

## Original Research Article

# Loco-regionally advanced breast cancer: evaluation of management of breast cancer with special reference to multimodal approach

Anshuman Panda<sup>1</sup>, Subrata Kumar Das<sup>1</sup>, Tapas Ranjan Gupta<sup>1</sup>,  
Gouri Shankar Kesari<sup>2</sup>, Sukanta Sen<sup>3\*</sup>

<sup>1</sup>Department of General Surgery, <sup>2</sup>Department of General Medicine, <sup>3</sup>Department of Pharmacology, ICARE Institute of Medical Sciences & Research, Haldia, West Bengal, India

**Received:** 21 August 2016

**Accepted:** 26 September 2016

### \*Correspondence:

Dr. Sukanta Sen,  
E-mail: [drsukant@gmail.com](mailto:drsukant@gmail.com)

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ABSTRACT

**Background:** Breast cancer is one of the most common human neoplasms, accounting for approximately one-quarter of all cancers in females worldwide and 27% of cancers in developed countries with a western lifestyle. The aims of this study were to evaluate the management of loco-regionally advanced carcinoma of breast with special reference to multimodal approach.

**Methods:** The study was conducted on patients with loco-regionally advanced carcinoma of breast, reporting for treatment in a large multi-specialty teaching institute. All patients of stage IIIB were initially treated with neo-adjuvant (induction) chemotherapy (3 cycles), except 4 patients in the study group offered surgery as initial treatment because of small tumor size with limited peau d'orange change in the skin. After this treatment all patients were reassessed with a thorough clinical examination and restaging work upto detect the response of the chemotherapy. All patients who achieved objective response (complete + partial) were offered surgery, followed by CT and RT.

**Results:** About 60% of the patients were in stage IIIB and 32% in stage IIIA. Majority of the tumors were in T4 category (64%). In 28% cases ipsilateral fixed lymph nodes were found. Histopathological examination revealed 76% (38) patients with infiltrating duct carcinoma, 4 patients (8%) had comedo carcinoma, 2 patients (4%) had lobular carcinoma, 2 patients (4%) had medullary carcinoma and 4 patients (8%) had mucinous carcinoma. Both nonresponsive (NR) and disease progression (DP) patients were in stage III B group. About 76.9% patients of stage IIIB (20) achieved partial response. Only 1 patient (33.3%) developed local recurrence after 10 months of completion of treatment. Median disease free survival (DFS) period of this group is 30.2 months. Recurrence rate is stage IIIA patients was 27.7% and in stage IIIB 37.5%. Maximum numbers of disease free patients were found in T3N1 group (85.7%). Patient with N2 and T4 disease chances of recurrence was more than N1 and T3 lesions.

**Conclusions:** Patients with LBAC who are able to complete treatment with chemotherapy, mastectomy, and postmastectomy radiation have a high probability of locoregional control. Neo-adjuvant chemotherapy can make inoperable locally advanced breast cancer operable and with the use of neo-adjuvant CT, breast conservation surgery is possible even in locally advanced breast cancer. Use of post-operative CT and RT can increase the disease free survival period. Use of multimodal treatment in the form of CT, surgery and radiotherapy can increase the disease free survival period in locally advanced breast cancer. The advent of successful multimodal regimens incorporating systemic treatment (chemotherapy or chemohormonal therapy) as well as local therapy (surgery and radiation) has significantly improved disease-free and overall survival as well as local-regional control. Longer follow-up of these conservatively treated patients will be needed, however, to determine whether local-regional control is preserved.

**Keywords:** Breast cancer, LABC, Multimodal approach, DFS, Outcome

## INTRODUCTION

Breast cancer is one of the most common human neoplasms, accounting for approximately one-quarter of all cancers in females worldwide and 27% of cancers in developed countries with a Western lifestyle.<sup>1</sup> Breast cancer can also occur in men, but it is more than 100 times more common in women than in men. It usually has bad prognosis due to delays in diagnosis.<sup>2</sup>

The global burden of breast cancer in women, measured by incidence or mortality, is substantial and rising in several countries.<sup>3</sup> Breast cancer, the most frequently occurring cancer in women, is a major public health problem, with 1,384,155 estimated new cases worldwide with nearly 459,000 related deaths.<sup>4</sup>

Breast cancer is highly heterogeneous in its pathological characteristics, some cases showing slow growth with excellent prognosis, while others being aggressive tumors. Current predictions and statistics suggest that both worldwide incidence of breast cancer and related mortality are on the rise. According to 2012 GLOBOCAN statistics, nearly 1.7 million women were diagnosed with breast cancer with 522,000 related deaths—an increase in breast cancer incidence and related mortality by nearly 18 % from 2008.<sup>5</sup> It has been predicted that the worldwide incidence of female breast cancer will reach approximately 3.2 million new cases per year by 2050. These numbers reflect the magnitude of breast cancer incidence, its effect on society worldwide and the need for urgency for preventive and treatment measures.<sup>6</sup>

