

**EFFECT OF NEOADJUVANT CHEMOTHERAPY ON AXILLARY LYMPH NODE STATUS IN LOCALLY ADVANCED BREAST CARCINOMA IN KUMAUN REGION OF UTTARAKHAND, INDIA**Rajeev Kumar Singh<sup>1</sup>, Vartika Tiwari<sup>1</sup><sup>1</sup>Department of General Surgery, Government Medical College, Haldwani, Uttarakhand, IndiaReceived : 14/05/2023  
Received in revised form : 24/06/2023  
Accepted : 05/07/2023**Keywords:**Locally advanced breast cancer,  
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DOI: 10.47009/jamp.2023.5.4.190

Source of Support: Nil,  
Conflict of Interest: None declared*Int J Acad Med Pharm*  
2023; 5 (4); 939-947**Abstract****Background:** Neoadjuvant chemotherapy has dramatically changed the management of locally advanced breast cancer. However the effect of NACT on lymph node status has been studied in very few trials in our region. **Materials and Methods:** We included 28 patients diagnosed with locally advanced breast carcinoma in Department of General Surgery, Government Medical College, Haldwani in the study who were given neoadjuvant chemotherapy. Clinical response of axillary lymph nodes to the chemotherapy was observed. **Result:** Most of the patients who presented to the surgery OPD were of 45-55 years of age with peak presentation in age of 48-50 years and 54-56 years of age. Lymph node clearance was observed in 42% of the patients given neoadjuvant chemotherapy. **Conclusion:** Neoadjuvant Chemotherapy is a reasonable alternative to upfront surgery in management of LABC.**INTRODUCTION**

Breast cancer is a major public health problem worldwide, with its incidence increasing not only in developed nations but also the less developed ones. According to GLOBOCAN 2018 estimates breast carcinoma is the second most commonly diagnosed cancer for both sexes combined and leading cause of mortality due to carcinoma among females.<sup>[1]</sup> The earliest known document to refer to breast carcinoma was the Smith Surgical Papyrus (3000-2500BC). It was Le Dran, who stated that breast carcinoma was a local disease that spread by the way of lymph vessels to axillary lymph nodes and routinely removed any enlarged axillary lymph nodes. In 1877, Banks and Moore advocated the resection of axillary lymph nodes even when palpable lymphadenopathy wasn't evident. In 1894, Halsted and Meyer reported completed dissection of axillary lymph node levels I to III which was later replaced by Pateys method of modified radical mastectomy. Patey and Dyson in 1948 stated that removal of pectoralis minor muscle allowed access to and clearance of axillary lymph nodes without removal of pectoralis muscle.<sup>[2-10]</sup> Breast carcinogenesis involves Tumour suppressor gene inactivation through promoter methylation as the earliest events in breast carcinogenesis,<sup>[11-15]</sup> which provides a background for accumulation of more genetic events. The resulting disruption of cell cycle control mechanisms and/or apoptosis-signaling pathways leads to disturbance of the balance between proliferation and apoptosis,<sup>[16-20]</sup> in turn leading to the growth of early lesions, which are usually polyclonal.

Activating mutations in and amplifications of (proto)oncogenes, also chromosomal imbalances, and inactivating mutations in tumour suppressor genes (such as p53), usually occur later, eventually resulting in selective outgrowth of clones with the highest proliferation/apoptosis imbalance. Increased proliferation will cause cells that are too far away from the nearest blood vessels to sustain oxygen and nutrient supply levels, resulting in hypoxia. This sets off a cellular survival program to cope with the hypoxic stress, inducing growth factor mediated angiogenesis and switch to anaerobic metabolism. In the latest pre-invasive stages, invasion related genes become activated, allowing cells to break down the basement membrane and extracellular matrix to invade the surrounding stroma. This provides access to lymph and blood vessels allowing cells to enter the lymphatics to pass on to lymph nodes to form locoregional metastases, as well as the bloodstream to form distant metastasis around the malignant ducts.<sup>[21-30]</sup>

