

# Effectivity of Neoadjuvant Chemotherapy on Locally Advanced Carcinoma of Breast: A Prospective Study

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DOI: <http://dx.doi.org/10.21276/ijcmsr.2021.6.2.11>

**How to cite this article:** Katapally Nagesh Reddy, Nithya Chandra, Geeta Rani, Sowjanya Nallapati. Effectivity of neoadjuvant chemotherapy on locally advanced carcinoma of breast: a prospective study. International Journal of Contemporary Medicine Surgery and Radiology. 2021;6(2):B57-B61.

## A B S T R A C T

**Introduction:** Locally advanced carcinoma of the breast is a common presentation of the mammary carcinoma and is classified into various stages depending on the cancerous growth as IIB, IIIA, IIIB or IV. Today the most common methods of treatment for LABC includes Neoadjuvant Chemotherapy with anthrax cyclones and taxanes, with surgery and radiation therapy. For receptor positive therapy, hormonal treatment may be added.

**Materials and methods:** 50 with LABC presenting for treatment were included into the study. Tumor was diagnosed and characterized by FNAC, TRU\_CUT biopsy and ECG and 2 D echo was done for the patients before the start of the neoadjuvant chemotherapy. Cyclophosphamide 500 mg/m<sup>2</sup>, Doxorubicin 60 mg/m<sup>2</sup> given intravenously, 5-Fluorouracil 500 mg/m<sup>2</sup> (CAF) was used for Chemotherapy.

**Results:** 44% incidence of locally advanced breast carcinoma among the patients presented for treatment was observed with the most common age group being 41-50 years. A 100% response was seen in 3 patients with IIIA grade tumor and 2 patients with Grade IIIB tumor. 91-99% reduction as seen in 2 and 1 patients of Grade IIIA and Grade IIIB respectively, 81-90% reduction was seen in 1 IIIA patient and 5 Grade IIIB patients and 1 Grade IIIC patient. 72-80% reduction was the most common type seen in 3 grade IIIA, 8 grade IIIB patients. No reduction of the tumour was observed in 3 Grade IIIB patients, and 1 case of inflammatory carcinoma also had no response.

**Conclusion:** The treatment for this condition is multinodal with the use of neoadjuvant chemotherapy, which helps in reducing the size of the tumor as well as increasing the longevity of life.

**Keywords:** Breast Cancer, Neoadjuvant Therapy, Inflammatory Carcinoma, Tumor

## INTRODUCTION

Locally advanced carcinoma of the breast is a common presentation of the mammary carcinoma especially seen in the developing countries. It is one of the frequent types of cancer among the women and is the second leading causes of death after lung cancer among the women<sup>1,2</sup>. The estimated incidence of breast carcinoma among the developing countries is 30-60% of the women and in the USA, it is 10-20%. In India, around 75,000 new cases occur every year with an overall incidence of 50-70% of the women presenting for treatment<sup>3</sup>. This higher incidence could be due to the lower economic status or the lack of proper knowledge among these women<sup>4</sup>.

The Locally advanced breast carcinoma is characterized by a range of clinical presentations including presence of a large primary tumor (>5 cm), which may be associated with or without involvement of skin or chest wall, fixed or matted axillary lymph nodes, or with the disease spread up to the

ipsilateral internal mammary, the supraclavicular nodes in the case of absence of evidence of distant metastases<sup>1</sup>. Rapid neoplastic evolution occurs in some patients and other have a long history of tumor growth<sup>1</sup>. The LABC is classified into various stages depending on the cancerous growth as IIB, IIIA, IIIB or IV according to the American Joint Committee for Cancer Staging and End Results Reporting<sup>5</sup>.

The wide spectrum of the presentations of the malignant breast tumors pose a great challenge for treatment. The oldest mode of treatment for breast carcinoma was surgery. There were different surgeries which were devised over a period of time for treatment and the technique which was followed was put forth by William Halsted. He described a complete removal of the breast with en bloc removal of the axillary lymph nodes, the muscles of the chest wall and sometimes a part of the chest wall itself, depending on the advancement in that area. This was the standard treatment of the breast cancer, but the prognosis after the surgery was not very good,

with the lifespan ranging from 13-20% at 5 years<sup>6</sup>.

With the advent of radiation, radical radiation was also tried, with the survival rate to be abysmal. With higher doses, many complications were also observed<sup>7,8</sup>. Later, a combination therapy was done for the operable cases and only radiation therapy was done to only those patients who were inoperable<sup>9</sup>. However, metastasis appeared in most of the women, signaling the failure in treatment<sup>10</sup>.