While technological advances in medical sciences and health care have made it possible to detect the disease early and to start the treatment early on to prevent the progress of the disease into a metastatic state, there are several unanswered questions with regard to the molecular mechanisms that underlie the aggressiveness of certain forms of this disease. Epidemiological studies suggest that addressing socio economic issues is utmost important, so that all women have equal access to medical care from screening to advanced treatment, and only such decisive action can help reduce the worldwide burden of breast cancer.<sup>7-9</sup>

Cancer has become one of the ten leading causes of death in India. Breast cancer is the most common diagnosed malignancy in India, it ranks second to cervical cancer.<sup>10</sup> An increasing trend in incidence is reported from various registries of national cancer registry project and now India is a country with largest estimated number of breast cancer deaths worldwide. It is estimated that there are nearly 2 to 2.5 million cancer cases at any given point of time in India.

Over 7 to 9 lakh new cases and 3 lakh deaths occur annually in India due to cancer.<sup>11,12</sup> In western world, there are better screening facilities and greater awareness

amongst people, thus cancer can be detected in early stages (Stage I or II), in those countries. The 5 year survival rates of these patients are as high as 80-90%.<sup>13</sup> In India, unfortunately due to lack of awareness, ignorance, inadequate scanty diagnostic and screening infrastructure, low socio economic condition many patients present late with a large, ulcerated or fungated tumor or pain from metastatic sites.

Basic aim of the treatment of breast cancer patients is to achieve a good loco-regional control of disease and a reasonably good quality of life. Different modalities of treatment are available for the management of breast cancer viz surgery, radiotherapy, chemotherapy and neoadjuvant hormonal therapy etc. Different trials have been done by using the above modalities separately or in combination to achieve the disease control and to increase disease free survival.

Surgery alone, in loco-regionally advanced carcinoma of breast results in a relapse of 30-50% of cases. The long-term cure rates exceeded 30%. Studies of the use of local therapy alone (surgery or radiation therapy) confirmed that most patients developed both distant metastatic disease and a high rate of local-regional failure. Combination surgery and radiation therapy regimens improved local control but did not influence long-term survival.<sup>14</sup>

The present concept of treatment of loco-regionally advanced breast cancer is to achieve a good loco-regional control and disease free survival as long as possible. Multimodality approach yielded, improved loco-regional tumor control and disease free survival as compared to any other modalities.

### *Aim*

The aims of this study were to evaluate the management of loco-regionally advanced carcinoma of breast with special reference to multimodal approach.

### *Objectives*

- To study the prognostic factors which may determine the response rates
- To determine the optimum local therapy for loco-regionally advanced cancer of breast
- To study the effect of neo-adjuvant chemotherapy on operable loco-regionally advanced breast cancer

## METHODS

The study was conducted on patients with loco-regionally advanced carcinoma of breast, reporting for treatment in a large multi-specialty teaching institute.

The institutional Ethics Committee permission was taken and prior written informed consent was obtained from all

the patients. Fifty patients of loco-regionally advanced carcinoma of breast (TNM stage III) were included in the study. Patients with inflammatory carcinoma of the breast, male breast cancer and metastatic breast cancer were excluded from the study. Study participants were divided into two groups as follows:

*Group 1:* Operable – 20 patients, where surgery offered as an initial treatment

*Group 2:* Inoperable- 30 patients, where induction chemotherapy and/or radiotherapy offered as an initial treatment

**Criteria of inoperability**

- Fungating growth
- Large tumor mass >10 cm in size with fixed axillary nodes
- Extensive skin oedema (>1/3 of breast)
- Fixation to the chest wall
- Edema of the arm

**Pre-treatment evaluation**

A detailed history was taken. Clinical examination included a thorough general physical and systemic examination. Both the breasts and axillas were examined carefully, to note the lump size, site, consistency, numbers, relation with skin and chest wall and fixity etc. Routine investigation included complete hemogram, urine analysis, BUN, and blood sugar estimation were done. A biopsy was performed in all cases, in the form of FNAC or incisional biopsy.

Metastatic workup included X-ray chest, LFTs, FNAC of suspected supraclavicular or cervical lymph nodes and an USG of abdomen and pelvis. Bone scan was only done where there was history of bone pain or any suspicious bony swelling. The histopathologies of all cases were reviewed by two pathologists separately. Histologic classification of breast cancer by Foote and Stewart was used. A diagrammatic representation of the tumor was drawn on the records for future comparison and follow-up.

**Staging**

All the patients were staged as per TNM classification. Loco-regionally carcinoma of breast marked as stage III breast cancer. Depending on T and N characteristic stage III is divided into IIIA and IIIB. Most of the stage IIIA tumors are operable and IIIB are inoperable (because of T4 lesions).

**Treatment protocol**

As per existing protocol of the study all patients of stage IIIA breast cancer were initially treated with surgery in

the form of modified radical mastectomy (MRM) except two patients in the study group due to large tumor with fixed axillary nodes offered neo-adjuvant chemotherapy as the initial treatment.

