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Original Research Article

Clinicopathological Study of CA Breast with Neoadjuvant Chemotherapy

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Abstract

Introduction: Breast Cancer (BC) is the most common diagnosed cancer among women in India. With the advent of population growth, changes in the lifestyle and migration from rural to urban areas, there is increase in Breast Cancer. The age adjusted incidence as high as 25.8 per 1,00,000 women and mortality 12.7 per 1,00,000 women. Locally advanced breast cancer (LABC) is a subset of breast cancer characterized by the most advanced breast tumor in the absence of distant metastasis. Neoadjuvant chemotherapy is the primary chemotherapy given to patient prior to surgery. This has been used for treatment of LABC with development and testing of increasingly effective agents particularly anthracyclines, dramatic response had been seen in significant proportion of patients.

Aim and Objective: Main objective is to evaluate the clinical /pathological response of primary tumor and lymph node to Neoadjuvant chemotherapy.

Methods: 58 female patients admitted to M.K.C.G. Medical College and Hospital after confirmation of LABC by core needle biopsy from 2019 to 2021 and was evaluated clinically with detailed history of the patients, physical examination of breast and axilla. Investigation like CBC, LFT, RFT and USG/MRI of Breast, axilla, abdomen, and Chest X-ray etc. are done. A prospective study was done with ethical clearance from ethical committee of M.K.C.G. Medical College & Hospital, Brahmapur, Odisha.

Observation: Overall occurrence of complete clinical response is 24% with maximum response is seen in triple negative breast cancer which is 38% and least in luminal B Her-2 positive where none shows complete clinical response. Complete clinical response is 42% in stage IIIA tumours which is more compared to stage IIIB tumours which is 9%.

Conclusion: Response to Neo adjuvant chemotherapy (NACT) is more in triple negative tumour compared to hormone receptor positive tumours where endocrine therapy along with chemotherapy plays a major role. Nodal status of the patients is an important prognostic factor as the clinically nodal negative patients has better response than the clinical nodal positive patients. More and more the LABC patients should be study with new drug regimen before surgery.

Keywords: Breast Cancer (BC), Locally Advanced Breast Cancer (LABC), Neoadjuvant Chemotherapy.

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer among women in India. With the advent of population growth, changes in the lifestyle, and migration from rural to urban areas, there is an increase in the incidence in BC in developing countries [1-5]. Earlier cervical cancer was most common cancer in Indian woman but now the incidence of BC has surpassed cervical cancer and is leading cause of cancer death [6,7].

Breast Cancer has ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100,000 women and morality 12.7 per 100,000 women. The age adjusted incidence rate of carcinoma of the breast was found as high as 41 per 100,000 women for Delhi, followed by Chennai (37.9), Bangalore (34.4) and Thiruvananathpuram District (33.7). A statistically significant increase in age adjusted rate over time (1982-2014) in all the PBCRs namely Bangalore (annual percentage change : (2.84%), Barshi (1.87%), Bhopal (2.00%), Chennai (2.44%), Delhi (1.44%) and Mumbai (1.42%) was observed. Mortality-to-incidence ratio was found to be as high as 66 in rural registries whereas as low as 8 in urban registries. Besides this, young age has been found as a major risk factor for breast cancer in Indian women [8].

Locally advanced breast cancer (LABC) is a subset of BC characterized by the most advanced breast tumours in the absence of distant metastasis [9].

Neo-adjuvant chemotherapy is the primary chemotherapy given to patient prior to surgery or radiotherapy. This has been used for treatment of LABC. With development and testing of increasingly effective agents particularly

anthracyclines, dramatic responses had been seen in significant proportion of patients [10-11]. Thus leading to interest in breast conservation treatment (BCT) in larger tumours and to the use of Neo-adjuvant chemotherapy in less advanced operable breast cancer [12-13].

Neo-adjuvant chemotherapy is having a number of theoretical and practical advantages in treatment of LABC including [10-13].

- Early treatment of Micro-metastasis.
- Limiting the rapid growth of metastatic foci after removal of primary tumour.
- Decreased emergence of chemo resistant clones.
- Extension of BCT to more patients with larger tumours.
- Perhaps greatest potential advantage of the approach is opportunity to observe clinical responses to treatment and to assess the effect by pathological examination of surgical specimen. Furthermore, if clinical / pathological response of primary tumour to Neoadjuvant chemotherapy correlates with or predicts the response of metastasis and the prognosis of the patient such as overall survival, it could greatly accelerate progress in designing newer treatmen [14-17].
- Though Neoadjuvant CT in the treatment of LABC had been used in clinical trials for the past 2 decades in the developing world, not many studies have been conducted in developing countries like ours, where LABC constitutes about 50% of cases. Hence this study was planned to evaluate the

clinico/ pathological response to Neoadjuvant CT in the treatment of LABC [18-21].