Various imaging modalities like sonomammogram, mammography, MRI and FNAC and Tru-cut biopsy often provide a useful aid in diagnosing Breast carcinoma and its staging. Once the diagnosis of breast carcinoma is made the type of therapy offered to a breast cancer patient is then determined by the stage of disease, the biologic subtype and the general health status of the patient.<sup>[2]</sup> Breast cancer is categorised into operable and advanced breast cancer for the management purpose. Advanced breast cancer is either locally advanced or metastatic disease. Recent guidelines from the U.S. National

Comprehensive Cancer Network describe LABC as AJCC stage III breast cancer; the definition includes breast cancer that fulfils any of the following criteria in the absence of distant metastasis.<sup>[31-33]</sup>

- Tumours more than 5 cm in size with regional lymphadenopathy (N1–3)
- Tumours 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 tumour stage

Locally advanced breast cancer is further divided into “operable” or “inoperable” based on the probability of achieving negative margins on histopathologic examination after an initial surgical approach that would provide long-term reduction in locoregional recurrence. Although the sequence of chemotherapy to surgery (pre vs. post) does not change overall survival,<sup>[35]</sup> neoadjuvant chemotherapy is warranted in inoperable LABC to improve the chances of R0 resection. LABC accounts for 10-20% in the West, while in India, it accounts for 30-35% of all cases and poses a significant therapeutic challenge.<sup>[34]</sup> The treatment of LABC has evolved from a single modality treatment, consisting of radical mutilating surgery or higher doses of radiotherapy in inoperable disease to multimodality management.<sup>[4,5]</sup> The introduction of neoadjuvant chemotherapy (NACT) in LABC offered us advantages like initiation of early systemic therapy, delivery of drugs through intact vasculature, down-staging of tumours, which makes inoperable tumours operable and renders tumours suitable for breast conserving surgery (BCS).<sup>[5,6]</sup> National Surgical Adjuvant Breast and Bowel Project (NSABP)-18 and Milan trials have shown that there have been no difference in disease free survival (DFS) and overall survival between the patients who had received NACT in comparison to the patients who had received postoperative adjuvant chemotherapy.<sup>[5]</sup> By downstaging of the tumour, chemotherapy can convert patients who are candidates for mastectomy to breast-conserving surgery candidates. Furthermore, it has potential to reduce excision volumes in patients with large cancer who are already candidates for breast conserving surgery thus improving cosmetic outcomes.<sup>[36]</sup> Another surgical advantage is downstaging of the axilla so that lymph node dissection can be avoided in selected patients reducing surgical morbidity. This has led NACT to gain a major foothold in the management of LABC. The use of Neoadjuvant chemotherapy in LABC dates back to 1973, when a regimen containing doxorubicin resulted in prompt tumour shrinkage and thereby facilitating subsequent radiation therapy or mastectomy. The use of NACT in LABC was based on the rationale that such patients present with a relatively high burden of micro-

metastasis and therefore initiating systemic therapy upfront at the earliest.<sup>[7]</sup> Factors that favour neoadjuvant therapy in patients with operable breast cancer include: lymph node-positive disease; high tumour volume-to-breast ratio; specific biological features of primary cancer (high grade, hormone receptor-negative, HER2-positive, triple negative cancer); younger age.<sup>[6]</sup> Anthracycline/ taxane-based chemotherapy regimens have been studied extensively in various prospective randomized trials and are frequently prescribed treatments in patients with operable breast cancer.<sup>[8,9]</sup> Regimens that have been tested in large multicenter phase III trials and yielded pCR rates of at least 15% and up to 20% are AC followed by docetaxel; docetaxel/ doxorubicin/ cyclophosphamide; epirubicin/ paclitaxel- cyclophosphamide/ methotrexate/ fluorouracil; and a dose-dense sequence of epirubicin and paclitaxel. Administration strategies includes the sequential, concurrent, and both sequential and concurrent delivery of agents and the dose-dense approaches.<sup>[10,11]</sup>

Neoadjuvant chemotherapy does, however, have potential disadvantages, including loss of pretherapy pathologic staging (tumor size and lymph node status). This raises the potential for both over- and undertreatment with chemotherapy and radiation therapy. Furthermore, neoadjuvant chemotherapy does lead to a delay in local and regional therapy and is associated with a small risk of tumor progression. Breast Carcinoma Staging system as per AJCC cancer Staging manual, Eighth Edition was followed. For all sites clinical staging (c) is determined using information identified prior to surgery or neoadjuvant therapy. There are three stage groups as per the guidelines anatomic stage which is based solely on anatomic extent of cancer as defined by the T, N, and M categories.<sup>[23]</sup>

