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Original research article

STUDY OF CLINICOPATHOLOGICAL RESPONSE TO NEOADJUVANT THERAPY IN LOCALLY ADVANCED BREAST CANCER, ANTHRACYCLINE VS ANTHRACYCLINE AND DOCETAXEL BASED CHEMOTHERAPY: AN EXPERIENCE FROM TERTIARY CANCER HOSPITAL

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Abstract

Background: Breast cancer is now the most common cancer in females in across the globe, Locally Advanced Breast Cancer (LABC) poses a significant clinical challenge. With the broad spectrum of presentations, survival rates for LABC vary significantly among the series, reflecting institutional differences in therapeutic policies and patient selection.

Aims and objectives: To analyze the response to neoadjuvant chemotherapy (NACT) andthe outcome (DFS and OS) of Locally Advanced Breast Cancer patients who received NACT at Our hospital for median follow up period of one & half years.

Materials and Methods: The study has been conducted in Burdwan Medical College and Hospital situated in Burdwan district (West Bengal). 60 Patients that had been admitted in surgery indoor of our hospital, diagnosed as having locally advanced breast cancer This study involved Department of General Surgery and Radiotherapy and also Departments of Pathology of Burdwan Medical College & Hospital, for the necessary laboratory tests and investigation data.

Results:. Median age at presentation was 45 years (range: 30-53years). Majority of the patients were postmenopausal (55%). Tumour stage was T4 in 33.33% patients. 41 (68.33%) patients presented with no axillary or single mobile ipsilateral axillary lymph node, whereas 19 (31.66%) patients had N2 or N3 disease. Hormone receptor positivity was seen in 16.66% patients. Most of the patients (80.4%) responded to NACT either in the form of complete or partial response (PR). Complete CR was seen in16.2% patients and PR was seen in 62.2% patients, 12.8% patients had stable disease (SD) and 6.8% patients had progressive disease (PD) after NACT. Pathological complete response (PCR) was seen in 10 (16.20%) patients. There was no significant difference in

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response when anthracycline and taxane-based chemotherapy was compared.

Conclusion: Although clinical and pathologic assessment of response to chemotherapy are significantly related to each other, yet pathologic response might prove to be a better predictor of survival and may help in deciding the chemotherapy drugs to be used after surgery. Neoadjuvant chemotherapy should be considered as a reasonable alternative for patients with LABC.

Keywords: Neoadjuvant therapy, Breast cancer, anthracycline, anthracycline, docetaxel, chemotherapy

Introduction

Breast cancer is now the most common cancer in many parts of India and the incidence varies from 12 to 31/100000, and is rising[1]. Breast cancer is the most common cancer in females with age-adjusted incidence rates of 124 /1, 00,000 populations in the USA[2]. In India approximately 75-80,000 new cases are diagnosed annually [3, 4]. The Annual Age Adjusted Rate (AAR) varies in urban population based cancer registries from 27.0 per 100,000 in Chennai to 33.4 per 100,000 in Delhi while in Barshi it is 7.2 per 100,000 populations [5]. Locally advanced breast cancer (LABC) accounts for 30-60% of breast cancer in developing countries while in USA it accounts for 10-20%[6]. LABC accounts for 10-20% in the West [7] while in India it accounts for 30-35% of all cases. Locally advanced breast cancer (LABC) is defined by presence of a large primary tumor (>5 cm or T3), associated with or without skin or chest-wall involvement (T4) or with fixed (matted) axillary lymph nodes or with disease spread to ipsilateral internal mammary or supraclavicular nodes in the absence of any evidence of distant metastases[7]. Locally Advanced Breast Cancer (LABC) poses a significant clinical challenge. With the broad spectrum of presentations, survival rates for LABC vary significantly among the series, reflecting institutional differences in therapeutic policies and patient selection. Although some series report five-year survival rates of greater than 70%[8,9], these series exclude patients with inflammatory disease, the most aggressive form of non-metastatic breast cancer. Overall the results of the treatment of LABC patients are dismal and no more than 30–40% of the patients are expected to be long-term survivors[10-14]. Advanced stage of breast cancer and poorresults of treatment represents a major public health problem of our country. The present standard of treatment for LABC is still evolving. In the past decade anthracycline-based chemotherapy in the neoadjuvant setting followed by surgery and locoregional radiotherapy, followed by hormonal therapy in hormone receptor positive patients, has been the standard. Taxanes are under intense investigation[15,16]. Combined or sequential use of anthracyclines and taxanes are both acceptable. Capecitabine and Gemcitabine have been recently incorporated into trials assessing NACT[17,18]. The first report of the use of induction chemotherapy for LABC was published in the 1970s[19]. The administration of systemic chemotherapy prior to local therapy is advantageous for women with locally advanced breast cancer, as it can render inoperable tumors respectable and can increase the rates of breast conservative surgeries[20-23]. First large trial to compare neoadjuvant with adjuvant chemotherapy, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18[24], demonstrated that neoadjuvant chemotherapy produces a significant clinical and complete response rate, pathological complete response rates, as well as increased rates of breast conserving surgeries. The administration of systemic chemotherapy prior to local therapy is advantageous for

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women with LABC since it can render inoperable tumors Respectable and can increase rates of breast conservative surgeries[25-28]. Neoadjuvant use of paclitaxel alone or in combination has been shown to result in superior response rates compared to anthracycline-based chemotherapy[29]. Docetaxel has been an extensively studied molecule in the treatment of breast cancer, either alone or in combination, and has been shown to produce higher response rates then anthracyclines alone[30-34].The changing risk profile in successive generations-improved education, higher socioeconomic status, later age at marriage and at first child and lower parity-may in combination partially explain the diverging generational changes in breast and cervical cancer in Mumbai in the last decades[35].

Materials and Methods

The study has been conducted in Burdwan Medical College and Hospital situated in Burdwan district (West Bengal). 60 Patients that had been admitted in surgery indoor of our hospital, diagnosed as having locally advanced breast cancer This study involved Department of General Surgery and Radiotherapy and also Departments of Pathology of Burdwan Medical College & Hospital, for the necessary laboratory tests and investigation data.

Inclusion criteria

1. Advance breast cancer diagnosed with FNAC or core biopsy
2. Tumor movable in relation to the chest-wall, and overlying skin
3. Age more than 18 years and female patient
4. **LABC:** Stages included were IIIA, IIIB, and IIIC (TNM staging was done according to AJCC breast cancer surgery 7th edition).
5. Patients with pre-chemotherapy clinical assessment of tumor size, with an established histological diagnosis of carcinoma on biopsy, and who had received four cycles of neo-adjuvant chemotherapy.