Aim and Objectives

To evaluate the clinical/pathological response of primary tumor and lymph node to Neoadjuvant chemotherapy.

Materials and Methods

Study Population: The study population are the female patients with breast lump attending the Surgery OPD in the MKCG Medical College & Hospital, Brahmapur, Odisha.

Study Design: Prospective Study.

Study Period: The study was conducted from July 2019 to June 2021

Place of Study: PG Department of Surgery, MKCG Medical College & Hospital, Brahmapur, Odisha.

Inclusion Criteria

1. Patients with breast tumor with size >5cm with mobile axillary lymph node.
2. Patients with breast tumor of any size with skin fixity.
3. Patient with breast tumor of any size with ipsilateral fixed axillary lymph node.
4. Patient with breast tumor of any size with chest wall fixity.

Exclusion Criteria

1. Patients with Bilateral breast cancer.
2. Patients with Inflammatory breast cancer.
3. Patients with multiple masses in single breast.
4. Pregnant female with breast cancer.
5. Patients with severe hepatic, renal or cardiac dysfunction.
6. Patients who are not willing for the study.
7. Patient with clinical evidence of distant metastasis.
8. Patient with other proven malignancies.
9. Patient with recurrent breast cancer.

Methods

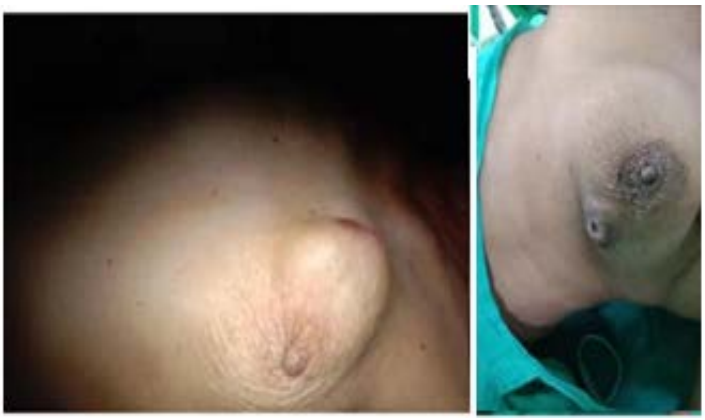
1. This is a prospective hospital-based study that was conducted in the department of general surgery along with the cooperation of department of radiotherapy in MKCG Medical College & Hospital, Brahmapur, Odisha.
2. All the female patients with breast lump to surgery OPD were examined and were subjected to CORE NEEDLE BIOPSY (CNB). Patients with biopsy proven LABC were admitted in the surgery inpatient ward.
3. Patients after admission were evaluated clinically with detailed history of the patient along with physical examination of the Breast and axilla, systemic examination of the cardiovascular system, respiratory system, and kidney function by using hematological and biochemical tests along with 2D Echocardiogram.
4. Patients in reproductive age were subjected to urine pregnancy test to know the active pregnancy status.
5. Patients were subjected to imagine studies like mammography, Ultrasonogram of breast and Axilla, MRI Breast and Axilla, High-resolution computed tomography (HRCT) Chest, Contrast-enhanced computed tomography (CECT) abdomen, Noncontract computed tomography (NCCT) Brain to assess the loco regional disease and distant metastasis. Then the initial values obtained from the physical examination, mammogram, Ultrasonogram, MRI and CNB were noted and keep them as baseline values before initiating Neo Adjuvant Chemotherapy.
6. The patients were subjected to 4 cycles of Neo Adjuvant chemotherapy. After 4 weeks from completion of the last cycle

of Neo Adjuvant chemotherapy the patient were assessed for response clinically by using physical examination of the breast and Axilla, Ultrasonogram of breast and Axilla, mammography and MRI and then patients underwent MRM who are fit for the surgery.

