

## Original Research Article

# Neo-adjuvant chemotherapy and the recurrence of breast cancer in a tertiary care rural hospital of West Bengal, India

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## ABSTRACT

**Background:** Prior studies have shown long-term outcome of Neo-Adjuvant Chemotherapy (NACT) for locally advanced breast carcinoma. The purpose of the current study was to analyse the number and pattern of breast cancer recurrence at a rural hospital of West Bengal, India. The study also tried to evaluate the type of therapy received by the recurrent patients during their primary presentation and compare the disease free survival rate of the patients receiving NACT and Adjuvant Chemotherapy (ACT).

**Methods:** A single institution (B.S. Medical College, Bankura) retrospective chart review in the year of 2011-2014 was performed. The Kaplan-Meier methods were used to calculate disease-free survival (DFS) from the date of initiation of NACT to the date of recurrence.

**Results:** Of 776 patients in four years (2011-2014) total numbers of breast cancer recurrent patients were 30. The Kaplan Meier survival analysis showed disease free survival of 5 years (95% confidence interval) in case of early stage breast cancer (EBC) and 2.5 years (95% CI) in locally advanced breast CA (LABC). It was 29 months (95% confidence interval [CI] 26.74-33.253) for recurrence free survival in case of patients treated with NACT and 60 months (95% confidence interval [CI] 58.13-61.86) for recurrence free survival in case of patients not treated by NACT i.e. ACT cases.

**Conclusions:** This study indicates multimodality Neo-Adjuvant chemotherapy helps to achieve complete pathological response in locally advanced breast cancer. Despite the recurrence free survival in NACT patients is significantly low than the patients who received adjuvant chemotherapy.

**Keywords:** ACT, Breast cancer, NACT, Recurrence

## INTRODUCTION

Breast cancer represents 14.1% of all new cancer cases in the U.S. In 2013, it was estimated that there will be 232,340 new cases of breast cancer and an estimated 39,620 people will die of this disease.<sup>1</sup> According to the National Women's Health Information Centre, about 10 percent of patients who receive a lumpectomy and radiation therapy for breast cancer will experience a recurrence within the following 12 years.<sup>2</sup> The risk of

breast cancer recurrence of an individual depends on a variety of factors and the treatment options of breast cancer are dependent upon size of tumour, location and stage of cancer.<sup>3</sup> The goal of chemotherapy given in the adjuvant or neoadjuvant setting in breast cancer is to eradicate occult distant metastases to ultimately improve disease-free survival.

Neoadjuvant chemotherapy (NACT) has been used in locally advanced breast cancer in order to convert a

previously un-resectable cancer into an operable one.<sup>4-6</sup> It has been widely administered in primarily operable breast cancer to reduce tumour volume and allow conservative surgery.<sup>7-9</sup> The down-staging of the primary tumour and the increase in breast conservation rates seems to be the clinical benefit of NACT.<sup>10</sup>

Neoadjuvant chemotherapy also has the capacity to completely clear the breast and axillary lymph nodes of invasive tumour before surgery.<sup>11</sup>

Several randomized clinical trials and a meta-analysis have shown similar survival rates after breast-conserving therapy and after mastectomy in patients with early breast cancer.<sup>12-17</sup> However, most of these observations are on the basis of western population. Little is known about the treatment outcome of breast cancer patients and their recurrence pattern at rural West Bengal, India, where the life-style, socio-economic level, awareness of cancer differ greatly from that of Western countries.

The purpose of the study is to analyse the number and pattern of breast cancer recurrence in the year 2011- 2014 at a rural hospital of West Bengal, India. The study also tried to evaluate the type of therapy received by the recurrent patients during their primary presentation and compare the disease free survival rate of the patients receiving NACT and ACT.

## METHODS

This descriptive study was carried out at B. S. Medical College, Bankura, West Bengal, over a period of four years (January 2011-December 2014). Institutional ethical committee clearance and informed consent from all the subjects were obtained.

### *Patient population*

This is a single Institution study. A retrospective analysis of the hospital records of Department of Surgery and Department of Radiotherapy of Bankura Sammilani Medical College, Bankura, West Bengal, was done. Total number of new Breast cancer patient presented in the Surgery and Radiotherapy OPD in each year was determined and out of this patient total number of recurrent breast cancer cases were identified. A total number of 776 patients were studied.

A recurrence was categorized as local (in case of primary breast conserving treatment, operation scar, or chest wall), regional (in the axillary lymph nodes, or the supra-clavicular region), or distant (metastasis to a distant site or a contra lateral or secondary tumour).<sup>18</sup>

Patients presented with recurrent breast cancer were studied thoroughly about their primary presentation, treatment protocol, disease free survival and pattern of recurrence. Patient demographics, tumour characteristics, treatment including neo-adjuvant and adjuvant systemic

and radiation therapy, recurrence and survival were obtained from both the database and the hospital tumour registry.

