breast cancer majority (94.2%) of the patients had an infiltrating ductal carcinoma.¹⁴ Chen et al, showed that Invasive ductal carcinoma was seen in 89.3% cases.¹⁵

IHC

In the total of 36 patients, maximum number of patients were ER, PR+ve, Her2neu-ve with a percentage of 58.3% (21 patients) followed by triple negative cases (7) i.e. 19.4% and triple positive cases (6) i.e. 16.6%.

In a study conducted by Chand et al, on the evaluation of Immunohistochemical Profile of Breast Cancer for Prognostics and Therapeutic Use a total of 100 cases were studied, 58 cases were ER and PR positive, 37 cases negative and 5 cases showed different expressions of ER and PR.¹⁶

In a study conducted by Bhattacharyya et al on the outcome of neoadjuvant chemotherapy in locally advanced breast cancer: A tertiary care centre experience, most of the patients had hormone receptor positivity with an average percentage of 55% patients.¹⁷

Neoadjuvant chemotherapy

There was a total of 29 cases (80.5%) who went for FAC as the neoadjuvant chemotherapy and the rest 7 patients (19.4%) received Taxane based chemotherapy.

Only triple negative patients (ER, PR-ve, Her2neu-ve) were given Taxane based chemotherapy.

In a study by Mustacchi et al on the role of taxanes in triple-negative breast cancer: literature review, showed Taxanes to be effective as first line chemotherapeutic agent for LABC in neoadjuvant and adjuvant setting.¹⁸

Relation of Her2Neu with the age group

In this study total number of patients found to be Her 2 neu + were 8 (22.2%) and were maximum found in the age group of >50 years.

In a study conducted by Prem Chand, Anubha Garg et al on the evaluation of Immunohistochemical Profile of Breast Cancer for Prognostics and Therapeutic Use 7 patients out of a total of 100 patients with breast cancer were HER2/neu positive, and 93 were HER2/neu negative.¹⁶

Sajib Chatterjee, Madan Mohan Mukherjee, Nemai Chandra Nath, Saugata Samanta concluded that in his study of a total of 50 cases, 15(30%) were Her-2/neu positive.¹⁹

Clinical response

A total of 12 patients (33.3%) showed clinical complete response whereas 18 patients (50%) of patients showed partial response clinically and 6 were clinically non responders (16.67%).

In a study conducted by Mukherjee et al, on the correlation of clinic-pathological and radiologic parameters of response to neoadjuvant chemotherapy in breast cancer a total of 14 (26.9%) patients had clinical complete response (cCR).¹⁴

In a study by H Narendra et al, on an analysis of response to neo-adjuvant chemotherapy in patients with locally advanced breast cancer with emphasis on pathological complete response, 26 (36%) patients out of 72 patients showed complete clinical response to neoadjuvant chemotherapy in LABC patients.²⁰

Radiological response

In this study 20 patients had radiological response and 16 patients did not show any radiological response. Out of 20 patients who responded radiologically, 6 patients (30%) were clinically complete responders, 10 patients (50%) were clinically partial responders and 4 patients (20%) were clinically non responders.

In a study by Mukherjee et al, on the correlation of clinic-pathological and radiologic parameters of response to neoadjuvant chemotherapy in breast cancer correlation of routine clinico-radiological criteria used to assess response clinically with the final pathological response

rates was not well established and described a combination of factors, one was dearth of literature on the subject and second was lack of uniformity in techniques of grading and assessing clinical and pathological response rates.¹⁴

Operative procedure

Only 4 (11.1%) patients opted for BCS whereas the rest 32 cases preferred MRM as the operative procedure of choice. All the patient who had a complete clinical response were given an option between BCS and MRM. Only 4 patients opted for BCS whereas the rest of the patients went for MRM.

V. Parmar et al, on "Breast conservation treatment in women with locally advanced breast cancer -Experience from a single centre" Breast conservation can safely be offered to women with locally advanced breast cancers who respond to neoadjuvant chemotherapy.¹¹

In a retrospective study at the Jefferson medical college, Schwartz and associates treated 189 women belonging to stage IIB and III with NACT 85 % had a response to the induction chemotherapy and 103 (64%) were treated by mastectomy while 55 (36%) had BCT.²¹

Early surgical complications

In our study a total of 12 (33.3%) patients developed post-operative complications and the most common post-operative complication was seroma formation (19.4%).