Following surgery these patients were treated with combination chemotherapy (CT) and radiotherapy (RT). Hormonal manipulation in the form of tablet tamoxifen was given to all post-menopausal patients.

All patients of stage IIIB were initially treated with neo-adjuvant (induction) chemotherapy (3 cycles), except 4 patients in the study group offered surgery as initial treatment because of small tumor size with limited peau orange change in the skin.

After this treatment all patients were reassessed with a thorough clinical examination and restaging work upto detect the response of the chemotherapy. All patients who achieved objective response (complete + partial) were offered surgery, followed by CT and RT.

Surgery in the form of modified radical mastectomy (MRM) was offered to most of the patients in this study group.

Three patients were offered conservative breast surgery in the form of quadrantectomy with axillary clearance. Those patients who were not responsive even after pre-operative CT and RT, were offered total mastectomy or total mastectomy to reduce the tumor bulk as much as possible to increase the quality of life of the patient.

In this study CAF regimen (cyclophosphamide, adriamycin and 5-fluorouracil) was used. Three cycles were given routinely. A dosage of 4500 to 5000 rad was administered by external beam radiation to chest wall, axilla of the affected side.

**Follow-up**

Patients were evaluated at 1 month and 3 months following completion of treatment to assess response.

**RESULTS**

Fifty patients with loco-regionally advanced breast cancer were included in the study.

**Table 1: Age group distribution of the study participants (n=50).**

Age group (years)	No. of the patients	Percentage
20-30	10	20
31-40	10	20
41-50	6	12
51-60	14	28
61-70	10	20

The age distribution of the patients showed maximum number of patients (28) in the age group of 51-60 years (Table 1). Average age of the patients was 52.93 years

(range 26-70 years). All 50 patients were presented with lump breast (100%) (Table 3).

**Table 2: Menopausal and parity characteristics of the patients (n=50).**

Menopausal status	Stage IIIA (%)	Stage IIIB (%)	Total (%)
Pre-menopausal	8 (16)	12 (24)	20 (40)
Post-menopausal	10 (20)	20 (40)	30 (60)
<b>Parity</b>			
≤3	12 (24)	17 (34)	29 (58)
>3	6 (12)	15 (30)	21 (42)

**Table 3: Frequency of signs and symptoms (n=50).**

Sign or Symptom	No. of the patients	Percentage
Lump breast	50	100
Pain in breast	20	40
Peu'd orange	6	12
Axillary lump	8	16
Skin ulceration	6	12
Nipple discharge	4	8
Swelling in arm	3	6

**Table 4: Site of tumor in the breast of the study participants (n=50).**

Site	No. of the patients	Percentage
Upper outer quadrant	22	44
Upper inner quadrant	4	8
Lower outer quadrant	10	20
<b>Lower inner quadrant</b>		
Central	4	8
> One quadrant	10	20

**Table 5: Correlation between patient's menopausal status versus growth rate of tumor, histological grade and axillary nodal status.**

Menopausal status	Growth rate		Histological grade			Axillary nodes	
	Fast	Slow	I	II	III	0-3	≥ 4
Premenopausal (n=20)	18	2	8	8	4	4	16
Postmenopausal (n=30)	14	16	4	12	14	18	12

**Table 6: Initial treatment offered for LABC patients.**

Treatment offered	No. of the patients stage IIIA	Stage IIIB	Total	Percentage
Neo-adjuvant chemotherapy	2	26	28	56
MRM	16	4	20	40
RT	-	2	2	4

Left breast involved in 36 cases (72%), whereas right breast involved in 14 cases (10%). Local examination of breast revealed that involved breast was slightly smaller in size than the normal breast in 60% of cases. In another 28% of the patients had bulkier breast. Size of the

primary tumor in the breast varied from 4 cm to a maximum of 12 cm. 92 % of the patients (46) had tumors more than 5 cms in their longest axis.

There was no patient with tumor measuring less than 2 cms in this study. About 60% of the patients were in

stage IIIB and 32% in stage IIIA. Majority of the tumors were in T4 category (64%). In 28% cases ipsilateral fixed lymph nodes were found. Histopathological examination revealed 76% (38) patients with infiltrating duct

carcinoma, 4 patients (8%) had comedo carcinoma, 2 patients (4%) had lobular carcinoma, 2 patients (4%) had medullary carcinoma and 4 patients (8%) had mucinous carcinoma.