Over the last 3 decades, adjuvant therapy had taken a firm hold in the treatment with the newer version, the neoadjuvant chemotherapy (NACT). NACT increases the rates of the breast conservation rather than radical removal, with minimization of the axillary lymph node surgery<sup>10,11</sup>. NACT also helps in the in vivo assessment of the tumor response and the identification of the prognosis, based on the degree of response.

Today the most common methods of treatment for LABC includes NACT with anthracyclines and taxanes, with surgery and radiation therapy. For receptor positive therapy, hormonal treatment may be added. In case of patients with Her2neu-positive disease, trastuzumab therapy is introduced. The response of the patients to induction therapy was good in both the primary tumor as well as the regional lymph node cases<sup>12</sup>.

This study was done to assess the various epidemiological characteristics, clinical presentations and treatment modalities for LABC.

## MATERIALS AND METHODS

This prospective hospital based study was done by the department of surgery at Mallareddy institute of medical sciences from June 2019 to January 2021. The nature of the study was explained in detail to the patients and informed consent was taken from them after attaining the clearance from our Institutional Ethical Committee. Out of the 114 patients with carcinoma breast, 50 with LABC presenting for treatment were included into the study based on the accepted definition of Stage III and inflammatory breast cancer. Patients who had distant metastasis were excluded from the study.

The histopathology of the growth was done with Fine Needle Aspiration Cytology (FNAC) procedure and stained appropriately for observation. TRU-CUT biopsy was done for receptor studies. All the patients were subjected to routine hematological investigations such as complete blood picture, hemoglobin estimation, Erythrocyte sedimentation rate. Blood work for Blood Sugar, Cholesterol, Lipid profile, kidney profile, and viral markers were done for all the patients. Complete metastatic workup was done with chest Xray, bone scan and ultrasound of abdomen. ECG and 2 D echo was also done for the patients before the start of the neoadjuvant chemotherapy. Cyclophosphamide 500 mg/m<sup>2</sup>, Doxorubicin 60 mg/m<sup>2</sup> given intravenously, 5-Fluorouracil 500 mg/m<sup>2</sup> (CAF) was used for Chemotherapy.

The response to the neoadjuvant chemotherapy was seen as the following:

## RESULTS

114 patients were admitted during the carcinoma of breast

while 50 of them were diagnosed as LABC (44%). The most common age group having LABC was 41-50 years with 17 (34%) affected patients, followed by 31-40 years age group with 13(26%) patients. 9 (18%) of the patients were in the 51-60 years age group and 6 (12%) were in 21-30 years age group (Fig:1).

All of the patients, at the time of admission presented with a lump (100%), followed by retraction of nipple seen in 14 (28%) of the patients, pain in 13 (26%). 8 (16%) of the patients had ulcer along with the lump and 6 (12) each had discharge from the nipple as well as swelling in the axilla (Table : 2)

58% of the upper outer quadrant was involved, 16% of the inner outer, 10% of central and upper inner each were involved. Lower inner was the least quadrant to be involved as seen in 6% (Fig: 2).

Majority of the patients had a tumour size of 5-8cms, as seen in 38 patients (76%), 7 (14%) has a size of <5cms, 4 had 8-10 cms and 1 patient (2%) had a tumour size of >10 cms (Table:2)

26 (52%) of the patients had N1 lymph node status, 22 (44%) had N2, and 2 (4%) had a status of N3 (Table : 4).

23 (46%) of the patients had IIIA group stage of breast carcinoma, out of which 12 of them had T3N1M0, 10 had T3N2M0, and 1 of them had T2N2 stage. 24 (48%) had IIIB stage of LABC, with 13 being T4bN1M0, 6 being T4bN2M0, 4 had T4aN2M0 and 1 was T4aN1M0. 2 patients belonged to IIIC stage and all of them were having T3N3M0. T4d stage of inflammatory cancer was seen in 1 (2%) of the cases (table: 5).

77.6% of the tumors were inoperable and 24% were operable. The positive response to the neoadjuvant chemotherapy was observed by the reduction of the tumour size and classified according to the stage.