In a study by Chandrakar et al on study the early complications of modified radical mastectomy performed, 10 cases (24.39) had surgical site infection, minimal seroma collection (<10 ml) was seen in 9 cases.²²

In a study by Kumar et al, on a prospective study of wound complications in cancer breast surgery following neoadjuvant chemotherapy, seroma formation was most common complication observed in 20% (12/60) patients followed by superficial surgical site infection in 6.67% (4/60) patients, deep surgical site infection in 2 patients (3.33%). Wound dehiscence in 2 (3.33%) patients.²³

Pathological response after surgery

In a total of 30 histopathological specimens, 23 patients showed residual disease (76.6%) and Complete pathological response was seen in only 7 patients (19.4%).

In a study by Mukherjee et al, on the correlation of clinic-pathological and radiologic parameters of response to neoadjuvant chemotherapy in breast cancer it is interesting to note that of those 14 patients with complete clinical response, only 6 patients (42.9%) had a correlating pathological complete response (pCR).

Conversely, of the 10 patients with pCR (19.2%), only 6 (60%) had correlating clinical response.¹⁴

In a study conducted by Tapesh Bhattacharyya, Suresh C Sharma et al, on the Outcome of neoadjuvant chemotherapy in locally advanced breast cancer: A tertiary care centre experience, pCR was seen in 24 (16.20%) patients.¹⁷

Adjuvant chemotherapy and radiotherapy

All patients were given taxane based adjuvant chemotherapy out of which 2 patients defaulted and did not receive the chemotherapy.

All patients received 5 cycles of radiotherapy for 5 weeks after completion of adjuvant chemotherapy.

In a study by Bria et al, on benefit of taxanes as adjuvant chemotherapy for early breast cancer: pooled analysis of 15,500 patients' taxane-based adjuvant chemotherapy for breast cancer seems to add a significant benefit in both DFS and OS over standard chemotherapy.²⁴

Hormone therapy

A total of 15 patients (41.6%) received Tamoxifen as hormonal therapy and 10 patients (27.7%) received Aromatase inhibitors.

All the premenopausal women who were hormone receptor positive received Tamoxifen as the hormonal agent and the post menopausal hormone receptor positive patients received Aromatase inhibitors.

Azizun-Nisa et al conducted a study the findings of which showed ER and PR were positive in 32.7% and 25.3% cases respectively. HER-2/neu was positive (3+) in 24.7% cases. ER positivity increased and HER-2/neu positivity decreased with rising age.²⁵

In a study by Reina Haque et al on Effectiveness of aromatase inhibitors and tamoxifen in reducing subsequent breast cancer, use of tamoxifen as an important drug to reduce subsequent breast cancer risks as the rate of such lesions was significantly reduced over the 13-year follow-up period in this group.²⁶

Post-operative follow up

In our study follow up at 3,6,12 and 18 months were done after completion of chemotherapy and radiotherapy. No recurrence was seen clinically and radiologically at 3 months and 6 months.

Out of a total of 30 patients, 4 (13.3%) patients developed local recurrence in which 2 (6.6%) developed at 12 months and 2 (6.6%) developed at 18 months.

Out of a total of 34 patients (including the non-responders), 5 (14.7%) patients developed distant metastasis in which 2 (5.8%) developed at 12 months and 3 (8.8 %) developed at 18 months.

In a study by Carrara et al, on Breast-conserving surgery in locally advanced breast cancer submitted to neoadjuvant chemotherapy the average months after surgery for recurrence was 81.3 months and was 26.4 and 27.1 months in general and LRR, respectively. At 36 months 72.4% of the general recurrence occurred and 76.5% of the LRR. The overall DFS rates at 36, 60 and 96 months were 77.9%, 68.9% and 67.0%, respectively.²⁷

In a study conducted by Bhattacharyya et al, on the Outcome of neoadjuvant chemotherapy in locally advanced breast cancer: A tertiary care centre experience at a median follow-up period of 44 months 36 patients (24.3%) developed relapse of which six patients developed locoregional recurrence, while 28 (18.9%) patients developed distant metastasis.¹⁷

CONCLUSION

Neoadjuvant chemotherapy was effective in downstaging 30 out of the 36 patients with locally advanced breast cancer based on clinical and radiological findings. Fairly good objective response to neoadjuvant chemotherapy was seen and that neoadjuvant chemotherapy downstages a good number of tumours and makes them operable and gives better loco-regional control ($p < 0.005$). All patients who showed complete clinical response (12 cases) were offered breast conservation surgery and 4 patients chose to go ahead with the same. The rest of the 8 patients went for Modified radical mastectomy due to the low economic strata, lack of awareness, education and fear of recurrence.

Complete pathological response was present in 7 cases (19.4%) and surgical outcome of the procedure assessment showed no significant relation in the chance of local and distal recurrence with respect to the surgery chosen suggesting that the type of surgery does not increase the chance of recurrence.

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