**Table 7: Response to initial treatment in the study participants.**

Initial Treatment	CR (%)	PR (%)	NR (%)	DP (%)	Total
Neo—adjuvant chemotherapy	2 (7.1)	21 (75)	3 (10.7)	2 (7.1)	28
MRM	20	-	-	-	20
RT	-	10 (50)	-	1 (50)	2
Total	22	31	3	3	50

**Table 8: Stage wise clinical response status after induction chemotherapy (n=28).**

Response	Stage IIIA No. of the patients (%)	Stage IIIB No. of the patients (%)	Total (%)
CR	1 (50)	1 (3.8)	2 (7.1)
PR	1 (50)	20 (76.9)	21 (75)
NR	-	3 (11.5)	3 (10.7)
DP	-	2 (7.6)	2 (7.1)
Total	2	26	28

**Table 9: Correlation of pre-operative clinical and post-operative pathological nodal status after induction chemotherapy.**

Clinical nodal status	No. of the patients	No. of patients in subgroup of pathologic nodal status			
		Nil	1-3	4-7	>7
N0	6	3	2	1	-
N1	14	1	9	3	1
N2	8	-	4	1	3
Total	28	4	15	5	4

The histopathology of ipsilateral lymph nodes available in 48 patients, who had undergone surgery as part of the treatment protocol. Of them 4 had no nodal disease, 21

had ≤ 3 lymph nodes, 12 had 4-7 lymph nodes and 11 had more than 7 lymph nodes. Disease free survival found as high as 80% for node negative patients but low (30%) in more than 7 lymph nodes positive patients.

**Table 10: Loco-regional therapy utilized.**

Local therapy	Stage IIIA		Stage IIIB		Total		Local recurrence	
	No	%	No	%	No	%	No	%
Surgery + RT	17	94.4	28	87.5	45	90	7	15.5
RT only	-	-	2	6.2	2	4	2	100
Surgery only	1	5.5	2	6.2	3	6	2	66.6
Total	18		32		50		11	

It is seen that near about 50% of the patients with 4 or more lymph nodes positive had tumors in outer quadrant, upper, more than lower. All patients with >4 lymph nodes positive had tumor more than 5 cm in the greatest diameter. Amongst the tumors extending into more than

one quadrant of the breast, 80% of them had more than 4 lymph nodes positive.

Comparison of histologically involved nodes and stage revealed that 47% of stage III patients had ≥4 lymph

nodes positive. A correlation of patient's menopausal status with rate of growth of tumor, its histological grade and axillary lymph node status revealed that pre-

menopausal patients have faster growing tumors which were histologically poorly differentiated and associated with 4 or more axillary lymph nodes (Table 5).

**Table 11: Post-treatment overall outcome of LABC patients in the study group (n=50).**

Treatment received	No. of patients Stage IIIA	Stage IIIB	Total	Recurrence (%)	DFS (Months)
Anterior CT > S> CT+RT	1	19	20	5 (25)	20.8
S> CT+RT	15	2	17	3 (17.6)	24.1
CT+RT > S> CT	-	5	5	4 (80)	18.2
Anterior CT > S (conservative)> CT+RT	1	2	3	1 (33.3)	30.2
RT	-	2	2	2 (100)	-
S	1	2	3	2 (66.6)	11.5
Total	18	32	50	17	

**Table 12: Post treatment recurrence of disease.**

Stage	No. of patients	Recurrence	Local	Distant	Both	Total (%)	DFS (months)
IIIA	18	-	3	1	1	5 (27.7)	23.8
IIIB	32		4	5	3	12 (37.5)	22
Total	50		7	6	4	17 (34)	

**Table 13: Results according to the stage of the patients (n=50).**

Stage	No. of patients	Local control	Survival	Disease free survival
IIIA	18	83.3%	88.8%	72.2%
IIIB	32	78.1%	87.5%	68.7%

Both nonresponsive (NR) and disease progression (DP) patients were in stage III B group. About 76.9% patients of stage IIIB (20) achieved partial response (Table 8).

Only 1 patient (33.3%) developed local recurrence after 10 months of completion of treatment. Median disease free survival (DFS) period of this group is 30.2 months (Table 11). Recurrence rate is stage IIIA patients was

27.7% and in stage IIIB 37.5% (Table 12). Maximum numbers of disease free patients were found in T3N1 group (85.7%).

Patient with N2 and T4 disease chances of recurrence was more than N1 and T3 lesions. Stage IIIA patients achieved 83.3% local control, whereas stage IIIB achieved 78.1%. Survival rate and disease free rate was almost equal on both group (Table 13).

**Table 14: Overall outcome (n=50).**

Outcome	Stage IIIA (%)	Stage IIIB (%)	Total (%)
No evidence of disease	13 (26)	20 (40)	33 (66)
Alive with disease	3 (6)	8 (16)	11 (22)
Dead	-	1 (2)	1 (2)
Lost to follow-up [after 21 months (mean) of follow-up]	2 (4)	3 (6)	5 (10)

**DISCUSSION**

Locally advanced breast cancer includes large operable tumors or those tumors considered inoperable but without

distant metastases.<sup>15</sup> With mastectomy alone, the reported local recurrence rate ranged from 6% to 40% and with irradiation alone, from 25-50%, even after doses of 8000 rads. Survival with either modality was 40-50% at 5 years

and 30% at 10 years.<sup>15</sup> Due to large size of the tumor and micro-metastases in loco-regional area radiotherapy or surgery alone were not able to achieve good loco-regional control. So, radiotherapy and surgery were combined to achieve better control. Pre-operative radiation therapy followed by surgery results in local control rates ranging from 11-45% and surgery followed by radiation therapy results in local control of 70-86% of tumors and 5 year survival rates of 30 -45%.<sup>14</sup> Local control of disease was better after combining surgery with RT but survival rates were not much different and the development of

subsequent distant metastases was reported in 65-89% cases.