A 100% response was seen in 3 patients with IIIA grade tumour and 2 patients with Grade IIIB tumor. 91-99% reduction as seen in 2 and 1 patients of Grade IIIA and Grade IIIB respectively, 81-90% reduction was seen in 1 IIIA patient and 5 Grade IIIB patients and 1 Grade IIIC patient. 72-80% reduction was the most common type seen in 3 grade IIIA, 8 grade IIIB patients. No reduction of the tumour was observed in 3 Grade IIIB patients, and 1 case of inflammatory carcinoma also had no response (Table : 6). Both ER and PR were positive in 23 (46%) of the cases,

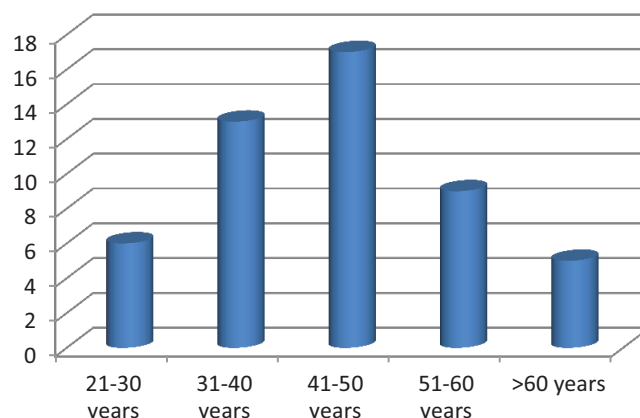


Figure-1: Age distribution of patients

Response	Explanation
Clinical complete response	No tumor palpable in the breast and in axilla
Clinical Partial Response	More than 50% reduction in tumor size
Stable disease	Less than 50% reduction in tumor size

**Table-1:** Response to adjuvant therapy

Symptom	Number of cases	Percentage
Lump	50	100%
Ulcer with lump	8	16%
Pain	13	26%
Retraction of nipple	14	28%
Nipple discharge	6	12%
Swelling as axilla	6	12%

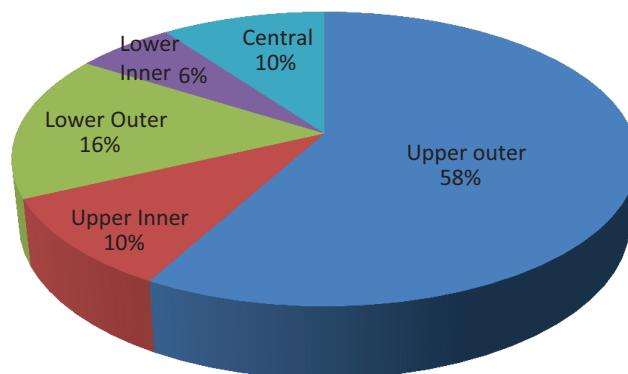
**Table-2:** Symptoms seen in patients

Tumour size	Number of patients	Percentage
< 5 cms	7	14%
5-8 cms	38	76%
8-10 cms	4	8%
>10 cms	1	2%

**Table-3:** Size of tumour

Lymph node status	Number	Percentage
N1	26	52%
N2	22	44%
N3	2	4%

**Table-4:** Lymph node status



**Figure-2:** Involvement of quadrants

Group stage	TNM stage	Number of Patients	Number of Patients	Percentage
IIIA	T3N1M0	12	23	46%
	T3N2M0	10		
	T2N2	1		
IIIB	T4aN1M0	1	24	48%
	T4aN2M0	4		
	T4bN1M0	13		
	T4bN2M0	6		
IIIC	T3N3M0	2	2	4%
Inflammatory Ca	T4d	1	1	2%

**Table-5:** Stage of the disease

Clinical response		IIIA	IIIB	IIIC
Complete (cCR)	100%	3 (6%)	2 (4%)	-
Partial (cPR)	91-99%	2 (4%)	1 (2%)	-
	81-90%	1 (2%)	5 (10%)	1 (2%)
	71-80%	3	8 (16%)	-
	61-70%	-	2 (4%)	1 (2%)
	51-60%	-	1 (2%)	-
Stable disease (SD)	1-50%	2 (4%)	2 (4%)	-
	0%	-	3 (6%)	-

**Table-6:** Response to neoadjuvant therapy

both ER/PR were negative in 20 (40%). ER positivity with PR negativity was seen in 5 (10%). ER negativity with PR

positivity was seen in 2 (4%). Overall receptor positivity is seen in 30 (60%) patients. Tamoxifen 20 mg O.D for 5 years

was advised to all patients with hormone receptor positive status

## DISCUSSION

Locally advanced breast carcinomas are highly advanced primary tumors which also include inflammatory breast cancers, which are a rare group of breast cancers having poor prognosis. Most of the LABC are palpable, but in case of diffusely infiltrated breast carcinoma, there is no dominant mass that can be palpated. Usually, the first step towards the diagnosis of LABC includes palpation of the skin, the breast, the axillary, cervical and supraclavicular lymph nodes. The size of the tumor, its fixation to the chest wall, the satellite skin nodules and the lymph nodes denote the presence of LABC<sup>13</sup>.