7. The pathological response was assessed after histo-pathological study of the resected primary tumour and regional lymph nodes after the surgery. OR in case of patients who do not underwent surgery CNB of breast and FNAC of the Lymph node were done to assess the pathological response.
8. The clinical response rates were calculated by comparing the post – chemotherapy value with pre-chemotherapy baseline values.
9. The patients were followed up for 6 months after the surgery or recording a complete pathological response. It was once in 2 weeks for first month and once monthly for newt 2 months and final visit were at the end of 6th month with first check-up were done after 14 days post operation. A total of 5 follow up checkup were done.
10. No other investigations in asymptomati patients were performed to detect the metastasis, since it was not cost effective, and it did not prolong the survival.
11. During the follow up period they were examined for the following actors,
12. Local Recurrence and Development of metastasis.

Local recurrence: Recurrence in the post mastectomy chest wall was most common in the first two years, so the patient was examined for any nodule in the post mastectomy chest wall.

Metastasis: Patient after mastectomy go on to develop metastasis. About 80% develop metastasis in about 5 to 10 years. So, patients during the follow up period need to be checked for metastasis. Patients were enquired for symptoms of metastasis like bone pain, headache, dyspnoea, haemoptysis, jaundice, and seizures. They were subjected to investigations like X-ray Chest, Ultrasonogram of the liver, X-ray of the Lumbar spine, alkaline phosphatase levels and CT brain to rule out metastasis.



(A&B): (LABC – Local Advanced Breast Cancer)

Results and Discussion

Table 1: AJCC stage-wise distribution of patients

Stage	No. of patients	Percentage
Stage IIIA	26	45%
Stage IIIB	32	55%
Stage IIIC	--	--

Based on the TNM stage grouping, the patients were categorized into 3 groups under stage III. Out of 58 patients (45%) were categorized under Stage IIIA. 18 patients (55%) were categorized under Stage IIIB. There were no patients under State IIIC.

Table 2: Age wise distribution of patients

Age	No. of patients	Percentage
< 50 years	28	48%
> 50 years	30	52%

Table 2 summarizes the patients according to age group, out of the 58 subjects enrolled, 28 patients (45%) were less than 50-year age group. 30 patients (52%) were aged above 50 years.

Table 3: Molecular types of patients

Molecular type	No. of patients	Percentage
Luminal A	13	22%
Luminal B Her 2 positive	15	25%
HER 2 positive Non luminal	9	15%
Triple negative	21	37%

Table 3 summarizes the number of patients belong to different molecular subtypes of the breast cancer. Out of 58 patients 13 patients (22%) are luminal A, 15 patients (26%) are Luminal B Her 2 positive, 9 patients (15%) are HER 2 positive Non luminal and 21 patients (37%) are Triple negative.

Table 4: Clinical response of patients

Clinical response	No. of patients	Percentage
Clinical complete response	14	24%
Clinical partial response	25	43%
No. response or stable disease	11	19%
Progressive Disease	8	14%
Total	58	100%

Table 4 shows that, the clinical response of 58 patients, out of the 58 patients the overall objective clinical response of 67% was observed. Complete clinical response of 14 Patients (24%) was noted. Partial clinical response was noted in 25 patients (43%). No response was observed in 11 patient (19%). However, 8 patients (14%) showed progressive disease. Out of the 8 patients, 3 of them had developed supraclavicular node, and 4 patients developed vertebral metastasis and 1 patient developed cerebral metastasis.

In similar studies conducted by Maraz B, Boross G, Cyanti *et al* an overall objective response of 60%, complete clinical response of 4%, partial clinical response of 56% had been reported. In their study there were no progressive disease observed after Neo adjuvant chemotherapy.

Table 5: Clinical response according to staging of breast cancer

Stage	No. of patents with Clinical				Percentage of Clinical response			
	CCR	CPR	NR	PD	CCR	CPR	NR	PD
Stage IIIA	11	8	5	2	42%	31%	19%	8%
Stage IIIB	3	17	6	6	9%	53%	19%	19%

Table – 5 shows that, compares clinical response of patients categorized under different groups of stage III Total of 26 patients were categorized under stage IIIA. Among the 26 patients complete clinical response was observed in 11 patients (42%), partial clinical response seen in

8 patients (31%), 5 patients (19%) showed no response. Progressive disease was seen in 2 patients (8%).