To reduce distant recurrence of disease, adjuvant chemotherapy was started along with surgery and RT. Five year's survival rates become 40-87% and 5 years relapse free survival became as high as 67% in those patients who responded to chemotherapy. Studies showed that overall survival of LABC patients was not much improved with adjuvant chemotherapy but disease free period increased considerably.

**Table 15: Complications following treatment.**

Complications	No. of patients		
	Stage IIIA	Stage IIIB	Total (%)
<b>Surgery induced (n=48)</b>			
Wound infection	2	1	3 (6.2)
Flap necrosis	1	3	4 (8.3)
Primary closure not possible	-	3	3 (6.2)
Fluids collection under the flaps	8	6	14 (29.1)
Arm oedema	2	4	6 (12.5)
<b>RT induced (n=47)</b>			
Skin desquamation	3	5	8 (17.0)
Erythema & induration	4	4	8 (17.0)
Lung fibrosis	-	1	1 (2.1)
<b>Chemotherapy induced (n=45)</b>			
Leucopenia	3	2	5 (11.1)
Thrombocytopenia	2	2	4 (8.8)
Alopecia	15	30	45 (100)
Vomiting	7	5	12 (26.6)

The problem in loco-regionally advanced breast cancer is the large tumor size with skin involvement, so majority of stage IIIB breast cancers are not operable. Preoperative RT can reduce the tumor size (75% cases in T3 lesion but only 25% cases in T4 lesions) but there was delayed post-operative wound healing and increased flap necrosis seen in these cases. Reddy and Reddy in their study of Indian women reported the average age of 45.1 years in Madras, which is close to the present study (52.1 years).<sup>16</sup> Most of the breast malignancies are adenocarcinomas, which constitute more than 95% of breast cancers.<sup>17</sup> Invasive ductal carcinoma (IDC) is the most common form of invasive breast cancer.

It accounts for 55% of breast cancer incidence upon diagnosis.<sup>18</sup> Breast carcinomas arise from the same segment of the terminal duct lobular unit (TDLU). The typing of invasive breast carcinoma and its histological variants is well established.<sup>19</sup>

JC Gupta and others found that incidence of cancer breast in Indian population is comparable in nulliparous and multiparous women upto 9 issues. The incidence is however, less in women having 6 issues suggesting that

really very high multiparity can be protective.<sup>20,21</sup> Ing et al. observed that in women who nurse their infants with only one breast, 90% carcinomas occurred in the unsuckled breast.<sup>22</sup> In the present study 40% of the patients' breast fed their children for 71-105 months. Only 12% breast fed their children for less than 35 months. In the present study, it was not possible to draw any definite correlation between parity, breast feeding, and age of first child birth with an incidence of breast cancer.

In the present study all 50 cases presented with lump breast, 40% of the cases were associated with pain in the breast, 12% cases were associated with ulceration or fungation. Nipple discharge and nipple retraction was found in 8% and 22% cases respectively.

In the present study, the size of the tumor included T2- 4%, T3- 32% and T4- 64%, majority of the patients in this study group had T4 lesion. Tumor size more than 10 cm was found in 16% cases and in 76% cases tumor size was 5-10 cm. P Jain and Khanna in their study found 50% cases with T2 lesion, 33% having T3 lesion and 10% with T4 and 7% with T1 tumors.<sup>23</sup> In the present

study only stage III patients were included, so incidence of T3 and T4 lesions were higher than the above study, where all stages of patients were studied. Due to delayed presentation majority of the patients had large tumor with skin or chest wall involvement. This also proves that ignorance, lack of medical knowledge, negligence and painless nature of the tumor leads to delayed presentation with advanced disease.

In this study, 68% cases had ipsilateral mobile nodes, 28% had ipsilateral fixed nodes and 4% cases were free of axillary nodes clinically. A positive correlation was found between size of lump and number of the histologically involved lymph nodes in the axilla. About 85% of the tumors measuring more than 10 cm had more than 4 axillary lymph node metastases.

