

Locally Advanced Breast Carcinoma: Three-year Experience from Tribal Rich Population of Central India

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Abstract

Background: Breast cancer is the most common cancer in the world, accounting for almost one in four cancer cases among women. In the past two decades, India has witnessed a substantial increase in the incidence of breast cancer and associated mortality. Locally advanced breast cancer (LABC) is the most frequent stage of presentation with varying clinical and biological characteristics. Multimodality treatment has improved the outcome in these patients. Poverty, ignorance, and illiteracy are among the major causes of delay in tribal rich population of Central India. The present study was undertaken to study the clinical presentation, molecular subtyping, and treatment provided and to find the 3 years survival of these patients of LABC.

Materials and Methods: A total of 105 patients were included in the study. These patients presented with Stage III-A, III-B, and III-C and inflammatory carcinoma of breast. Clinical staging with basic demographic profile was noted. Core needle biopsy was done to establish the diagnosis along with molecular subtyping. Metastatic workup consisted of computed tomography scan of chest and abdomen along with complete blood profile and serum alkaline phosphatase level. Pre-treatment photograph was taken in all patients to document the exact site of tumor in the breast. Neoadjuvant chemotherapy (NACT), followed by surgery and radiotherapy, was adopted as treatment. Treatment responses to chemotherapy were assessed after 3–4 cycles of various chemotherapy regimens.

Results: Sixty-two (59%) patients were clinical Stage III B followed by 29 patients of Stage IIIA (27.6%). Nine patients had Peau d'orange skin changes and five patients had supra clavicular nodal enlargement (stage III C). All patients had lump as first symptom, skin ulceration was present in 35 (33.3%). Seventy-six (72.3%) patients completed at least 3–4 cycles of chemotherapy and came for reevaluation in surgical OPD. 58/76 (76%) patients developed response to chemotherapy, 23 were complete clinical response, 35 were partial response, and 14 patients had less than 25% reduction in tumor size and four patients progressed to metastatic disease in the form of liver (three patients), lung and liver metastasis (one patient). All poor responders and 12/35 partial responders (26/76) were given further chemotherapy with different molecules to complete all NACT cycles preoperatively. Six of these patients still had inoperable disease that needed flap or skin graft coverage of the wound. Modified radical mastectomy was performed in all 72 patients. Supraclavicular node dissection was done in three cases and six patients needed flap or skin graft coverage of mastectomy wound. There was no significant wound healing delay. Sixteen patients had seroma formation; flap necrosis was observed in five patients. Mild-to-moderate lymphedema was seen in 23/72 (31.9%) patients. 43/50 patients completed adjuvant chemotherapy. 58/72 (80.5%) patients received radiation therapy (RT). Other patients were lost to follow-up. Histopathology was found to be infiltrating ductal carcinoma in 93% of cases. All patients were followed up every 3 months by clinical examination and necessary investigations. Forty-four of 58 patients (75.8%) were alive for at least 1 year. Six of these patients died within 1 year. Three-year disease-free survival is 57.6% (15 out of 26 patients who completed 3 years of treatment). Most common site of metastasis was liver, followed by bones, liver and lung combined, and lung alone.

Conclusion: LABC is most common of breast cancer stage in central part of India having tribal rich population. NACT, surgery, RT, hormone therapy, and immunotherapy are mainstay of multimodality treatment. About 75% of patients develop response to chemotherapy and become operable. Many patients do not complete their treatment. The results of inflammatory carcinoma remain to be dismal despite multimodality treatment.

Key words: Inflammatory carcinoma, Locally advanced breast carcinoma, Modified radical mastectomy, Neoadjuvant chemotherapy, Radiation therapy

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www.ijss-sn.com

Month of Submission : 04-2021
Month of Peer Review : 04-2021
Month of Acceptance : 05-2021
Month of Publishing : 06-2021

INTRODUCTION

Breast cancer is the most frequent cancer in women worldwide.^[1] In the past two decades, India has witnessed a substantial increase in the incidence of breast cancer and associated mortality,^[2] it has become the most common cancer in India in 2012, surpassing cervical cancer.^[3] This