In this hospital the diagnosis of breast cancer of all patients was obtained by fine needle aspiration biopsy of the primary tumour and any involved axillary lymph node. Each patient was examined by a multidisciplinary team to confirm the diagnosis.

The staging work-up included a complete history and physical examination, complete blood cell count with differential and platelet counts, blood chemistry analysis, electrocardiography, chest radiograph, abdominal computed tomography or abdominal ultrasonography at presentation and in case of NACT administration after four cycle of chemotherapy.

Breast cancer patients with primary tumours greater than 5 cm (T3), with skin or chest wall involvement (T4), or with matted axillary adenopathy (N2) were defined as having locally advanced breast cancer (LABC). All of the patients were treated with a uniform multimodality regimen that included dose- and time-intense neoadjuvant Inj 5-FU 500 mg/m<sup>2</sup> slow intra-venous, Inj Doxorubicin 50 mg/m<sup>2</sup> slow intra-venous, Inj Cyclophosphamide 500 mg/m<sup>2</sup> dissolved in 5% dextrose to run over 1 hour, cycles repeated every 21 days. Four cycles were followed by surgery.

Clinical responses to neoadjuvant chemotherapy were classified by the following criteria: complete response (CR), a total resolution of the breast tumor and axillary adenopathy based on physical and radiographic examination; partial response (PR), a 50% or greater reduction of the product of the two largest perpendicular dimensions of the breast mass and axillary adenopathy; minor response (MR), a less than 50% reduction of the product of the two largest perpendicular dimensions of the breast mass and axillary adenopathy; no change in clinical status; and progressive disease.<sup>19</sup>

A complete pathological response (pCR) was defined as having no residual invasive tumor in the breast surgical specimen removed following neoadjuvant therapy; patients with residual carcinoma in situ were considered to have a pCR.<sup>20</sup> Responding patients underwent modified radical mastectomy with level III axillary clearance after four cycles of chemotherapy. Two cycles of chemotherapy with same regimen was given after surgery in LABC patients.

Early stage breast cancer and node negative patients were treated with modified radical mastectomy with axillary clearance followed by six cycles of adjuvant chemotherapy with Inj 5-FU 500 mg/m<sup>2</sup> slow intra-venous, Inj Doxorubicin 50 mg/m<sup>2</sup> slow intra-venous, Inj Cyclophosphamide 500 mg/m<sup>2</sup> dissolved in 5% dextrose to run over 1 hour, cycles repeated every 21 days. In node positive cases Taxane based regime was used.

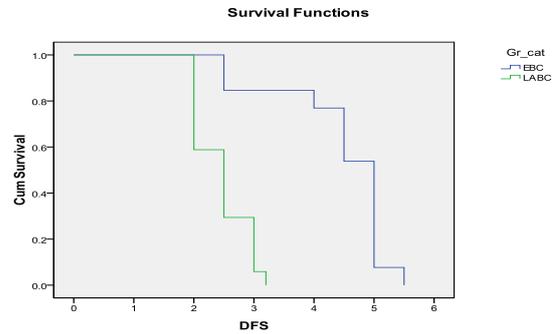
**Statistical analysis**

The Kaplan–Meier methods were used to calculate disease-free survival (DFS) from the date of initiation of NACT to the date of recurrence. Comparisons were made using Log-Rank test.

**RESULTS**

Of 776 patients in four years (2011, 2012, 2013, 2014) total breast cancer recurrent patient were 30 (Table 1 and 2). 53.3% (n=16) of recurrent patients were initially presented with LABC and all of them received NACT for it. All of these patients achieved complete pathological response after NACT treatment. The average disease free survival of these patients was 2.4 years (Table 3 and 4). 46.66% (n=14) of recurrent patients were initially presented with early stage breast cancer. 11 of them received post-operative chemotherapy (ACT) and 3 of them got NACT as treatment protocol. The average disease free survival of early breast cancer patients were

4.8 years. 3 of the early stage breast cancer patient who received NACT had average disease free survival of 2.3 years (Table 3 and 4).



Time in years, EBC-Early stage breast cancer, LABC-Locally advanced breast cancer

**Figure 1: Survival analysis (time in years) according to initial tumour grading**

**Table 1: Total no of breast cancer patients in different Departments in 2011-2014.**

Year	Total No of Breast cancer patients attended Radiotherapy & Surgery dept.			No of Recurrent patients out of total patients		
	RTD	Surgery	Total	RTD	Surgery	Total
2014	173	49	222	1	8	09
2013	155	50	205	2	6	08
2012	160	46	206	3	2	05
2011	105	43	143	1	7	08

**Table 2: Recurrence events in four years.**

	2014 (n=09)	2013 (n=08)	2012 (n= 05)	2011 (n=08)
Local	06	08	03	04
Regional	03	-	03	04
Distant	-	-	-	-

**Table 3: Clinico-pathological features of recurrent breast cancer patients.**

	Total number of recurrent patient (n)	Treatment regime	pCR achieved after NACT	Average disease free survival
2014	n=09	NACT+MRM+CT (n=05)	n=05	2.5 years
		MRM+CT (n=04)	n=0	5 years
2013	n=08	NACT+MRM+CT (n=05)	n=05	2.7 years
		MRM+CT (n=03)	n=0	4.6 years
2012	n=05	NACT+MRM+CT (n=03)	n=03	2 years
		MRM+CT (n=02)	n=0	4.75 years
2011	n=08	NACT+MRM+CT (n=06)	n=06	2.25 years
		MRM+CT (n=02)	n=0	5 years

MRM= Modified Radical Mastectomy.