It suggests that regional lymph nodes have a role in initiation and maintenance of anti-tumor immunity.<sup>24</sup> Prognosis is dependent upon the number of lymph nodes and their level in the axilla.<sup>25</sup> The size of the metastatic deposit within the node (less than 0.2 cm versus more than 0.2 cm) and extension of the metastatic disease across the lymph node capsule affects the treatment failure rate.<sup>25</sup>

The histological type of the tumor also affects the prognosis. The infiltrating duct carcinoma has a bad prognosis, whereas medullary, mucinous and other types are prognostically better when present in pure state. Premenopausal status, lymphatic invasion, blood vessel invasion, presence of mixed mucinous carcinoma and poor histological grade were other adverse prognostic factors.<sup>26</sup>

In the present study 76% of the tumors were of infiltrating duct carcinoma, mucinous and medullary carcinoma were seen in 8% and 4% cases respectively. In a similar study JC Gupta et al found infiltrating scirrhous carcinoma in 91.5% cases, probably showing that this is the commonest histological form of carcinoma.<sup>20</sup>

There is direct relationship between the degree of histological differentiation and survival. In the present study 40% patients were grade II (moderately differentiated) and 36% patients were poorly differentiated (Grade III).

In Ludwig trials, it was found that 5 year disease free survival rate was 86% for grade I tumors versus 57% for grade III tumor and hence tumor grade was a statistically significant factor for predicting disease free survival.<sup>27</sup> In the present study showed that 48% of the patients had 4 or more positive axillary lymph nodes and 43% had 3 or less positive axillary lymph nodes. Disease free survivals in 3 or less lymph were positive group was 71%, whereas it was 40%  $\geq$  4 lymph node positive group.

Haagensen and Donegan and Fisher et al in their study found that larger tumor size correlated with higher

incidence of axillary lymph nodal metastases, a higher incidence of four or more positive nodes and a higher tumor recurrence rate.<sup>25,28</sup> The present study findings have also supported the above result. Surgery is the mainstay of treatment for a long time. Haagensen and Stout in their study of 35 cases of locally advanced carcinoma treated with radical mastectomy found 0%, 5 year cure rate and greater than 50% incidence of local recurrence.<sup>29</sup>

Arnold and Lesnick reported that 5 year survival rate for patients with T3N0 disease was 77%, whereas T4N0 was 65% and local recurrence rate was 27%.<sup>30</sup> Study conducted by Fracchia et al found local recurrence rate in patients with positive nodes after surgery alone was 25%.<sup>31</sup>

In the present study, 3 patients were treated with only surgery, without post-operative RT or CT (as they refused CT and RT). Disease recurrence found in 66.6% cases with median disease free survival of 11.5 months. Out of 2 patients, 2 were stage IIIB and one was stage IIIA.

Due to poor results of locally advanced breast cancer with surgery alone, investigators started treating the patients of LABC with local radiotherapy. Ruben et al of Guy's hospital in London, treated inoperable stage III breast cancer patients with radiation therapy alone, and found high local recurrence rate (72%).<sup>32</sup> Rao et al study with radiation alone showed disease recurrence rate of 51%.<sup>33</sup> The outcome of these patients was more favorable because one third of his patients had tumor without skin or chest wall involvement.

In the present study 2 patients of stage IIIB breast cancer were treated with local radiotherapy (as they refused surgery and CT), but local recurrence rate was found 100%. This result is not comparable with others because only two patients in this study were treated with radiotherapy, the tumor size was more than 10 cm with skin and chest wall involvement.

Patients performance status was poor, so high dose radiotherapy was not given. Brown et al in their study treated LABC patients with surgery and post-operative radiotherapy and found local recurrence rate of 14% and 5 years survival rate of 45.5%.<sup>34</sup>

In the present study 45 patients were treated with surgery and radiotherapy as local treatment and found local recurrence rate of 15.5%. This result is almost similar to the results of Brown et al and relapse free rate is much better than the study of Fracchia et al.<sup>31</sup>

But in the present study chemotherapy was added with surgery and RT, but in other two studies, the patients were treated only by surgery and post-operative RT, CT was not added. Probably this is the cause of local recurrence rate of present study.

Primary tumor showed 50% to 75% objective response in 65% of cases after 2 cycles of CAF regimen. Similar study by Rubens and associates found neo-adjuvant CT with AV (Adriamycin and vincristine) for 4 cycles produced objective responses of 83% cases.<sup>35</sup> Buzdar et al of MD Anderson Cancer Centre used 3 courses of neo-adjuvant CT (CAF) in 174 stage III patients and found objective response of 88%.<sup>36</sup> The present study showed after 3 cycles of induction CT (CAF) on 28 patients, 82.1% patients showed objective response to therapy. Complete response was found in 7.1% cases.

In the present study the response of neoadjuvant ct is comparable with other studies e.g studies by Schwatz et al or Buzdar et al where objective response (CR + PR) was 85-88%, though the number of patients in the present study were small, still the response of primary tumors to neo-adjuvant CT is amazing and encourageable.<sup>36,37</sup> Numerous studies have been carried out to test the efficacy of multimodality approach using CT, surgery and RT for stage III disease.

Hartobagyi et al treated 174 patients of LABC with neo-adjuvant CT followed by surgery and post-operative CT and RT, achieved 95% local control and median disease free interval DFS was 30 months. Bristol IJ et al treated patients of LABC by combination CT and RT and found disease free survival of 26 months.