Fischer et al. (1997) conducted a randomized double-blind trial to assess if preoperative doxorubicin (Adriamycin) and cyclophosphamide (Cytosan; AC) therapy yields a better outcome than postoperative AC therapy. They concluded that Preoperative chemotherapy is as effective as postoperative chemotherapy, permits more lumpectomies, is appropriate for the treatment of certain patients with stages I and II disease, and can be used to study breast cancer biology.<sup>[12]</sup> Wolmark et al. (2002) conducted a National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18 was initiated in 1988 to determine whether four cycles of doxorubicin/cyclophosphamide given preoperatively improve survival and disease-free survival (DFS) when compared with the same chemotherapy given postoperatively. After a nine follow-up they concluded that patients assigned to preoperative chemotherapy received notably more lumpectomies than postoperative patients, especially in tumours with greater than 5cm at study entry.<sup>[13]</sup> SibylleLoibl et al. (2006) analysed the surgical data of a representative data subset of 607 patients enrolled in the German Preoperative Adriamycin Docetaxel

[GEPARDUO] study. The prospective, multicentre, phase III study randomly assigned patients with operable breast cancer ( $\geq$  or = 2 cm) to neoadjuvant 8-week dose-dense doxorubicin plus docetaxel or a 24-week schedule of doxorubicin plus cyclophosphamide followed by docetaxel (AC-DOC). Breast conservation was attempted in 493 (81.2%) patients, but 43 patients eventually required mastectomy, thus resulting in a breast-conserving surgery rate of 74.1%. Breast-conserving re-excision was performed in 61 patients (12.4%). Factors associated with a significantly higher breast-conserving surgery rate were a prechemotherapy tumour size  $\leq$  40 mm, non-lobular histological characteristics, treatment with AC-DOC, clinical response, post chemotherapy tumour size  $\leq$  20 mm, and treatment in a larger centre ( $>$ 10 enrolled patients). They concluded that Breast conservation after neoadjuvant chemotherapy is feasible in most patients with operable breast cancer.<sup>[14]</sup> Beriwal et al. (2006) undertook a prospective study to determine patterns of ipsilateral breast tumour recurrence (IBTR) and local-regional recurrence (LRR) after neoadjuvant chemotherapy and breast-conserving therapy (BCT). A total of 153 breast cancer patients were treated with neoadjuvant chemotherapy followed by conservative surgery and radiation therapy between 1980 and 2002. They concluded that BCT results in a low rate of IBTR and LRR in appropriately selected patients. Advanced stage at presentation is associated with increased risk of IBTR, although overall recurrence is low.<sup>[15]</sup> Rastogi et al. (2008) conducted NSABP B-29 to determine whether four cycles of doxorubicin and cyclophosphamide administered preoperatively improved cancer DFS and Overall survival (OS) compared with AC administered postoperatively.<sup>[38]</sup> van Nes et al. (2009) conducted Preoperative Chemotherapy in Primary Operable Breast Cancer (POCOB) study to compare preoperative with postoperative chemotherapy in patients with early breast cancer concerning breast conserving therapy (BCT) procedures, disease free survival (DFS) and overall survival (OS).<sup>[16]</sup> Min et al. (2010) conducted a prospective study to analyse clinical outcomes in patients who exhibited local-regional recurrence (LRR) and ipsilateral breast tumour recurrence (IBTR) after being treated by BCS and RT following NCT. In total, 251 breast cancer patients treated with Breast Conservative Surgery (BCS) and radiotherapy (RT) following Neoadjuvant Chemotherapy (NCT) between 2001 and 2006 were included. They concluded that In patients with locally advanced disease, who were clinically node-positive at presentation, BCS after NCT resulted in acceptably low rates of IBTR and LRR. Mastectomy should be considered as an option in patients who present with clinical stage III tumours or who are not treated with adjuvant hormone suppression therapy, because they exhibit high IBTR rates after NCT and BCS.<sup>[17]</sup> Pinto et al. (2011) studied 94 patients of locally advanced breast carcinoma, out of which 60 patients were