Table 6: Clinical response according to molecular types

Molecular type	Total Case	CCR		CPR		CNR		PD	
Luminal A	13	3	23%	4	30%	4	30%	2	17%
Luminal B : Her 2 Positive	15	-	-	9	60%	3	20%	3	20%
HER 2 positive: Non luminal	9	3	33%	3	33%	1	12%	2	22%
Triple negative	21	8	38%	9	43%	3	14%	1	5%

Table 7: Pathological response of patients

Pathological response	No. of patients	Percentage
Pathological complete response (PCR)	12	23%
Pathological Non-Responders (PINV)	42	77%

Among the 32 patients grouped under stage IIIB, 3 patients (%) showed complete clinical response, 17 patients (53%) showed partial clinical response, no response was detected in 6 patients (19%), progressive disease was observed in 6 patients (19%)

In our study, percentage of complete response was higher for patient, in stage IIIA than for the patient in stage IIIB. In a similar study conducted by Hortobogyi, Ames and Ruzdar *et al*, in the department of Medical Oncology, in Anderson Hospital, Houston, it was reported that complete clinical response after Neo adjuvant chemotherapy was better for patient in stage IIIA then for patient in stage IIIB.

Table 6 compares clinical response of patients categorized under different molecular subtypes. Out of 13 patients luminal A Complete clinical response was observed in 3 patients (23%), partial clinical response seen in 4 patients (30%). 4 patients (30%) showed no response. Progressive disease was seen in 2 patients (17%).

Out of 15 patients Luminal B Her 2 positive complete clinical response was observed in none of the patients, partial clinical response seen in 9 patients (60%). 3 patients (20%) showed no response. Progressive disease was seen in 3 patients (20%)

Out of 09 patients HER 2 positive Non luminal Complete clinical response was observed in 3 patients (33%), partial clinical response seen in 3 patients (33%). 1 patient (12%) showed no response. Progressive disease was seen in 2 patients (22%).

Out of 21 patients Triple Negative Complete clinical response was observed in 8 patients (38%), partial clinical response seen in 9 patients (43%), 3 patients (14%) showed no response. Progressive disease was seen in 1 patient (05%).

Out of 58 patients, 54 patients were operated, and 4 patients are not operated due to vertebral metastasis – PCR rates calculated taking the 54 operated patients as total for assessing the response.

Table 8: Pathological response according to staging

Stage	PCR	Percentage	PCR	Percentage
Stage III A	8	30%	18	70%
Stage III B	4	14%	24	86%

Table 7, out of the 54 patients operated 12 patients (23%) showed pathological complete response (PCR) and remaining 42 patients showed invasive tumor cells (PINV) in the specimen. 4 patients are not operated and received radiotherapy for vertebral metastasis.

Table 8 compares the pathological response of patient in our study group categorized under stage IIIA and Stage IIIB.

Out of the 26-patient grouped under stage IIIA, 8 patients (30%) showed complete pathological response and 18 patients were pathological non responders (70%). Out of 32 patients included under stage IIIB 4 patients are not operated and received radiotherapy for vertebral metastasis. Then from 28 patients who underwent surgery 4 (14%) showed complete pathological response and 24 (86%) patients were pathological non responders (77%).

Table 9: Pathological response according to molecular types

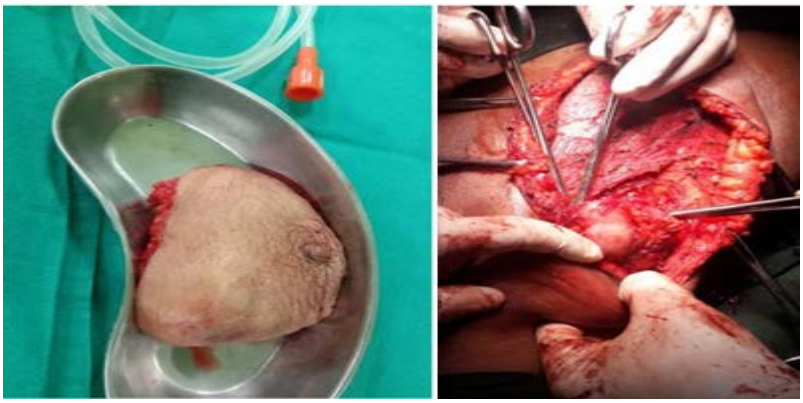
Molecular Type	PCR		PINV		Total
	No.	%	No.	%	
Luminal A	3	27%	8	73%	11
Luminal B : Her 2 Positive	0	00	13	100%	13
HER 2 positive Non luminal	2	22%	7	78%	9
Triple negative	7	33%	14	67%	21

The GeparTri trial found, NACT with decetaxel, doxorubicin and cyclophosphamide (TAC) produced a PCR of 21% (Papademetriou *et al*., 2010).