Results

Median age at presentation was 45 years (range: 30-53years). Majority of the patients were postmenopausal (55%). Tumour stage was T4 in 33.33% patients. 41 (68.33%) patients presented with no axillary or single mobile ipsilateral axillary lymph node, whereas 19 (31.66%) patients had N2 or N3 disease. Hormone receptor positivity was seen in 16.66% patients.

Table 1: Patient characteristics

Patient characteristics	Number of patients (%)
Age	
<35 years	17(28.33%)
>35 years	43(71.66%)
T stage	
T2	19(31.66%)
T3	21(35%)
T4	20(33.33%)

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N node	
N0,n1	41(68.33%)
N2,n3	19(31.66%)
Menopause status	
Premenopausal	27(45%)
Postmenopausal	33(55%)
ER, PR status	
Positive	10(16.66%)
Negative	8(13.33%)

Chemotherapy regimens

GR 1 (n=30) patients received only anthracycline-based chemotherapy and GR 2 (n=30) patients received combination of anthracycline and taxane-based chemotherapy with median number of cycles being six.

Table 2

Group	Number of patients (%)
1	30(50%)
2	30(50%)

Response to neoadjuvant chemotherapy

Most of the patients (80.4%) responded to NACT either in the form of complete or partial response (PR). Complete CR was seen in16.2% patients and PR was seen in 62.2% patients, 12.8% patients had stable disease (SD) and 6.8% patients had progressive disease (PD) after NACT. Pathological complete response (PCR) was seen in 10 (16.20%) patients. There was no significant difference in response when anthracycline and taxane-based chemotherapy was compared.

Table 3: Clinicopathological variables

Clinicopathological variables	Number of patients (%)
Clinical	
CR	11(18.2%)
PR	37(62.2%)
SD	8(12.8%)
PD	4(6.8%)
Pathological	
CR	10(16.2%)
PR	40(64.2%)
SD	7(10.8%)
PD	3(4.1%)
Histology	
Ductal	56(93.33%)

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Lobular	4(6.8%)
Grade	
1	8(12.2%)
2	42(54.7%)
3	10(13.5%)
Undetermined	0
ECE	
Present	11(18.2%)
Absent	49(81.8%)
LVSI	
Present	18(29.1%)
Absent	42(64.2%)
Margins	
Positive	6(9.5%)
Free	54(90%)

Surgery

All patient undergone MRMwith axillary clearance

Pattern of failure

At a median follow-up period of 12 months, 12 patients (20%) developed relapse of which four patients developed locoregional recurrence (LRR) while three patients developed distant metastases and two patients had recurrence in the contralateral breast. Among four patients with LRR, one patients developed local recurrence, three patient developed axillary lymph node recurrence. Lung, liver and bones were the common sites of distant relapse.

Table 4

Pattern of failure	Number of patients (%)
Median follow up	12 MNTS
Min	12
Max	19
Relapse	
Local relapse	4
Axillary relapse	3
Distant metastasis	3
Contralateral breast	2

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Table 5: Age distribution of study subjects

Age in years	Group-1		Group-2	
	Frequency	Percent	Frequency	Percent
30-39	7	23.3	12	40
40-49	12	40	11	36.7
50-59	11	36.7	7	23.3
Total	30	100	30	100
Mean age (yrs.) Range	44.53 ± 7.60 (30-55)		42.06 ±7.82 (31-53)	

Median age at presentation was 45 years (range: 30-53 years). Majority of the patients were postmenopausal (55%).

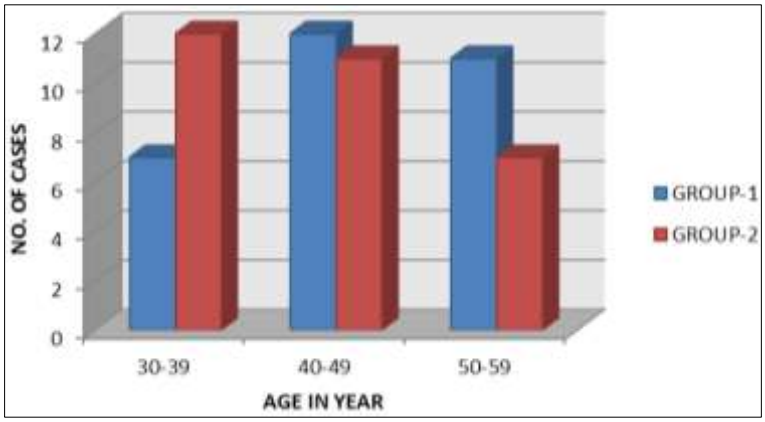

Fig 1: Age distribution

Table 6: T Before and After NACT in 2 Groups

	Group-1		Group-2	
	Mean	Sd	Mean	Sd
Before	3.03	0.81	3.03	0.85
After	1.76	1.30	2.06	1.36
P-value	<0.0, 001, HS		<0.0001, HS	
Mean change	1.26	0.74	0.97	0.72
P-value	0.1095,ns			

Before NACT

1. In group 1 tumor stage was t3 in 36.66% of patients
2. In group 2 tumor stage was T4 in 36.66% of patients

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After NACT

In Group 1 Group 2tumor stage was T2 in 40% of patient respectively.

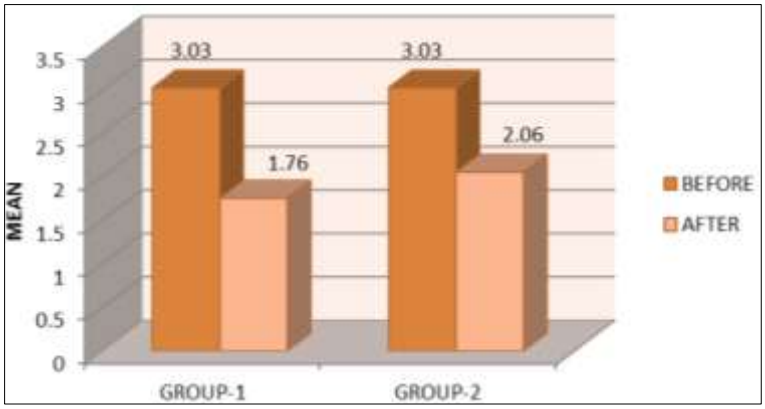

Fig 2: T-Score before and after NACT in 2 group

Table 7:N before and after NACT in 2 Groups

	Group-1		**Group-2**	
	Mean	**Sd**	**Mean**	**Sd**
Before	1.3	0.53	1.26	0.58
After	0.60	0.56	1.0	0.98
P-value	<0.0001, HS		0.1870,ns	
Mean change	0.70	0.59	0.26	1.08
P-value	0.1947, NS			

Before NACT

- 20(66.6%) patients presented with no axillary or single mobile ipsilateral axillary lymphnode, whereas 10 (33.33%) patients had N2 or N3 disease in group 1 and group 2 respectively.