hormone receptor positive and 34 were hormone receptor negative. They observed strong correlation between an increased probability of achieving pCR and negative expression of hormone receptors and HER2neu over expression.<sup>[18]</sup> Prabhudesai et al. (2011) analysed 98 breast cancer patients with LABC and pathological response determined using NSABP grading in both breast tissues and axillary lymph nodes. They observed that likelihood ratio of pCR and lymph node negativity was significant in subjects receiving more than three cycles of chemotherapy and Log rank Mantel Cox test showed significant pCR with equality of response distributions for different levels of tumor size.<sup>[19]</sup> Shin et al. (2013) conducted a retrospective study to evaluate the local recurrence (LR) rate depending on the use of neoadjuvant chemotherapy (NCT) and to determine the oncologic safety of breast-conserving surgery (BCS) after NCT by comparing LR between patients treated with BCS and mastectomy in clinical stage III breast cancer patients.<sup>[18]</sup> Cho et al. (2013) conducted a comparative study to investigate oncologic outcomes of breast-conserving surgery (BCS) in patients receiving neoadjuvant chemotherapy (NCT) to treat locally advanced breast cancer (LABC). They concluded that BCS after NCT is a safe option for LABC that responded well to NCT. Shrinking tumours with NCT allows more opportunities to apply BCS without compromising outcomes.<sup>[19]</sup> Barranger et al. (2015) conducted a prospective non-randomized study (2007-2012) to analyze 168 patients who received neoadjuvant chemotherapy (NCT).<sup>[20]</sup> Karanlik et al. (2015) conducted a retrospective study to compare the clinical outcome in T2 breast cancer patients who underwent preoperative chemotherapy (PC) and who did not. The study showed that PC significantly decreases the re-excision in patients undergoing BCS with primary T2 breast tumours. The data suggested that any patient with a tumour greater than 2 cm might be considered for PC to increase BCS success with final negative margins.<sup>[21]</sup> Arlow et al. (2018) studied 1,468 New Jersey State Cancer Registry (NJSCR) patients with a primary breast cancer diagnosed between 1998 and 2003 who underwent neoadjuvant chemotherapy. He concluded that patients undergoing breast-conservation after neoadjuvant therapy appeared to have better survival than patients undergoing mastectomy without radiation.<sup>[37]</sup> Choudhary et al. (2020) studied 1500 cases of breast cancer out of which 600 were LABC, 425 patients were started on NACT and observed that pCR was achieved in 59 cases, 17% in hormone positive cases, 25% in HER2/neu cases. They observed that during the study period 54 cases relapsed, 8 cases had a local relapse and 46 cases had a systemic relapse. They observed that the factors affecting pCR were absence of ER/PR expression and stage II disease.<sup>[38]</sup> The purpose of this study is to evaluate whether downstaging could be achieved in patients with LABC, thus making the patient eligible for conservative surgeries like BCS or mastectomy

without compromising local control and survival. Radiation therapy to the breast and supraclavicular fossa in women with BCT and chest and supraclavicular fossa in women with MRM to a dose equivalent of 50 GY remains standard. Therefore NACT followed by locoregional therapy which includes surgery and radiotherapy is now an accepted strategy.

## MATERIALS AND METHODS

### Aim of the study

To determine the effect of neoadjuvant chemotherapy on operability of tumour mass and axillary lymph node status in locally advanced breast carcinoma.

### Objectives of the study

**The present study has the following objectives:**

1. Post neoadjuvant staging of the tumour

This prospective randomized clinical study was conducted after clearance from Board of Studies and Ethical committee in Dr. Sushila Tiwari Government Hospital, Haldwani, Nainital.

### Sample Size

We took prospective, randomized, double-blind, trial conducted by Rastogi Priya, Stewart J., et al,<sup>[38]</sup> as the reference study. We calculated the sample size using the software Epiinfo 7.2.2.2, taking the value of and a confidence interval of 90%, expected frequency 95% and confidence limits 5%, which came to be about 50 patients.

However due to less OPD owing to Covid epidemic in the first year of study, the sample size was decreased to 28 patients.