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is partly due to an actual decrease in the incidence of cervical cancer. However, mostly due to a rapid rise in the number of breast cancer cases, the incidence of this disease has been consistently increasing, and it is estimated that it has risen by 50% between 1965 and 1985. Breast cancer is more common in the younger age group in India between 40 and 49 years of age. Many of these patients are below 30 years.^[4] Locally advanced breast cancer (LABC) is aggressive form of breast cancers. Although in the western world, only 10–20% of all breast cancer patients present as LABC, in India, 30–60% present as a LABC. Probable reasons for this higher incidence of LABC in India and other developing countries are illiteracy, poverty, limited availability of screening, and poor access to health-care facilities. LABC is a subset of breast cancer characterized by the most advanced breast tumors in the absence of distant metastasis. The need to identify labc as a separate group of breast cancers arose in view of the high associated rate of locoregional and systemic failure in the absence of metastasis at the time of presentation. The LABC definition includes any of these criteria, tumors more than 5 cm in size with regional lymphadenopathy (N1–3), tumors of any size with direct extension to the chest wall or skin, or both (including ulcer or satellite nodules), regardless of regional lymphadenopathy, presence of regional lymphadenopathy (clinically fixed or matted axillary lymph nodes, or any of infraclavicular, supraclavicular, or internal mammary lymphadenopathy) regardless of tumor stage.^[5]

There is wide variation in clinical presentation of LABC from subtle skin involvement to huge tumor size with or without ulceration. It also includes bulky primary tumors without nodal metastasis. This poses a significant therapeutic challenge. Multimodality treatment has become the treatment of choice that aims to control locoregional disease and prolonging the survival rate with preservation of form and function of breast as far as possible, thus improving quality of life. Neoadjuvant chemotherapy (NACT) using anthracyclines and taxanes with or without trastuzumab (for patients with Her2neu-positive status) followed by surgery and radiation therapy (RT) is mainstay of treatment. Hormonal therapy is added for receptor-positive disease. About 70% of the women respond to NACT, 22% clinical complete response (cCR), and 49% partial response (PR).^[6] Modified radical mastectomy is the most performed surgery post NACT. Breast conserving therapy (BCT) is not universally practiced across India. Resource constraints, lack of expertise, and unavailability of good pre-operative mammography are some of the limitations. In carefully selected patients, BCT can be safely practiced in 30%.^[7]

The present study was undertaken to evaluate demographic profile, clinical presentation, stage, molecular subtypes,

treatment modalities, and 3 years follow-up of patients presented in the tribal rich population of Central India.

MATERIALS AND METHODS

Study subjects and design: One hundred and five patients of invasive breast cancer of clinical Stage III A, III B, and III C and inflammatory breast cancer (LABC as defined by the NCCN and TNM classification) presenting in the Department of Surgery, N.S.C.B. Govt. Medical College, Jabalpur, between March 2017 and February 2020 were included retrospectively. Ethical committee clearance was not needed as this was a retrospective observational study.

Clinical staging with basic demographic profile was noted. Core needle biopsy was done to establish the diagnosis along with molecular subtyping. Metastatic workup consisted of computed tomography scan of chest and abdomen along with complete blood profile and serum alkaline phosphatase level. Pre-treatment photograph was taken in all patients to document the exact site of tumor in the breast. NACT, followed by surgery and radiotherapy, was adopted as treatment. Treatment responses to chemotherapy were assessed after 3–4 cycles of various chemotherapy regimens.

NACT response was assessed as complete clinical response if no palpable tumor in the breast and axilla, PR, if >50% reduction in the size of tumor, stable disease, if <50% reduction and progression, and if tumor size increased or patient developed metastasis.

All patients with early breast cancer and metastatic breast cancer at presentation were excluded from the study.

Statistical Analysis

Contiguous data are expressed as mean and median. Categorical data were analyzed as proportion and percentage. Analysis was done using MS Excel and SPSS.

RESULTS

Two hundred and forty patients of breast cancer were admitted during the study period. One hundred and five (43.5%) patients were LABC with mean age of 47.4 years (range 28–86 years). Sixty-seven patients (63.8%) belonged to 40–60 years, 15 patients (14.2%) were younger than 40 years, and others were more than 60 years old. About 54.3% of women were premenopausal. Two of the patients had bilateral breast carcinoma, one 35 years old and other was 62 years old, both of the patients had bilateral LABC. Five patients (including one with bilateral disease) had one or more close family member with a history of breast or

ovarian cancer. Genetic testing was advised but could not do in any of these patients due to financial constraints. Eighteen patients were illiterate, 67 received education below primary level. Twelve patients went to middle school, five to higher secondary, and three were graduates. Progressively increasing lump of mean 8.2 months (range – 3 months–2 years) duration was the most common symptom (100%). Thirty-five patients had skin ulceration of varying size from 1 cm to 15 cm [Table 1].

Size of the lump ranged from 4 to 20 cm with a mean size of 6 cm. Median lump size was 5.5 cm with most patients (56.5%) having lump size between of 5 and 8 cm. Axillary node enlargement was present in 79 (75.2%) patients, 36 (34.2%) patients had matted or fixed axillary lymphadenopathy (N2 nodal stage), and 5 (4.7%) patients had supraclavicular node enlargement (N3 nodal stage).

Overall prevalence of luminal A, luminal B, HER2-enriched, and TNBC subtypes of breast cancer was 33.3%, 17.1%, 30.4%, and 34.2%, respectively [Table 2].