After NACT

1. **In Group 1:** 29(96.6%) patients presented with no axillary or single mobile ipsilateral axillary lymph node, whereas 1 (3.33%) patients had N2 or N3 disease.
2. **In Group 2:**24(80%) patients presented with no axillary or single mobile ipsilateral axillary lymph node, whereas 6 (20%) patients had N2 or N3 disease.

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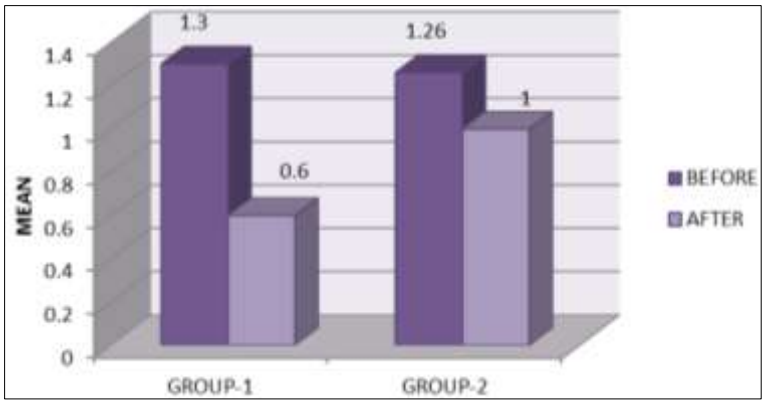

Fig 3: N-Score before and after NACT in 2 groups

Table 8: Stage before and after chemotherapy in Group-1 and Group-2

		Number	1a	2a	3a	2b	3b	3c	P-value
Group-1	3a	20	2(10)	14(70)	3(15)	1(5)	0	0	<0.001,HS
	3b	10	0	1(10)	4(40)	0	5(50)	0	
Group-2	3a	19	0	14(73.7)	4(21.1)	1(5.2)	0	0	<0.001, HS
	3b	11	0	1(9.1)	0	3(27.3)	3(27.3)	4(35.3)	

Before NACT

Majority of patients was in stage 3a in group 1 20(66.66%) and in group 2 19(63.33%) respectively.

After NACT

Majority of patients was in stage 2a in group 1 and in group 2 15 (50%) respectively.

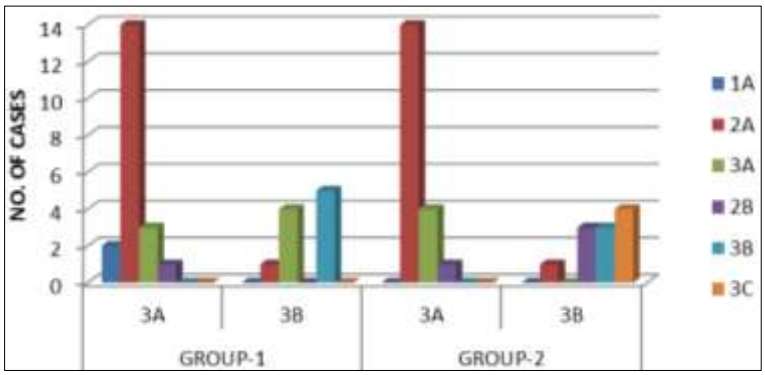

Fig 4: Stage before and after chemotherapy in group 1 and group 2

Table 9: FNAC in 2 groups

FNAC	Group-1		Group-2		P-Value
	Frequency	Percent	Frequency	Percent	
DC	27	90	29	96.7	0.612,NS
LC	3	10	1	3.3	

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27(90%) of patients in GROUP 1 and 29(96.7%) of patients in GROUP 2 was DUCTAL CARCINOMA.

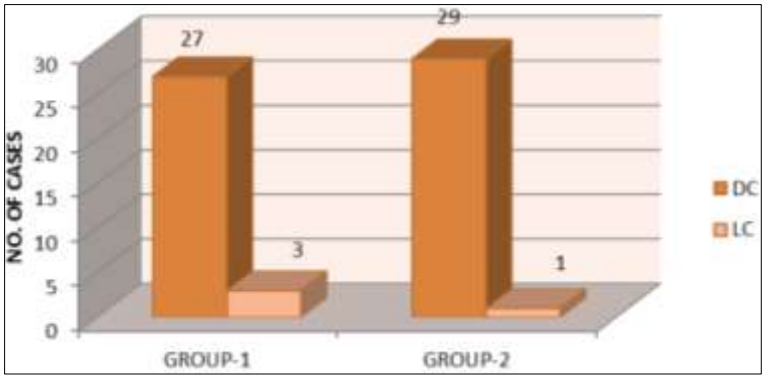

Fig 5: FNAC in groups

Table 10: True cut biopsy in 2 groups

	Group-1		Group-2		P-Value
	Frequency	**Percent**	**Frequency**	**Percent**	
IDC	27	90	29	96.7	0.612,NS
ILC	3	10	1	3.3	

27(90%) of patients in group 1 and 29(96.7%) of patients in group 2 was invasive ductal carcinoma

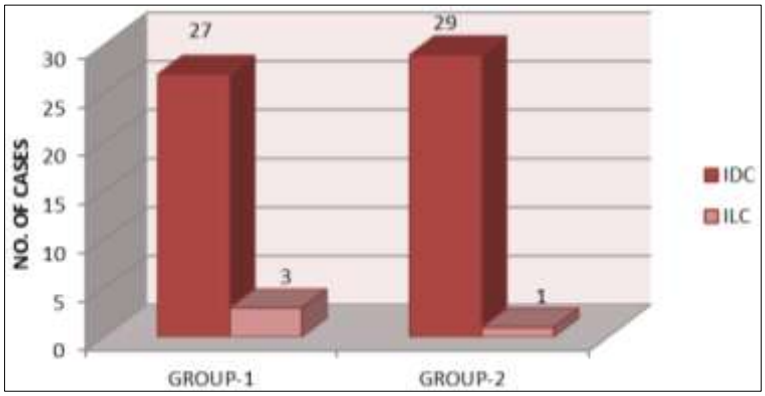

Fig 6: True cut biopsy in 2 groups

Table 11: ER in 2 groups

	Group-1		Group-2	
	Frequency	**Percent**	**Frequency**	**Percent**
Positive	7	70	3	30
Negative	7	87.5	1	12.5
P-value	0.588, NS			

10(16.66%) of patients are ER receptor positive 8(13.33%) of patients are ER negative.