### Sampling Technique

We included 28 patients diagnosed with locally advanced breast carcinoma in Department of General Surgery, Government Medical College, Haldwani in the study who were given neoadjuvant chemotherapy. Sampling method was non-randomised convenient sampling to collect the samples. Tumour size and volume was assessed pre and post chemotherapy and the tumour were staged post neoadjuvant chemotherapy. Downstaging of the tumour was analysed and whether a change in surgical options available assessed.

### Study Population

The study subjects were chosen as per the inclusion and exclusion criteria.

### Inclusion Criteria

- Patients with age more than 18 years and less than 80 years
- Locally Advanced Breast Carcinoma
- Patients giving consent to be part of the study

### Exclusion Criteria

- Patients with co-morbid conditions like Diabetes Mellitus, Ischemic heart diseases etc.
- Patient with metastatic disease
- Patient with contraindication for chemotherapy
- Patient with early stage breast carcinoma
- Patients not giving consent to be part of the study
- Pregnancy

- Immunocompromised patient

### Study Procedure

After approval from the Institutional Ethical committee this study was carried out on 28 patients with the diagnosis of Locally advanced breast carcinoma in the Department of General Surgery, Government Medical College, Haldwani from January 2021- September 2022 and all patients were selected as per inclusion and exclusion criteria. Prior to admission, proper screening along with detailed clinical evaluation of each patient was carried out in the form of the following: complete blood count, routine biochemistry, bleeding time, clotting time, urine examination, chest x-ray and ECG.

Each patient included in the study as per the inclusion and exclusion criteria was assigned preoperative TNM staging, size and volume of the tumour mass was assessed and given standardized neoadjuvant chemotherapy of CAF regimen for 4 cycles, following which tumour was reassessed and lymph node status assessed.

### Neoadjuvant Chemotherapy Regimen

Each patient given standardized neoadjuvant chemotherapy of CAF regimen for 6 cycles.

### Staging Of Breast Carcinoma

AJCC breast carcinoma staging was used for pre and post chemotherapy breast cancer stages.

### Statistical Analysis

The data was entered into the Microsoft excel and the statistical analysis was performed by statistical software SPSS version 21.0. The Quantitative (Numerical variables) were present in the form of mean and SD and the Qualitative (Categorical variables) were present in the form of frequency and percentage. Geometric mean of percentage reduction in tumor volume was calculated.

## RESULTS

The demographic characteristics of the study population are depicted in Table 1 and is diagrammatically represented in Figure 1. Table 1 reveals that most of the patients who presented to the surgery OPD were of 45-55 years of age with peak presentation in age of 48-50 years and 54-56 years of age. [Table 1 and Figure 1].

The region wise distribution of the study population is demonstrated in [Table 2] and is represented in [Figure 2]. From [Table 2], it is seen that Most of the patients in the study population belong to the Nainital District of Uttarakhand. [Table 2 and Figure 2].

[Figure 3] depicts the line diagram between the age of menarche and number of patients.

All the patients studied were having locally advanced breast carcinoma and were given six cycles of Neoadjuvant chemotherapy based on TNM staging of breast carcinoma at the time of presentation was done. Patients were regularly monitored in each visit for any chemotherapy side effects and reduction in the tumor size and volume. Tumor volume calculation was done using sonomammogram after

the 4th and 6th cycle of Neoadjuvant chemotherapy. Lymph node status was assessed using clinical and radiological evaluation. Pre-Chemotherapy and Post-NAC staging and tumor volume of the breast carcinoma of these 28 patients is presented in [Table 4].

Response After Neoadjuvant Chemotherapy to lymph node positive locally advanced breast carcinoma is depicted in [Table 6].

Response After Neoadjuvant Chemotherapy to lymph node positive locally advanced breast carcinoma is shown in the form of a three-dimensional bar diagram in [Figure 5].

Response After Neoadjuvant Chemotherapy to lymph node negative locally advanced breast carcinoma is given in [Table 7].

Response After Neoadjuvant Chemotherapy to lymph node negative locally advanced breast

carcinoma is shown in the form of a three-dimensional bar diagram in [Figure 6].

Lymph node clearance was observed in 42% of the patients given neoadjuvant chemotherapy.

Lymph Node Status after NACT in the sampled patients is given in [Table 8].

Lymph Node Status after NACT in the sampled patients is shown with the help of a pie chart in [Figure 7].

[Figure 11] shows the ultrasound of patient before and after NAC.