All patients were subjected to NACT using dose dense anthracycline-based chemotherapy. Seventy-six (72.3%)

Table 1: Demographic profile of patients

Age	47.4 years (28–86 years)
Patients with below poverty live card	96 (91.4%)
Menopausal status	
Premenopausal	57 (54.3%)
Postmenopausal	48 (45.7%)
Duration of symptoms (months)	
<3	14 (13.3%)
3–6	25 (23.8%)
6–12	59 (56.1%)
>12	07 (6.6%)
Symptoms	
Lump	105 (100%)
Ulcer	35 (33.3%)
Nipple discharge	6 (5.7%)
Nipple areola distortion	14 (13.3%)
Pain	29 (27.6%)
Axillary swelling	16 (15.2%)
Arm lymphedema	11 (10.4%)
Peau d'orange	9 (8.5%)
Clinical stage	
III A	27
III B	69
III C	5
Inflammatory carcinoma	09

Table 2: Molecular subtypes (performed by IHC) of the patients

Type	n (%)
Luminal A	35 (33.3)
Luminal B	18 (17.1)
Her-2 enriched	32 (30.4)
Triple negative	36 (34.2)

patients completed at least 3–4 cycles of chemotherapy and came for reevaluation in surgical OPD. 58/76 (76%) patients developed response to chemotherapy, 23 were complete clinical response, 35 were PR, and 14 patients had less than 25% reduction in tumor size and four patients progressed to metastatic disease in the form of liver (three patients), lung and liver metastasis (one patient) [Figure 1]. All poor responders and 12/35 partial responders (26/76) were given further chemotherapy with taxanes to complete all NACT cycles preoperatively. Eight patients had complete response with PR in 12 patients. Six of these patients still had inoperable disease that needed flap or skin graft coverage of the wound.

Modified radical mastectomy with level II or III axillary clearance was performed in all 72 patients. Supraclavicular node dissection was done in three cases. Six patients needed latissimus dorsi myocutaneous flap coverage of mastectomy wound. There was no significant wound healing delay except for three patients who needed resuturing of their wounds. Sixteen patients had seroma formation; flap necrosis was observed in five patients. Mild-to-moderate lymphedema was seen in 13/72 (18%) patients [Table 3]. 43/50 patients completed adjuvant chemotherapy. 58/72 (80.5%) patients received RT.

Histopathology was found to be infiltrating ductal carcinoma in 93% of patients. In patients who had cCR,

Table 3: Post-operative complications

Complication	n=72 (%)
Minor wound infection healed spontaneously	8 (11.1)
Complete wound dehiscence needed closure	1 (1.3)
Flap necrosis	
<2 cm wide	5 (6.9)
>2 cm wide	2 (2.7)
Seroma beyond 2 weeks	16 (22.2)
Shoulder pain and restricted range of motion	15 (20.8)
Paresthesia on medial side of arm	8 (11.1)
Lymphedema	23 (16.5)

Table 4: Histopathology

Parameter	n (%)=72
Tumor type	
Infiltrating duct carcinoma	67 (93)
Medullary carcinoma	3 (4.1)
Colloid carcinoma	2 (2.7)
Pathological complete response	16/31 patients with complete clinical response 22.2
Mean number of involved nodes	4.5 (range 0–13)
Nodal stage	
N0	16 (22.2)
N1 (1–3 nodes)	14 (19.4)
N2 (4–9 nodes)	25 (34.7)
N3 (10 or more/supraclavicular nodes)	17 (23.6)

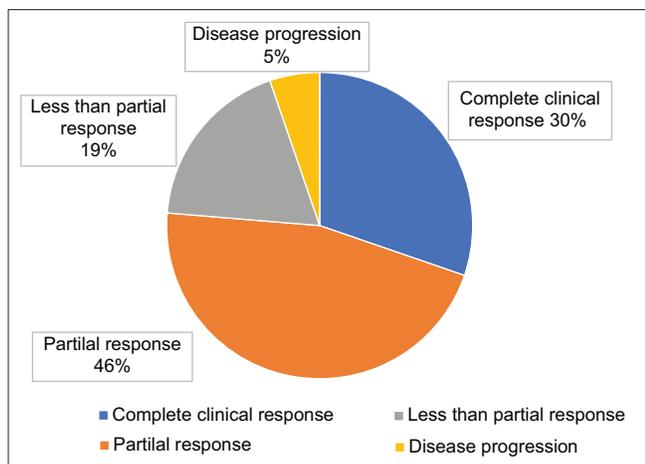


Figure 1: Response to chemotherapy after 3–4 cycles of chemotherapy

post-operative histology was showing no residual tumor only microcalcification/dysmorphic calcification with hyalinization, fibrosis, and sclerosis at the site of tumor [Table 4].