Neoadjuvant therapy helps in down staging the LABC patients. It has today become one of the standard approaches for the treatment of inoperable LABC. Earlier these patients were treated with total mastectomy or with primary radiation therapy. But with these methods also, the prognosis and the incidence of metastasis is not reduced too much. After the advent of neoadjuvant therapy, this method has become more sought after as there is a conservation of breast and an increase in the longevity of life<sup>14</sup>.

In the present study, the dominant age group to be affected was 41-50 years age group, followed by 31-40 years. A study by Gedam et al reported a mean age to be 42.4 years with the most predominant year to be 41-50 years followed by 31-40 years, corroborating our study<sup>15</sup>. Goel et al found breast cancer to be more common among the 30-40 years age group<sup>16</sup>.

44% of the people admitted with breast carcinoma had LABC. In a similar study by Gedam et al, a 37.5% of incidence of LABC among the patients admitted for breast cancer was observed<sup>15</sup>. Chopra reported more than 50% of the patients presenting for treatment to have LABC<sup>17</sup>.

All the patients presented with a lump, 28% had retracted nipple and 26% had pain. An addition of ulcer was seen in 16% of the patients and 12% had discharge from the nipple. Gedam et al also reported a 100% incidence of lump on the breast similar to our study<sup>15</sup>.

46% of the patients had IIIA group stage of breast carcinoma, out of which 12 of them had T3N1M0, 10 had T3N2M0, and 1 of them had T2N2 stage. 48% had IIIB stage of LABC, 2 patients belonged to IIIC stage and T4d stage of inflammatory cancer was seen in 1 (2%) of the cases. In a study by Gedam et al, 55.6% of the patients had IIIA stage, 37.8% were IIIB and 4.4% were IIIC. 42.2% of the IIIA were T3N1M0 and required modified radical mastectomy<sup>15</sup>. Inflammatory carcinoma was seen only in 1 patient, which was similar to others studies.<sup>15,18-20</sup>

10% of the patients had 100% reduction in the tumor and 50% had partial reduction. A 100% response was seen in 3 patients with IIIA grade tumor and 2 patients with Grade IIIB tumor. 91-99% reduction as seen in 2 and 1 patients of Grade IIIA and Grade IIIB respectively, 81-90% reduction was seen in 1 IIIA patient and 5 Grade IIIB patients and 1 Grade IIIC patient. 72-80% reduction was the most common type seen in 3 grade IIIA, 8 grade IIIB patients.

No reduction of the tumour was observed in 3 Grade IIIB patients, and 1 case of inflammatory carcinoma also had no response. In a study by Valero et al, 17% of the patients had complete clinical remissions and 68% of them had partial remission. In another study by Conte et al, a 15% complete clinical remission was observed and had a 3 year rate of progression free survival in 54%<sup>18</sup>. Similar results were found in another study by Chu et al<sup>21</sup>. In another study by Klein et al, a 25.2% of the patients showed a partial clinical response while Bear et al reported 26.1% of the same<sup>22,23</sup>. 13% had a complete clinical response in a study by Viswambaran et al with an objective response seen in 87% of the patients<sup>24</sup>.

For the predictive and prognostic value in breast cancer, the estrogen receptor is a well established factor. It has been suggested that the breast cancer can be categorized into endocrine responsive and non responsive state for early diagnosis and treatment<sup>25</sup>. Therefore, it is critical to test for the estrogen and progesterone receptor factors for the appropriate treatment. Both ER and PR were positive in 23 (46%) of the cases in the present study, while both ER/PR were negative in 20 (40%). ER positivity with PR negativity was seen in 5 (10%). ER negativity with PR positivity was seen in 2 (4%). Overall receptor positivity is seen in 30 (60%) patients. In an study from Mumbai, both ER and PR positivity was found in 32.6% and 46.1% of the cases<sup>26</sup>.

## CONCLUSION

This study revealed that the diagnosis of LABC should be done at the early stages for proper treatment and conservation of breast. For this, proper knowledge is required among the women, especially that of the lower socioeconomic group. Therefore proper education is mandatory to these women. Moreover the treatment for this condition is multimodal with the use of neoadjuvant chemotherapy, which helps in reducing the size of the tumor as well as increasing the longevity of life.

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**Source of Support:** Nil; **Conflict of Interest:** None

**Submitted:** 08-04-2021; **Accepted:** 02-05-2021; **Published online:** 27-06-2021