Before chemotherapy, the tumor was complicated with regional ulceration and infection, and surgery was difficult. However, after chemotherapy the ulcer healed and edema subsided and was operated. This has been shown in [Figure 12].

**Table 1: Demographic characteristics of the study population**

Age group (Years)	No. of Patients
38-40	1
40-42	2
42-44	2
44-46	4
46-48	3
48-50	5
50-52	4
52-54	2
54-56	5
Total	28

**Table 2: Region wise distribution of Study Population**

District	No. of Patients
Almora	5
Bageshwar	4
Champawat	1
Nainital	15
Pithoragarh	1
U.P.	2

**Table 3: The distribution of breast carcinoma over age of menarche**

?

**Table 4: ?**

**Table 5: Downstaging of the Breast carcinoma after NAC**

Breast Carcinoma Stage at Presentation	Post Neoadjuvant chemotherapy breast carcinoma stage			
	IA	IB	IIA	IIB
IIB	1	2	5	0
IIIA	0	1	5	4
IIIB	1	1	3	3

**Table 6: Response After Neoadjuvant Chemotherapy to lymph node positive locally advanced breast carcinoma**

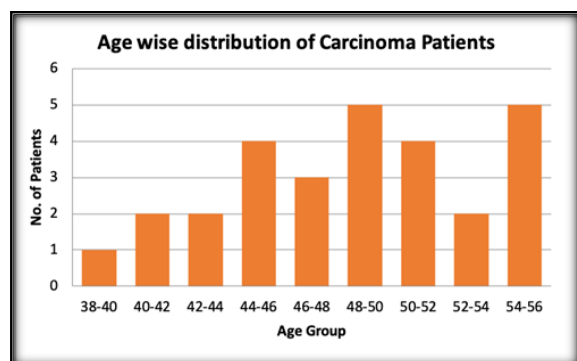
Stage	Lymph Node Positive	Number of Partial Responders
II B	4	4
III A	12	9
III B	7	6

**Table 7: Response After Neoadjuvant Chemotherapy to lymph node negative locally advanced breast carcinoma**

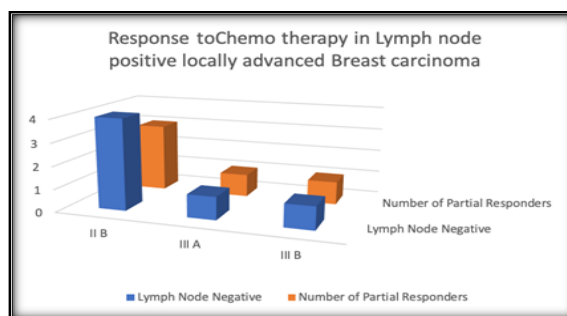
Stage	Lymph Node Negative	Number of Partial Responders
II B	4	3
III A	1	1
III B	1	1

**Table 8: Lymph Node Status after NACT**

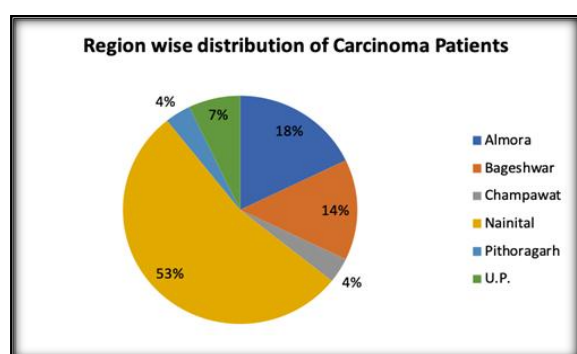
Lymph node Clearance	No lymph node clearance	Total Patients
11	15	26



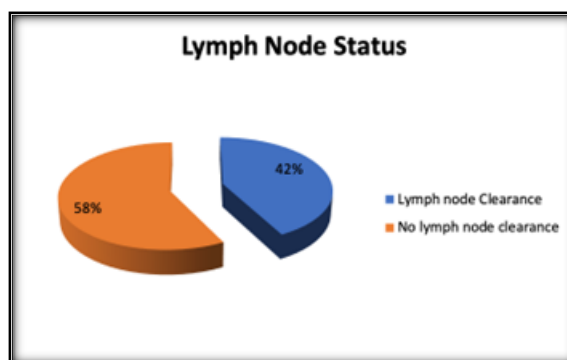
**Figure 1: Demographic characteristics of the study population**