Figure 1 shows Kaplan Meier curve for disease free survival time according to initial tumour grading. Disease

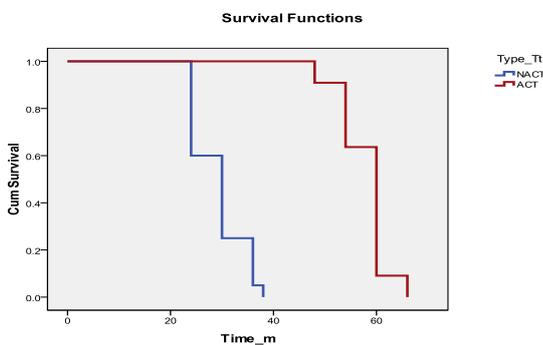
free survival is significantly affected by initial tumor grading. It is 5 years (95% confidence interval) in case of

early stage breast cancer (EBC) and 2.5 years (95% CI) in locally advanced breast CA (LABC). In Figure 2 the Kaplan Meier survival analysis showed 29 months (95% confidence interval [CI] 26.74-33.253) for recurrence free

survival in case of patients treated with NACT and 60 months (95 % confidence interval [CI] 58.13-61.86) for recurrence free survival in case of patients not treated by NACT i.e. ACT cases.

**Table 4: Treatment pattern of recurrent breast cancer patients in four consecutive years and average disease free survival.**

LABC (n=16, 53.3%)		Average disease free survival	Early Breast cancer pt (n=14, 46.66%)	Average disease free survival	Average disease free survival	
NACT	ACT	2.4 years	ACT	4.8 years	NACT	2.33 years
16	-		11		3	



Time in months, NACT- neo-adjuvant chemotherapy, ACT- adjuvant chemotherapy

**Figure 2: Survival analysis of cancer patients according to type of therapy.**

**DISCUSSION**

In the present study it was found that locally advanced breast cancers recur more commonly than that of the early stage breast cancer cases. This is in agreement of previous studies done by Levy A et al and Newman LA.<sup>21,22</sup>

The present study also showed that all the patients who received NACT for their initial treatment achieved complete pathological response (cPR) before surgery. This observation is comparable with that of Henry M. Kuerer et al who demonstrated that neo-adjuvant chemotherapy has the capacity to completely clear the breast and axillary lymph nodes of invasive tumours before surgery.<sup>10</sup> Hung WK et al, Stuart A McIntosh et al Poole GV et al also showed the same response in their studies.<sup>23-25</sup>

All the 16 LABC patients who had recurrence in the present study received full course of NACT treatment and achieved complete pathological response after it. Nevertheless their average recurrence free survival was 2.8 years. Whereas the average recurrence-free survival of patients who did not receive NACT was found to be

4.8 years. Surprisingly, 3 early stage breast cancer diseases in our study who received NACT as their initial treatment also showed average disease free survival comparable to LABC patients. This finding contradicts with the observations of the previous studies that showed LABC patients who have achieved cPR after NACT have a significantly improved disease free survival rate.<sup>26</sup> Although a Meta-analysis done by Davide Mauri et al showed that neo-adjuvant therapy was apparently equivalent to adjuvant therapy in terms of survival and overall disease progression. They also pointed out, NACT compared with ACT, was associated with a statistically significant increased risk of loco-regional recurrence when radiotherapy without surgery was adopted.<sup>27</sup>

The possible explanation of decrease in recurrence free survival of patients who achieved complete pathological response after NACT may be given by some very recent advances in cancer therapy that deals with cancer stem cells. Few recent studies have demonstrated that Neo-adjuvant Chemotherapy for breast cancer can cause release of tumour cells and increases circulating tumour cells.<sup>28,29</sup> Increase in number of circulating cancer stem cells in circulation after NACT in breast cancer was also demonstrated in some studies.<sup>30-32</sup> This dislodgment of cancer stem cells in circulation may sort out future direction of cancer chemotherapy.

**Limitations**

This is a single institution study. The hormone receptor status of the breast cancers could not be done due to financial constraints of the patients. The pre-op breast imaging was also not performed in this rural medical college.

**CONCLUSION**

This study indicates multimodality Neo-Adjuvant chemotherapy helps to achieve complete pathological response in locally advance breast cancer. Despite the recurrence free survival in NACT patients is significantly

low than the patients who received adjuvant chemotherapy.

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