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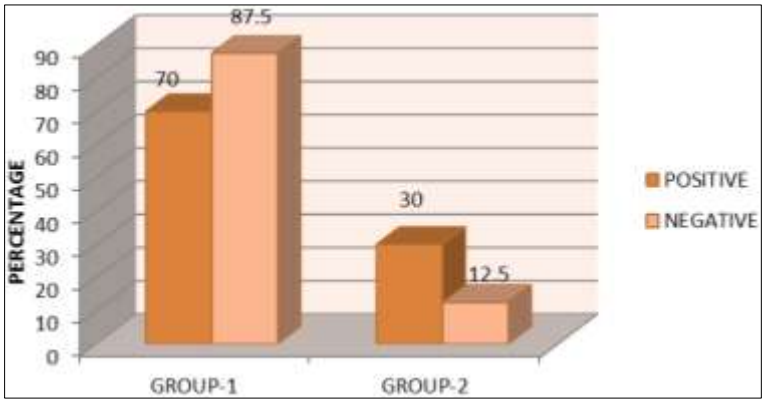

Fig 7: ER in 2 groups (%)

Table 12:PR in 2 groups

	Group-1		Group-2	
	Frequency	**Percent**	**Frequency**	**Percent**
Positive	7	70	3	30
Negative	7	87.5	1	12.5
P-value	0.588, NS			

10(16.66%) of patients are PR receptor positive 8(13.33%) of patients are PR negative

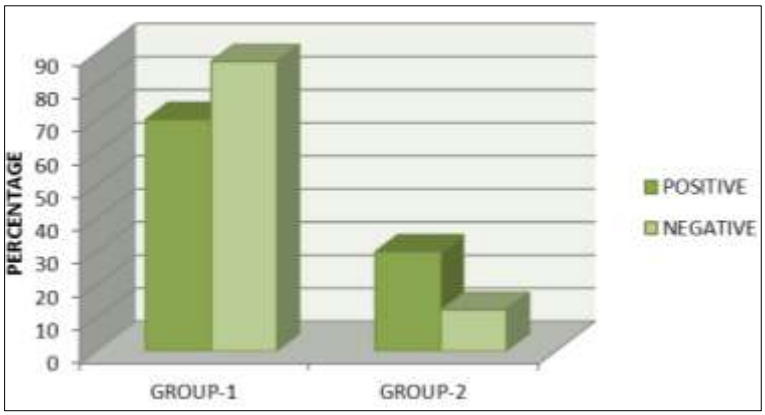

Fig 8: PR in 2 groups (%)

Table 13: Grades in 2 groups

Grades	Group-1		Group-2	
	Frequency	**Percent**	**Frequency**	**Percent**
1	4	13.3	4	13.3
2	22	73.3	20	66.7
3	4	13.3	6	20
P-value	0.920, NS			

Majority of patients are in grade 2 in group 1 22(73.33%) and group 2 20 (66.7%)

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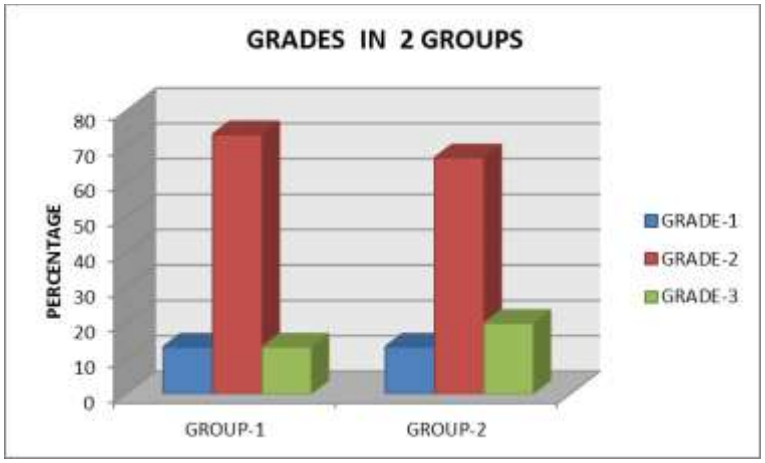

Table 14: Clinical response in 2 Groups

Response	Group-1		Group-2	
	Frequency	Percent	Frequency	Percent
PR	19	63.3	18	60.0
CR	6	20.0	5	16.7
PD	0	-	4	13.3
SD	5	16.67	3	10.0
P-value	0.216, NS			

On clinical assessment,
Complete response was seen in [GR 1-20% cases (6/30), GR 2-16.7%(5/30)]
Partial response was seen in [GR 1-63.33% (19/30), GR 2-60%(18/30)60%
Stable diseases was seen in [GR 1-16.67%(5/30), GR 2-10%(3/30)]
Progressive diseases was seen in GR 2-13.33%(4/30) AND no progression of diseases was seen in GR 1

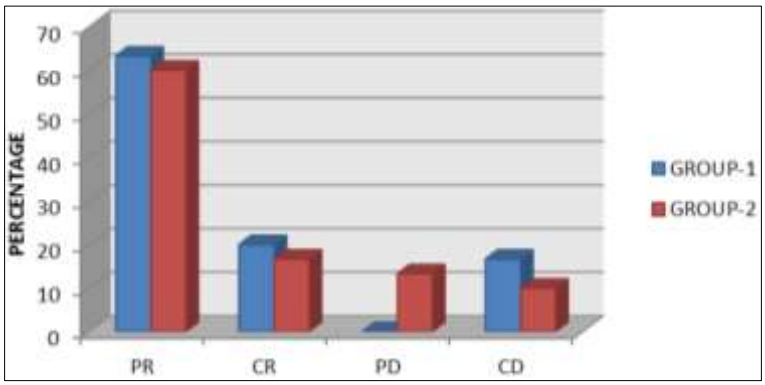

Fig 9: Clinical response in 2 groups

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Table 15: Pathological response in 2 groups

RESPONSE	Group-1		Group-2	
	Frequency	Percent	Frequency	Percent
PCR	6	20	4	13.3
PPD	0	-	3	10.0
PPR	20	66.7	19	63.3
PSD	4	13.3	4	13.3
P-Value	0.388, NS			

On pathological assessment,complete response was seen in [GR 1-20% cases (6/30), GR 2-13.3%(4/30)]
Partial response was seen in [GR 1-66.7% (20/30), GR 2-63.3%(19/30)]
Stable diseases was seen in [GR 1-13.3%(4/30), GR 2-13.3%(4/30)]
Progressive diseases was seen in GR 2-13.33%(4/30) and no progression of diseases was seen in GR 1