**Figure 6: Response After Neoadjuvant Chemotherapy to lymph node negative locally advanced breast carcinoma**



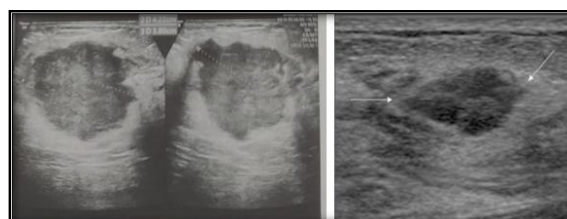
**Figure 2: Region wise distribution of Study Population**



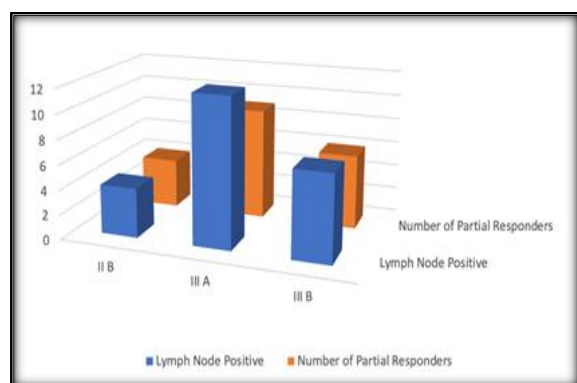
**Figure 7: Lymph Node status after NAC**



**Figure 3:**



**Figure 11: USG of the patient before and after AC**



**Figure 5: Response After Neoadjuvant Chemotherapy to lymph node positive locally advanced breast carcinoma**

## DISCUSSION

Historically patients who presented with breast carcinoma were treated with definitive surgical therapy and role of neoadjuvant chemotherapy was initially used in unresectable, advanced or inflammatory breast carcinoma with the aim being to shrink the primary tumor. Now neoadjuvant chemotherapy is increasingly being used to improve surgical options and also acquire information regarding response of tumor to chemotherapy regimen. This allows for discontinuation of ineffective chemotherapy regimen to avoid toxicity.<sup>[39-42]</sup>

Local recurrence rate for LABC are usually high with an alarming low long-term survival rate. Haagensen and Stout had classified LABC into operable and inoperable types. For operable LABC, radical surgery is routine intervention accompanied with post-operative chemotherapy and radiotherapy, and pre-operative NAC is rather optional for breast



conservation purposes. But for inoperable LABC complicated with skin ulcer, skin edema and adhesion with chest wall, direct operation mostly failed to prevent early local recurrence and distant metastases. Consequently, effective treatments are employed to relieve infiltration before surgery for inoperable LABC. The preoperative treatment includes systematic chemotherapy and local radiotherapy. Previous studies have confirmed that LABC.<sup>[43]</sup>

is usually complicated with distant micro-metastases, which could possibly develop into new metastases if only simple regional treatment measures were taken. Therefore, recent treatment schemes for LABC are usually centered on pre-operative NAC to control the local symptoms, which could be improved converting inoperable LABC into operable state. It has been proven that this method can effectively inhibit distant metastases and improve overall survival rate. Most clinical researches tailored Anthracycline as the principal agent of NAC scheme, and appended Taxane to improve the therapeutic effect of the chemotherapy. Results from such studies showed that, about 30 to 46% of operable LABC cases could achieve pathological complete response (pCR) after NAC, and 80% could achieve partial response (PR). However, previous reports on the effectiveness of NAC on inoperable LABC were rather less promising.