All patients were followed up every 3 months by clinical examination and necessary investigations. Forty-four of 58 patients (75.8%) were alive for at least 1 year. Six of these patients died within 1 year. Three-year disease-free survival (DFS) is 57.6% (15 out of 26 patients who completed 3 years of treatment). Most common site of metastasis was liver, followed by bones, liver and lung combined, and lung alone.

DISCUSSION

Over the past 10 years or so, breast cancer has been rising steadily, and for the 1st time in 2012, breast cancer was the most common cancer in women in India, a way ahead of cervical cancer. This is partly due to an actual decrease in the incidence of cervical cancer. The annual percentage change in the incidence ranged from 0.46 to 2.56 for breast cancer.^[7] LABC includes wide range of breast cancers with advanced primary tumors or advanced axillary nodal stage or both. It also includes an aggressive subgroup with poorer prognosis, inflammatory breast cancer.^[8] Despite being easily palpable, LABC constitutes 30–60% of patients, although in the USA, only 10–20% of all breast cancer patients are LABC. Patient factors are the major cause for delayed presentation, followed by system delay.^[9] Probable reasons of delay are illiteracy, poverty, and unavailability of resources and unawareness is an outcome of constant neglect due to patient and system factors. Multimodality treatment employing NACT, locoregional therapy, RT, hormone therapy, and immunotherapy are standard of

care. The intent of NACT specifically in the LABC includes earlier treatment of subclinical distant micrometastases, downstaging of the primary tumor, which may then allow for operability (including breast conservation surgery in some instances), and the ability for an *in vivo* assessment of response to specific systemic agents.^[9] It is not clear, if there is any survival advantage from NACT specifically in LABC. The results of the neoadjuvant versus adjuvant chemotherapy trials in primary operable breast cancer demonstrate equivalent outcomes.^[10,11] Addition of taxanes to anthracycline-based regimen improved DFS and OS in high-risk patients regardless of age, menopausal status, the number of nodes involved, and hormone receptor status.^[12] The pathological complete response (pCR) has been shown to be an independent prognostic factor. Anthracyclines as NACT produced pCR rates of 2–13% and taxanes used either alone or with anthracyclines have shown to improve pCR rates to 16–20% and cCR from 18% to >25%.^[13,14] The addition of post-operative RT to surgery showed an improvement in local control and DFS.^[15] Infiltrating lobular carcinomas form 2%–7% of the total breast cancers and mucinous carcinomas form 2%–3% of the special types of cancers. Mucinous carcinoma is more aggressive.^[16] NACT may even permit breast preservation for patients with LABC. Overall pooled prevalence of luminal A, luminal B, HER2-enriched, and TNBC subtypes of breast cancer was 0.33 (95% CI 0.23–0.44), 0.17 (95% CI 0.12–0.23), 0.15 (95% CI 0.12–0.19), and 0.30 (95% CI 0.27–0.33), respectively.^[17] About 34% of patients in our study were triple negative.

Parmar *et al.* published role of BCT in LABC post-NACT. Of the 664 women analyzed, 71% (469/664) of the women responded to NACT (22% cCR and 49% PR) and 28.3% (188/664) underwent BCT. At a median follow-up of 30 months, local relapse rate was 8% after BCT and 10.7% after mastectomy.^[6] All our patients underwent mastectomy as facilities for good mammogram, sentinel node biopsy is not available.

At our center, 105 (43.5%) patients were LABC with mean age of 47.4 years (range 28–86 years). Sixty-seven patients (63.8%) belonged to 40–60 years, 15 patients (14.2%) were younger than 40 years, and others were more than 60 years old. About 54.3% women were premenopausal. This is comparable to various studies published in India.

The overall rate of complications of surgery was almost like other studies. In a study by Pramod *et al.*, overall incidence of lymphedema was 41.1% and clinically significant lymphedema (moderate-to-severe lymphedema and symptomatic mild lymphedema) was observed in 16.8%.^[18] This is comparable to our study.

CONCLUSION

LABC is considered an aggressive type of breast cancer and responsible for poor prognosis, resulting in low survival. It is most common stage in our institution of tribal rich population of central India. Poverty, illiteracy, unawareness, and non-availability of resources are major causes for delay in diagnosis. Multimodality treatment is mainstay of treatment. Majority of patients respond to NACT, many of these patients can be offered breast conserving treatment. Overall prognosis is poorer. The quality of life and survival can be made better by optimizing therapy in this complex group of disease.

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How to cite this article: Mishra A, Damde H, Yadav P. Locally Advanced Breast Carcinoma: Three-year Experience from Tribal Rich Population of Central India. *Int J Sci Stud* 2021;9(3):42-46.

Source of Support: Nil, **Conflicts of Interest:** None declared.