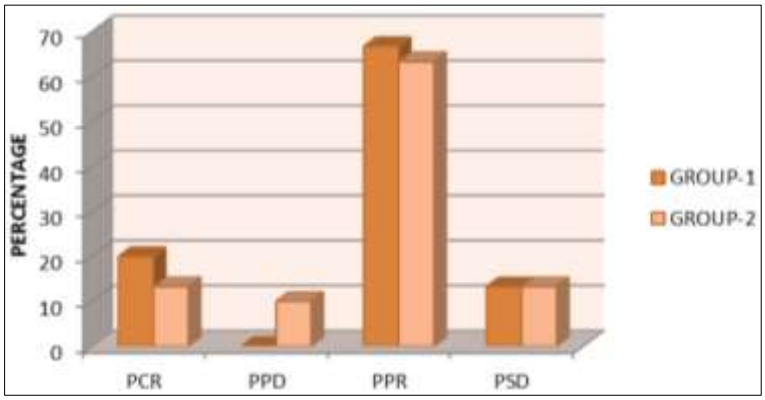

Fig 10: Pathological response in 2 groups

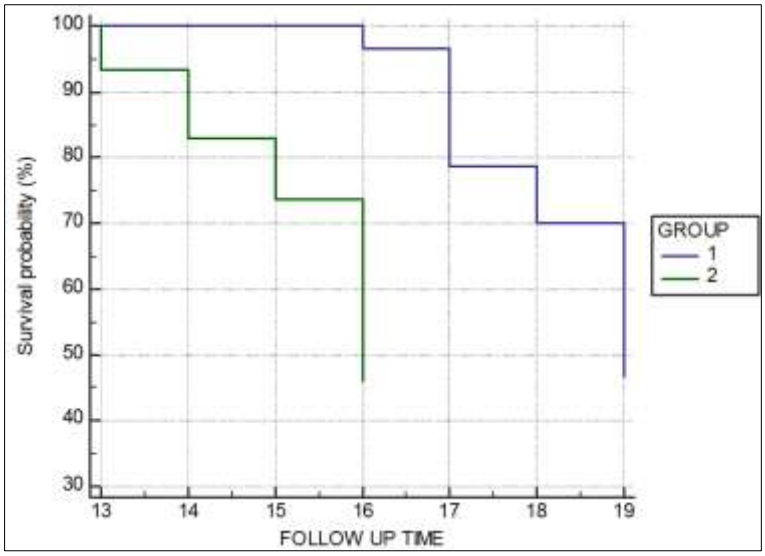

Fig 11: Kalpan meier curve for overall survival.

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Meier Survival curve for overall survival of locallyadvanced breast cancer patients who received neo adjuvant chemotherapy

Median OS was 19 months IN GROUP 1 AND 16 months IN GROUP 2, respectively [Figures 1 and, Table 16].

Table 16: Median survival of group-1 and group-2 for overall survival

Group	Median	95% confidence interval for median	
Group-1	19.0	19	19
Group-2	16.0	16	16

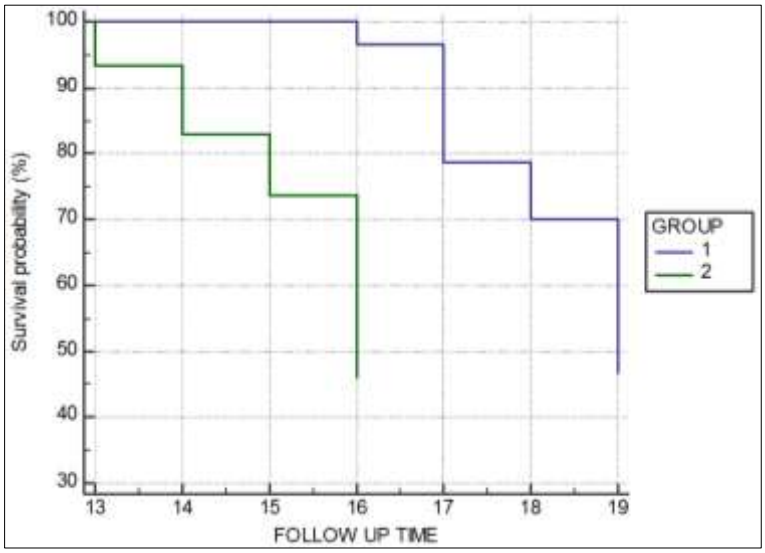

Fig 2: Kaplan Meier Survival curve for disease free survival oflocally advanced breast cancer patients who received neo adjuvant chemotherapy

Median DFS was 12 months IN group 1 and 6 months in group 2, respectively [Figures 2 and, Table 17].

Table 17: Median survival of group-1 and group-2 for disease free survival

Group	Median	95% confidence interval for median	
Group-1	12.2	7.70	12.20
Group-2	6.10	5.70	6.60

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Table 18: Comparison of survival curves (log-rank test)

Log-rank test	Chi2-value	D.F.	P-value
Overallsurvival	15.70	1	0.0001, highly significant
Disease free survival	7.6623	1	0.0056, highly significant

DFS and OS are statistically significant in group 1

Table 19: Treatment response

Survival	Group-1	Group-2	Hazard ratio	95% C.I.	P-value
Overall survival	19	20	0.2599	0.087-0.77	0.001, HS
DFS	26	25	0.3358	0.11-0.97	0.0056,HS

Adding docetaxel to the AC led to a significant increase in OS [Table 19], with "log-rank (Mantel-Cox) test" p-*value* 0.001 (<0.05). The hazard ratio was 0.2599 (95% confidence interval, 0.087–0.77; Figure 1). The DFS was also significantly improved [Table 19], with "log-rank (Mantel-Cox) test" p-value 0.0056 (<0.05),hazard ratio 0.3358 and 95% confidence interval ratio 0.11–0.97 [Figure 2]

Discussion

Neoadjuvant chemotherapy is known to be beneficial for down-staging patients with LABC. There is paucity of literature pertaining to outcome of NACT in LABC in India where majority of breast cancer patients present with advanced disease. The aim of the study was to assess the use of NACT in patients with LABC at an Indian tertiary care center. The Indian scenario presents a contrast to the western world, with most cases being diagnosed in advanced stages. Patients coming with early nodepositive disease are less-common presentations at oncology centers.The important components of a multimodality approach for breast cancers include radiotherapy for locoregional control and chemotherapy for both primary as well as metastatic disease.The lymph nodal status remains the most important prognostic factor for resulting in the dismal survival in patients, especially presenting with extensive nodal involvement.

Chemotherapy has come a long way, evolving from traditional CMF regimes to Anthracyclines to Taxanes to modern innovations in targeted therapies. Anthracyclinebased chemotherapy is better tolerated in terms of acute side-effects, but long-term sequel (cardio toxicity, secondary leukemia) are worrisome. The reported trials with Taxanes demonstrated comparable reduction in the risk of recurrence and death[36,37].

Theintroduction of Taxanes in early-staged breast cancer treatment constitutesan important advance over the historic experience with alkylator and Anthracycline-based chemotherapy. The first report on adjuvant Taxane therapy was CALGB 9344. In this much-scrutinized study, node-positive disease patients were randomly assigned to receive either four cycles of AC or the same regimen followed by four cycles of Paclitaxel. The Paclitaxel-containing regimen had a consistently lower rate of relapse,

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which became apparent at early 21 months of follow-up andhas been sustained in 5 years. This study showed that AC–Paclitaxel is superior to AC chemotherapy.