In the present study patients with CT followed by surgery and post-operative RT and CT, the disease recurrence was found in 25% of cases and median disease free survival was 20.8 months, whereas patients in the first group had stage IIIB disease (19 out of 20), where as in second group most of the patients had stage IIIA disease (15 out of 17).<sup>38,39</sup>

That is why, disease control was better in second group. The post treatment disease recurrence in the study group was 34% and average disease free survival was 18.4 months. The present study's recurrence rate of the disease is higher than the other studies, because most of the patients (64%) in this study group had stage IIIB disease and 51 patients were not treated as per the standing protocol of this study.

Those 45 patients who were treated the standing protocol of this study had only recurrence rate of 21%, which is comparable with other studies. But the present study's overall DFS is near to other studies, though the number of patients and follow up period is very short in this present study.

In the present study all post-menopausal patients irrespective of ER status received tamoxifen and premenopausal patients with low grade tumors (histopathologically) also received tamoxifen. Total of 38 patients got tamoxifen in addition to combination CT as systemic therapy. About 26.3% developed distant

metastasis in their follow up period and median disease free period was 12.5 months.

## CONCLUSION

Major conclusions from our study are as follows: Locally advanced breast cancer is the commonest form among the patients who present with breast cancer for the treatment in Indian setting; Majority of the patients of LABC are in post-menopausal age group; Upper outer quadrant of the breast is the commonest site for development of primary carcinoma of breast; Infiltrating duct carcinoma is the commonest histopathological type found in breast carcinoma patients; Larger the size of tumor, more is the chance of axillary lymph nodes involvement and more the number of axillary nodes involvement, more is the chance of disease recurrence; Neo-adjuvant chemotherapy can make inoperable locally advanced breast cancer operable and with the use of neo-adjuvant CT, breast conservation surgery is possible even in locally advanced breast cancer.

Use of post-operative CT and RT can increase the disease free survival period; Use of multimodal treatment in the form of CT, surgery and radiotherapy can increase the disease free survival period in locally advanced breast cancer; Stage IIIB breast cancer patients has got more chance of local recurrence than stage IIIA patients, but overall survival period is almost same in both the groups; In conclusion of the present study it is obvious that the multimodality approach using judicious combination of surgery with chemotherapy and radiotherapy, is necessary to get good results in locally advanced breast cancer.

Since the numbers of patients are small and follow-up period is short, it is not possible to come to a definite conclusion from the present study. Further randomized control trials are required to establish the role of present study protocol on survival of the LABC patients.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

## REFERENCES

1. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, Van de Vijver MJ, editors. WHO Classification of Tumours of the Breast. Fourth ed. IARC; Lyon. 2012;4. ISBN.13.
2. Peter B, Bernard L. World Cancer Report. International Agency for Research on Cancer; WHO Press; Lyon, France. 2008.
3. Coughlin SS, Ekwueme DU. Breast cancer as a global health concern. *Cancer Epidemiol.* 2009;33:315-8.

4. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin.* 2014;64(1):52-62.
5. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on day/month/year.
6. American Cancer Society. Global cancer facts and figures, 2<sup>nd</sup> edn. American Cancer Society, Atlanta. 2011.
7. Tao Z, Shi A, Lu C, Song T, Zhang Z, Zhao J. Breast Cancer: Epidemiology and Etiology. *Cell Biochem Biophys.* 2015;72(2):333-8.
8. Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer.* 2013;132(5):1133-45.
9. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136(5):E359-86.
10. Gupta S, Rao YN, Agarwal SP. Emerging strategies for cancer control for women in India. 50 Years of Cancer control in India. 2003. [Last accessed on 2016 Jun 30]. Available from <http://www.medindia.net/education/MinistryofHealth/pg192to203.pdf>.
11. Rao YN, Gupta S, Agarwal SP. National cancer control programme: Current status and strategies, 50 Years of cancer control in India; 2003. [Last accessed on 2016 Jul 14]. Available from <http://www.medindia.net/education/MinistryofHealth/pg192to203.pdf>.
12. Kamath R, Mahajan KS, Ashok L, Sanal TS. A Study on Risk Factors of Breast Cancer among Patients Attending the Tertiary Care Hospital, in Udupi District. *Ind J Com Med.* 2013;38(2):95-9.
13. Christiaens MR, Cataliotti L, Fentiman I. Comparison of the surgical procedures for breast conserving treatment of early breast cancer in seven EORTC centres. *Eur J Cancer.* 1996;32A:1866-75.
14. Hunt KK, Ames FC, Singletary SE, Buzdar AU, Hortobagyi GN. Locally advanced non-inflammatory breast cancer. *Surg Clin North Am.* 1996;76(2):393-410.
15. Swain SM, Sorace RA, Bagley CS, Danforth DN Jr, Bader J, Wesley MN, et al. Neo-adjuvant chemotherapy in the combined modality approach of locally advanced non-metastatic breast cancer. *Cancer Res.* 1987;47(14):3889-94.
16. Reddy RS, Reddy CR. Carcinoma of the breast: Its incidence and histological variants among South Indians. *Ind J Med Sc.* 1958;12:228.
17. Vinay K, Abul KA, Jon CA, Nelson F. Robbins and Cotran Pathologic Basis of Disease. Eight ed. Elsevier; Lyon. France. 2010.
18. Ehemann CR, Shaw KM, Ryerson AB, Miller JW, Ajani UA, White MC. The changing incidence of in situ and invasive ductal and lobular breast carcinomas. *Cancer Epidemiol Biomarkers Prev.* 2009;18(6):1763-9.
19. Makki J. Diversity of Breast Carcinoma: Histological Subtypes and Clinical Relevance. *Clin Med Insights Pathol.* 2015;8:23-31.
20. Gupta JC. Breast lumps in Jabalpur area. *Ind J Surg.* 1983;268-73.
21. Pandya B, Wahane SM, Narang R. Clinical Profile of Fibroadenoma in Rural Vidharbha: A Geographical Entity in Central India. *Inter J Rece Scient Res.* 2015;6(7):5117-20.
22. Ing R, Yio JH, Petrakis NL. Unilateral breast feeding and breast cancer. *Lancet.* 1972;2:124-7.
23. Jain P, Khanna S, Khanna NN. Clinicopathological correlation in carcinoma breast. *Ind J Surg.* 1989;25.
24. Crile G (Jr). Breast cancer- A personal perspective. *Surg Clin North Am.* 1984;64:1145-9.
25. Flisher B, Slack NH. Number of lymph nodes examined and prognosis of breast carcinoma. *Surg Gynaecol Obstet.* 1970;131:79-88.
26. Devita TV (Jr), Hellman, Rosenberg A. *Cancer Principles and Practice of Oncology*, 5<sup>th</sup> Ed. Lippincott-Raven. 1997;75(5):771-5.
27. Gelber RD. Ludwig Breast Cancer trial LBCS III: chemo- and endocrine adjuvant treatment in postmenopausal patients. *Recent Results Cancer Res.* 1984;96:102-9.
28. Haagensen CD. *Diseases of the breast.* Philadelphia; WB Saunders. 1971;622-30.
29. Haagensen C, Stout A. Carcinoma of the breast II: Criteria of operability. *Ann Surg.* 1943;118(6):1032-51.
30. Arnold D, Lesnick G. Survival following mastectomy for stage III breast cancer. *Am J Surg.* 1979;137(3):362-6.
31. Fracchia AA, Evans JF, Eisenberg BL. Stage III carcinoma of the breast. A detailed analysis. *Ann Surg.* 1980;192(6):705-10.
32. Rubens RD, Armitage P, Winter PJ, Tong D, Hayward JL. Prognosis in inoperable stage III carcinoma of the breast. *Eur J Cancer.* 1977;13(8):805-11.
33. Rao DV, Bedwinek J, Perez C, Lee J, Fineberg B. Prognostic indicators in stage III and localized stage IV breast cancer. *Cancer.* 1982;50(10):2037-43.
34. Lippman EM, Lichter SA, Danforth ND. *Diagnosis and management of breast cancer.* London, Philadelphia: WB Saunder Co. 1988;272-92.
35. Rubens RD, Sexton S, Tong D, Winter PJ, Knight RK, Hayward JL. Combined chemotherapy and radiotherapy for locally advanced breast cancer. *Eur J Cancer.* 1980;16(3):351-6.
36. Buzdar AU, Singletary SE, Booser DJ, Frye DK, Wasaff B, Hortobagyi GN. Combined modality treatment of stage III and inflammatory breast cancer. M.D. Anderson Cancer Center experience. *Surg Oncol Clin N Am.* 1995;4(4):715-34.

37. Schwartz GF, Birchansky CA, Komarnicky LT, Mansfield CM, Cantor RI, Biermann WA, et al. Induction chemotherapy followed by breast conservation for locally advanced carcinoma of the breast. *Cancer.* 1994;73(2):362-9.
38. Hortobagyi GN, Blumenschein GR, Spanos W, Montague ED, Buzdar AU, Yap HY, et al. Multimodal treatment of locoregionally advanced breast cancer. *Cancer.* 1983;51(5):763-8.
39. Bristol IJ, Woodward WA, Strom EA, Cristofanilli M, Domain D, Singletary SE, et al. Locoregional treatment outcomes after multimodality management of inflammatory breast cancer. *Int J Radiat Oncol Biol Phys.* 2008;72(2):474-84.

**Cite this article as:** Panda A, Das SK, Gupta TR, Kesari GS, Sen S. Loco-regionally advanced breast cancer: evaluation of management of breast cancer with special reference to multimodal approach. *Int J Res Med Sci* 2016;4:4767-77.