Table shows pathological response based on molecular types.

Out of 13 patients of Luminal A type pathological Complete response was observe in 3 patients (27%), invasive cells seen in 8 patients (73%).

Out of 15 patients of Luminal B Her 2 positive type pathological Complete response was observed in none of the patients, invasive cells seen in 13 patients (100%).



(C) (D)

(C) & (D): Resected Breast Mass after Neo Adjuvant chemotherapy.

Out of 9 patients of Her 2 positive non-luminal type pathological complete response was observed in 2 patients (22%), invasive cells seen in 7 patients (78%). Out of 21 patients tipple negative type pathological complete response was observed in 7 patients (33%), invasive cells seen in 14 patients (67%).

Table 10: Resected tumor margin status according to stage

Stage	No. of patients with resected margin free of tumor	Percentage
Stage IIIA	25/26	96%
Stage IIIB	27/28	96%
Total	52/54	96%

Out of 58 patients 54 patients undergone surgery with 4 patients in stage IIIB undergone radiotherapy and they did not undergo surgery. Table 10 shows number of patients with resected margin free of tumor in stage IIIA and Stage IIIB. There were 25 (96%) patients with resected margin free of tumour out of 26 patients operated in stage IIIA. Among 28 patients undergone surgery in stage IIIB, 27 (96%) were found to have resected margin free of tumor. Hence over all tumor free resected margin of 96% was detected in our study.

A similar study conducted by Allassus, Chuq, Burton *et al*, had reported tumor free resected margin of 92% in patients of LABC in stage III after Neo-adjuvant chemotherapy.

Table 11: Nodal status of the patients

Nodal Status	No. of patients	Percentage
Clinical node negative (cN-ve)	9	15%
Clinical node positive (cN+ve)	49	85%
Total	58	100%

Table 11 shows the nodal status of patients with respect to the stage. Out of the 58 patients 9 patients (15%) are Clinical node negative (cN-ve) and remaining 49 patients (85%) are clinical node positive (cN+ve).

Table 12: Pathological response according to nodal status

Nodal Status			No. of patients	PC	Percentage
Clinical (cN-ve)	node	negative	09	3	33%
Clinical (cN+ve)	node	positive	49	09	18%

Table 12 shows pathological response with respect to nodal status. Out of the 09 patients of the Clinical node negative (cN-ve) 03 patients (33%) show pathological complete response.

Out of the 49 patients of the Clinical node positive (cN-ve) 09 patients (18%) show pathological complete response.

A study conducted by Mamtani *et al* shows a PCR rate of 49% for nodal positive breast cancer.

Table 13: Incidence of metastasis

Stage	No. of patients	No. of patients with metastasis	Follow up period	Response of the patient with metastasis to NACT	
				Clinical	Pathological
Stage IIIA	26	1	5 months	CNR	PINV
Stage IIIB	32	1	4 months	CPR	PINV

During the follow up period, 1 patient in stage IIIA who was assessed to have clinical no response / histopathologically invasive cell was detected to have pulmonary metastasis after a period of 5 months.

Another patient categorized under stage IIIB was detected to have cerebral metastasis after a period of 4 months; this patient has clinical partial response / histopathologically invasive cell.

It was evident from the above-mentioned facts in our study that patients, who had a complete clinical response, had a comparably good prognosis than those

patients who showed a partial or no response to Neo adjuvant chemotherapy.

Conclusion

From this study it was evident that

- Response to Neo adjuvant chemotherapy (NACT is more in triple negative tumor compared to hormone receptor positive tumors where endocrine therapy along with chemotherapy plays a major role.
- NACT could downstage the disease so as to make the inoperable tumor to operable one and to plan breast conservation for operable disease.
- Patients who show better response to chemotherapy are shown to have good prognosis.
- Patients who did not respond to NACT or who showed disease progression during NACT were predicted to have poor prognosis compared to those who had shown objective response to NACT.
- NACT also made it possible to resect locally advanced disease with tumor free margin in most cases.
- Nodal status of the patient is an important prognostic factor as the clinically nodal negative patients has better response than the clinical nodal positive patients.
- More and more the LABC patients should be studied with new drug regimen before surgery.

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