We conducted this study to evaluate whether addition of docetaxel to a standard neo-adjuvant chemotherapy regimen (AC) in locally advanced breast cancer would prolong time to recurrence or survival.

The median age of presentation in our study is 45 years, which is quite comparable with other studies.

Raina *et al*.[38] in an early breast cancer study reported median age of 47 years whereas Min *et al*.[39] showed median age of presentation was 49 years.

Segal *et al*. reported from North America that the median age of LABC patients was 57 years (Range = 28-88 years)[40].

In Turkey,the median age of LABC patients was 47 years (range = 17-74 years)[41].

In another study, Bines *et al*.analyzed LABC patients on NACT prospectively. In that study median age was 50 years.

Premenopausal patients constituted 45% of all LABC cases in the present study.

In the randomized study on operable LABC by Deo *et al.*, premenopausal patients were 40 and 50% in two arms of the study[42].

Forty-eight percent of the cases were premenopausal in a study on LABC patients in Italy[43].

A study from North America reported that 38% of LABC patients werepremenopausal[44].

In another study, Bines *et al.*, analyzed LABC patients on NACT prospectively with 47% premenopausal patients.

Min *et al*. showed 42.6% of our patients were premenopausal, which is slightly lower than other studies by Yadav *et al*.[45] and Chen *et al*.[46].

In present study showed estrogen receptor positivity in GR1-70%,GR-2-30%.

A study by Raina *et al*. showed estrogen receptor (ER) positivity of 64% [47].

Western literature reported ER positivity of around 60-80%.

In an earlier study by Raina *et al.*,on Indian patients, the ER positivity was 50.5%[48].

Redkar *et al.* reported 43.9% ER positivity in breast cancer patients by enzyme immunoassay[49].

Bines *et al*., analyzed LABC patients on NACT prospectively,54% ER+ tumors, 21% her-2 positive

The differences in ER status in Indian and Caucasian patients could be due to lower average age at presentation or racial differences.

Median number of NACT cycles used in our patients was six. There is a lot of variation in the number of cycles of chemotherapy that are given in neoadjuvant setting in the literature[50].

Majority of our patients achieved maximal response after six cycles of NACT. 50% of the patients received anthracycline based chemotherapy as per institutional protocol and 50% of patients received combined anthracycline and taxane-based chemotherapy as per protocol.

Bines *et al.,* analyzed LABC patients on NACT prospectively,64% were Stage IIIB tumors.

NSABP-27[141] and a study by Min *et al*. showed PCR rate after NACT of 26.1% and 20% respectively. Many other studies showed variable PCR ranging from 4% to 40%.

In my study Clinical CR was observed in 18.2% in the NACT group, with an overall

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response rate of (CR + PR) 80.4%. Pathological CR (PCR) was seen in 16.2% of the cases.

An earlier Indian study showed an overall RR of 62% with 4% PCR.

A Study from Turkey reported an overall clinical response of 88% (CR 14.9% and PR 73%).

Hurley *et al.* reported 17% PCRin LABC patients with Docetaxel, Cisplatin, and Trastuzumab therapy.

In a study by Baldini *et al.*,the PCRrate was 3.3% with standard CEF.

Kuerer *et al.* reported a PCR rate of 12% with four courses of FAC chemotherapy in the neoadjuvant setting.

Other studies reported a response rate of 60-93% including 10-20% CRs.

Pathological CR has been shown to be an independent predictor of prolonged DFS/OS but very few patients achieve PCR and that too is dependent upon the type of chemotherapy.

Earlier trials testing anthracyclines as NACT produced PCR rates of 2-13% and there was no difference in DFS/OS.

Subsequently, taxanes have been used either alone or with anthracyclines and it has shown to improve PCR rates.

Single agentdocetaxel has produced PCR rates of 16-20% and clinical complete responses of 18% to more than 25%.

In combination with anthracyclines PCR rates of 10% to >20% are reported depending upon the stages of tumor included in that particular study.

In the present study, the neoadjuvant chemotherapy responding group (CR and PR) had significantly better survival than the non-responding group (SD and PD). Similar observation was also reported by others.

Patients achieving CR had a five-year DFS and OS of 75 and88%, respectively, with PR intermediate prognosis, with no response and very poor survival, in the study by Deo *et al.*

Patients were with PCR OS 100% and without PCR the OS was 83%, in four-year in the study by Hurley *et al.*

Eltahir *et al.* reported a five-year probability survival of 74% in patients who achieved CR with NACT and 36% in patients who achieved PR.

The NSABP trial has shown that use of taxanes with doxorubicin sequentially did show a better response rates in terms of superior partial and complete response both in ER positive and negative patients.

In present study we did not observe any change in the tumor type following chemotherapy.

Honkoop *et al*. noted that in a case with mixed ductal-mucinous carcinoma before chemotherapy, only the mucinous component was left after chemotherapy.

It was noted by some that lobular carcinoma was not or less responsive to chemotherapy probably because of its high stromal content.

Masters *et al*. noted no difference in the responsive-ness of invasive ductal or lobular carcinoma.

Well differentiated tubular carcinomas were found to be resistant to primary chemotherapy by Sinn *et al.*

When we analyzed different prognostic factors, we found that response to chemotherapy was an important determinant of DFS. Patients who responded to

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chemotherapy had significantly better DFS when compared with patients who had stable or PD after NACT.

In this study Kaplan-Meier survival curve analysis with log-rank (MantelCox) test shows a statistically significant disease-free survival and overall survivalin favor of the docetaxel-containing study arm, with OS p-value 0.001 (<0.05). The hazard ratio was 0.2599 (95% confidence interval, 0.087–0.77; Figure 1). DFS p-value 0.0056 (<0.05), hazard ratio 0.3358 and 95% confidence interval ratio 0.11–0.97 [Figure 2]

In the NSABP-28 study, 3060 patients were randomly assigned to AC (AC-1529) versus AC followed by Paclitaxel (AC-PTX 1531). Addition of Paclitaxel to AC significantly reduced the hazard for DFS by 17%. The 5-year DFS was 76% (±2%) for patients with AC-PTX compared with 72% (±2%) for AC.

To assess the advantage of adjuvant Taxane chemotherapy over standard chemotherapy, Bria *et al*. performed a pooled analysis of phase III trials. The absolute benefits in DFS and OS were in favor ofTaxanes, ranging from 3.3% to 4.6% and from 2% to 2.8%, respectively. Considering all the phase III trials, Taxane-based adjuvant chemotherapy for early breast cancer seems to add a significant benefit in both DFS and OS over standard chemotherapy.