Jai Min Ryu et al in their study of Relationship Between Breast and Axillary Pathologic Complete Response According to Clinical Nodal Stage studied a total of 6,597 patients and of them, 528 (9.5%), 3,778 (67.8%), and 1,268 (22.7%) patients had cT1, cT2, and cT3 disease, respectively. Regarding cN stage, 1,539 (27.7%), 2,976 (53.6%), and 1,036 (18.7%) patients had cN0, cN1, and cN2 disease, respectively. pCR occurred in 21.6% (n = 1,427) of patients, while ApCR and pathologic complete response (ypCR) occurred in 59.7% (n = 3,929) and ypCR 19.4% (n = 1,285) of patients, respectively. The distribution of biologic subtypes included 2,329 (39.3%) patients with hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative disease, 1,122 (18.9%) with HR-positive/HER2-positive disease, 405 (6.8%) with HR-negative/HER2-positive disease, and 2,072 (35.0%) with triple-negative breast cancer. Among the patients with BpCR, 89.6% (1,122/1,252) had ApCR. Of those with cN0 disease, most (99.0%, 301/304) showed ApCR. Among patients with cN1-2 disease, 86.6% (821/948) had ApCR.

#### **Age and gender distribution and the stage of presentation**

In my study most of the patients were of 45-55 years of age with peak presentation in age of 48-50 years and 54-56 years of age. And most achieved their menarche by 12-14 years of age and 60% of the cases were postmenopausal. Twenty eight percent of the patients at the time of presentation were at stage IIB, thirty nine percent were at stage IIIA and 32% were at stage IIIB. This was in accordance with the study by

Priyanshu Choudhary et al on Neoadjuvant chemotherapy in locally advanced breast cancer: Clinicopathological characteristics and correlation with pathological complete response; where the median age of diagnosis was 46 years (range 24-72 years). Fifty four percent cases were postmenopausal, 54% had a left sided cancer, 45% right sided cancer, 1% had bilateral breast cancer. The median duration of symptoms was 5 months. The clinical stage according to AJCC staging system was Stage IIB – 11% (32), IIIA – 21% (58), IIIB – 60% (169) and IIIC – 8% (24). Sixty five percent (186) cases presented with clinical skin involvement and 80% (228) patients has clinical node positivity

#### **Symptoms**

Most common symptom by which the patients presented was breast lump with the mean duration of symptom occurrence being 4 months. 30% of them had associated pain and 25% of the study group had skin involvement in form of dimpling, edema or ulceration.

#### **Resolution**

Fisher B et al, conducted study on the effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer under NSABP B-18 trial and observed that breast tumor size was reduced in 80% of patients after preoperative therapy; 36% had a cCR. Tumor size and clinical nodal status were independent predictors of cCR. Twenty-six percent of women with a cCR had a pCR. Clinical nodal response occurred in 89% of node-positive patients: 73% had a cCR and 44% of those had a pCR. There was a 37% increase in the incidence of pathologically negative nodes.

In accordance to this study we observed that breast tumor size was reduced in 81% of patients after preoperative therapy and clinical nodal response occurred in 42% of the patients. Mean percentage reduction in size that was observed was to be approximately 68% of initial tumor volume however cCR was not observed in any patient in my study. In my study it was observed that 87% of stage II B patients and stage III B responded to NACT and 76% of Stage III A responded to NACT.

#### **Follow-up**

During the followup time of 6 months after surgery the patients were given adjuvant chemotherapy and radiotherapy and no locoregional recurrence has been observed during this period.

#### **Complications**

Grade 3/4 toxicity occurred in 45% cases, the most common were diarrhea, neutropenia, CINV, oral mucositis and thrombocytopenia.

#### **Limitations**

Nevertheless, some limitations worth mentioning in this study are the facts that only 28 cases were included and short follow up time of 6 months. The results would be more persuasive if we could include more cases and increase the follow-up time. Another limitation is that there is no comparison with other group and lack of randomization. Still, LABC is a major clinical problem in kumaon region of

uttartakhand, India and a common presentation in many parts of the world. In this study, it is proved that inoperable LABC can be converted into operable states by effective NAC, and prognosis be improved as well.

## CONCLUSION

With these results I conclude that Preoperative therapy can reduced the size of most breast tumors and decreases the incidence of positive nodes also inoperable LABC can be improved by NAC converting it into operable status. Although the long-term survival rate of these patients couldn't be assessed due to short time of follow up but quality of life were considerably improved. As this study is by no mean perfect with short research time duration, limited number of follow-up cases longer than 5 years and incomplete clinical data, however, our findings proved that effective NAC could convert inoperable LABC into operable states, and significantly improve the prognosis. With better future follow-ups and a more comprehensive clinical data, the results of the synthetic treatment of inoperable LABC would be more convincing.

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