It can be well interpreted from these studies on breast cancer that incorporation of Taxanes, eitherPaclitaxelorDocetaxel,assubstituteorsequentialadditiontoAnthracycline-based regimens can contribute significantimprovement in outcomes, especially among women with node-positive breast cancer in whom the vast majority of these trials have been conducted. The addition of Paclitaxel to AC consistently proved advantageous. However, the effect was largest among those whose tumors were hormone receptor negative and who received no adjuvant Tamoxifen compared with all other patients.

In another study,showsAdding Paclitaxel to the AC led to a significant increasein DFS [Table 3], with "log-rank (Mantel-Cox) test"P-value 0.021 (<0.05). The hazard ratio was 0.295(95% confidence interval, 0.104–0.835; Figure 1). The OS was also significantly improved [Table 3], with"log-rank (Mantel-Cox) test" P-value 0.034 (<0.05),hazard ratio 0.308 and 95% confidence interval ratio0.103-0.917 [Figure 2].

In this study, the administration of a non–cross-resistant drug, docetaxel, as a single agent, after completion of treatment with a standard therapy AC, improved the DFS and OS, which were statistically significant, with acceptable toxicity. Because of the small accrual of patients, the impact of tumor size, nodal status (N1, N2) and hormonal positivity status could not be used for multivariate Cox regression analysis. Because of the limited accrual of patients and also the period of median follow-up, it is inappropriate to conclude the survival advantage in our study. With subsequent follow-up, more information regarding DFS will be gathered. Increasing accrual of patients in the trial and a longer median follow-up will definitely give us a clearer picture.

Conclusion

Although clinical and pathologic assessment of response to chemotherapy are significantly related to each other, yet pathologic response might prove to be a better predictor of survival and may help in deciding the chemotherapy drugs to be used after surgery. Neoadjuvant chemotherapy should be considered as a reasonable alternative for patients with LABC. Although the results in our study are compatible with previous results, there are limitations, There is disparity in the number of patients, number of cycles administered before surgery and in the median follow-up of the two groups. This

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study analyzes the outcome of patients who received NACT in the small number of LABC patients from our single tertiary center in Burdwan west Bengal and our results are comparable with the results reported from other centers. The present study demonstrates Clinico-pathological variables such as nodal status, response to chemotherapy and pathological tumor size had significant impact on DFS.NACT contributes to improved operability without jeopardizing overall survival.

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References

1. Two-year Report of the Population Based Cancer Registries: 1999-2000. National Cancer Registry Programme (Indian Council of Medical Research).
2. Ries LA, Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, editors. SEER Cancer Statistics Review, 1975-2005. Bethesda, MD: National Cancer Institute, 2008. Available from: http://seer. cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site.
3. Sinha R, Anderson DE, McDonald SS, Greenwald P. Cancer risk and diet in India. J Postgrad Med. 2003;49:222-8.
4. Chopra R. The Indian scene. J Clin Oncol. 2001;19:106-11.
5. Nandkumar. National Cancer Registry Programme (ICMR). First All India report, 2001-2002.
6. Valero VV, Buzdar AU, Hortobagyi GN. Locally advanced breast cancer. Oncologist 1996;1:8-17
7. Valero VV, Buzdar AU, Hortobagyi GN. Locally Advanced Breast Cancer. Oncologist. 1996;1:8-17.
8. Klefstrom P, Grohn P, Heinonen E, Holsti L, Holsti P. Adjuvant postoperative radiotherapy, chemotherapy, and immunotherapy in stage III breast cancer. II. 5-year results and influence of levamisole. Cancer. 1987;60:936-42.
9. Toonkel LM, Fix I, Jacobson LH, Bamberg N, Wallach CB. Locally advanced breast carcinoma: results with combined regional therapy. Int J Radiat Oncol Biol Phys. 1986;12:1583-7.
10. Arnold D, Lesnick G. Survival following mastectomy for stage III breast cancer. Am J Surg. 1979;137:362.
11. Fracchia AA, Evans JF, Eisenberg BL. Stage III carcinoma of breast: A detailed analysis. Ann Surg. 1980;192:705-10.
12. Bruckman JE, Harris JR, Levene MB, Chaffey JT, Hellman S. Results of treating stage III carcinoma of the breast by primary radiationtherapy. Cancer. 1979;43:985-93.
13. Zucali R, Uslenghi C, Kenda R, Bonadonna G. Natural history and survival of inoperable breast cancer treated with radiotherapy and radiotherapy followed by radical mastectomy. Cancer. 1976;37:1422-31.
14. Rubens RD, Armitage P, Winter PJ, Tong D, Hayward JL. Prognosis in inoperable stage III carcinoma of the breast. Eur J Cancer. 1977;13:805-11.
15. Buzdar AU, Singletary SE, Theriault RL, Booser DJ, Valero V, Ibrahim N, *et al.* Prospective evaluation of paclitaxel versus combination chemotherapy with

ISSN:0975-3583,0976-2833 VOL13, ISSUE 05,2022

fluorouracil, doxorubicin, and cyclophosphamide as neoadjuvant therapy in patients with operable breast cancer. J Clin Oncol. 1999;17:3412.

16. Smith IC, Heys SD, Hutcheon AW, Miller ID, Payne S, Gilbert FJ, *et al*. Neoadjuvant chemotherapy in breast cancer: significantly enhancedresponse with docetaxel. J Clin Oncol. 2002;20:1456.
17. Wenzel C, Bartsch R, Locker GJ, Hussian D, Pluschnig U, Sevelda U, *et al*. Preoperative chemotherapy with epidoxorubicin, docetaxel and capecitabine plus pegfilgrastim in patients with primary breast cancer. Anticancer Drugs. 2005;16:441-5.
18. Schneerweiss A, Bastert G, Huober J, Wallwiener D, Hamerla R, Lichter P. Neoadjuvant therapy with gemcitabine in breast cancer. Oncology. 2004;18:27-31.
19. DeLena M, Zucali R, Viganotti G, Valagussa P, Bonadonna G. Combined chemotherapy radiotherapy approach in locally advanced breast cancer. Cancer Chemother Pharmacol. 1978;1:53-9.
20. Swain SM, Sorace RA, Bagley CS, Danforth DN Jr, Bader J, Wesley MN, *et al*. Neoadjuvant chemotharpy in the combined modality approach of locally advanced non metastatic breast cancer. Cancer Res. 1987;47:3889-94.
21. Hortobagyi GN, Blumenschein GR, Spanos W, Montague ED, Buzdar AU, Yap HY, *et al*. Multimodal treatment of locoregionally advanced breast cancer. Cancer. 1983;51:763-8.
22. Powels TJ, Hickish TF, Makris A, Asley SE, O'Brien SE, Tidy VA, *et al*. Randomized trial of chemo endocrine therapy started before or after surgery for treatment of primary breast cancer. J Clin Oncol 1995;13:547-52.
23. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, *et al*. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 1998;16:2672-85.
24. Wolmark N, Wang J, Fisher B, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl CancerInst Monogr. 2001;30:96-102.
25. Swain SM, Sorace RA, Bagley CS, Danforth DN Jr, Bader J, Wesley MN, *et al*. Neoadjuvant chemotherapy in the combined modality approach of locally advanced non metastatic breast cancer. Cancer Re.s 1987;47:3889-94.
26. Hortobagyi GN, Blumenschein GR, Spanos W, Montague ED, Buzdar AU, Yap HY, *et al*. Multimodal treatment of loco regionally advanced breast cancer. Cancer. 1983;51:763-8.
27. Powels TJ, Hickish TF, Makris A, Ashley SE, O'Brien ME, Tidy VA, *et al*. Randomized trial of chemoendocrine therapy started before or after surgery for treatment of primary breast cancer. J Clin Oncol. 1995;13:547-52.
28. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, *et al*. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 1998;16:2672-85.
29. Buzdar AU, Singletary SE, Theriault RL, Booser DJ, Valero V, Ibrahim N, *et al*. Prospective evaluation of Paclitaxel versus combination chemotherapy with fluorouracil, doxorubicin and cyclophosphamide as neoadjuvant therapy in patients with operable breast cancer. J Clin Oncol. 1999;17:3412-7.
30. Gradishar WJ. Docetaxel as neoadjuvant chemotherapy in patients with stage III

ISSN:0975-3583,0976-2833 VOL13, ISSUE 05,2022

Breast cancer. Oncology. 1997;11:15-8.

31. Amat S, Bougnoux P, Penault-Lorca F, Fetissof F, Cure H, Kwiatkowski F, *et al*. Neoadjuvant Docetaxel for operable breast cancer induces a high pathological response and breast conservation rate. Br J Cancer. 2003;88:1339-45.
32. Philip PA, Thatai LC, Vishnubhotla P, Biernat L, Flaherty L, LoRusso P, *et al*. Phase II study of Doxorubicin, Docetaxel and 5FU in patients with locally advanced breast cancer. Proc Am Soc Cli Oncol. 2000;19:1309.
33. Lee YJ, Doliny P, Gomez-Fernandez C, Powell J, Reis I, Hurley J, *et al*. Docetaxel and cisplatin as primary chemotherapy for treatment of locally advanced breast cancer. Clin Breast Cancer 2004;5:371-6.
34. De Matties A, Nuzzo F, D'Aiuto G, Labonia V, Landi G, Rossi E, *et al*. Docetaxel plus Epirubicin as neoadjuvant treatment in patients with large operable or locally advanced breast cancer. Cancer. 2002;94:895-901.
35. Dhillon PK, Yeole BB, Dikshit R, Kurkure AP, Bray F. Trends in breast, ovarian and cervical cancer incidence in Mumbai, India over a 30-year period, 1976–2005: An age–period–cohort analysi. Br JCancer. 2011;105:723-30.
36. John C. Adjuvant systemic chemotherapy for patients with node positive breast cancer. 40th Annual meeting. New Orleans, LA: American Society of Clinical Oncology; 2004. p. 28-35.
37. De Laurentiis M, Cancello G, D'Agostino D, Giuliano M, Giordano A, Montagna E, *et al.* Taxane-based combinations as adjuvant chemotherapy of early breast cancer: A meta-analysis of randomized trials. J Clin Oncol. 2008;26:44-53.
38. Raina V, Bhutani M, Bedi R, Sharma A, Deo SV, Shukla NK, *et al*. Clinical features and prognostic factors of early breast cancer at a major cancer center in North India. Indian J Cancer. 2005;42:40-5.
39. Min SY, Lee SJ, Shin KH, Park IH, Jung SY, Lee KS, *et al.* Locoregional recurrence of breast cancer in patients treated with breast conservation surgery and radiotherapy following neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys. 2011;81:e697-705.
40. Segal R, Dent SF, Verma S, Gerller S, Young V, GoelR, *et al*. Changingdemographics of locallyadvancedbreastcancer: Data from aregional cancer centre. ASCO 2006.
41. Erol K, Baltali E, Altundag K, Guler N, Ozisik Y, Onat DA, *et al*.Neoadjuvant chemotherapy with cyclophosphamide, mitoxantrone, and 5-fluorouracil in locally advanced breast cancer. Onkologie. 2005;28:81-5.
42. Deo SVS, Bhutani M, Shukla NK, Raina V, Rath GK and Purkaysth J. Randomized trial comparing neo-adjuvant versus adjuvant chemotherapy in operable locally advanced breast cancer. J Surg Oncol 2003;84:192-7.
43. Baldini E, Gardin G, Giannessi P G Evangelista G, Roncella M,Prochilo T, *et al*. Accelerated versus standard cyclophosphamide, epirubicin and 5-fluorouracil or cyclophosphamide, methotrexate and 5-fluorouracil: a randomized phase III trial in locally advanced breast cancer. Ann Oncol. 2003;14:227-32.
44. Segal R, Dent SF, Verma S, Gerller S, Young V, Goel R, *et al*. Changingdemographics of locally advanced breast cancer: Data from a regional cancer centre. ASCO 2006.
45. Yadav BS, Sharma SC, Singh R, Singh G. Patterns of relapse in locally advanced

ISSN:0975-3583,0976-2833 VOL13, ISSUE 05,2022

breast cancer treated with neoadjuvant chemotherapy followed by surgery and radiotherapy. J Cancer Res Ther. 2007;3:75-80.

46. Chen AM, Meric-Bernstam F, Hunt KK, Thames HD, Oswald MJ, Outlaw ED, *et al*. Breast conservation after neoadjuvant chemotherapy: The MD Anderson cancer center experience. J Clin Oncol. 2004;22:2303-12.
47. Raina V, Kunjahari M, Shukla NK, Deo SV, Sharma A, Mohanti BK, *et al*.Outcome of combined modality treatment including neoadjuvant chemotherapy of 128 cases of locally advanced breast cancer: Data from a tertiary cancer center in northern India. Indian J Cancer. 2011;48:80-85.
48. Raina V, Taneja V, Gulati A. Estrogen receptor status in breast cancer. The Indian Practitioner. 2000;53:405-07.
49. Redkar AA, Kabre SS, Mitra I. Estrogen and progesterone receptorsmeasurement in breast cancer with enzyme-immunoassay and correlation with other prognostic factors. Indian J Med Res. 1992;96:1-8.
50. Hortobagyi GN, Ames FC, Buzdar AU, Kau SW, McNeese MD, Paulus D, *et al*. Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy. Cancer. 1988;62:2507-16.