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To Compare the Effects of Adjuvant and Neoadjuvant Chemotherapy on Outcome of Stage Iii Carcinoma Breast

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Abstract
Introduction: *Carcinoma breast accounts for 26% of all newly diagnosed cancers in females and are responsible for 15% of the cancer related death in women. It is seen rarely before the age of 30. Thereafter, its incidence rises rapidly. In developing countries, it accounts for 1% -3% deaths. It causes 5,19,000 deaths in a year world wide about 9,00,000 women are diagnosed per year. Incidence of breast cancer is 0.26/1,00,000 in males and 20.01/1,00,00 in females.*
Materials and Methods: *This is a comparative observational study conducted at Rajendra Institute of Medical Sciences, Ranchi from January 2018 to December 2019, which included patients of TNM stage IIIA and IIIB breast carcinoma, half of whom were treated with adjuvant chemotherapy and other half were treated with neoadjuvant chemotherapy along with standard surgical procedure like MRM/toilet mastectomy. Thereafter parameters required for evaluation of outcome were studied. Data was collected through preformed proformas. Patients aged less than 70 years with clinically palpable, primary breast cancer confirmed by Tru-Cut biopsy/FNAC with hormonal status and Her2 neu status and fit for treatment with surgery, cytotoxic chemotherapy, were considered eligible for the study. The total sample size 40 cases (stage 3 breast cancer) 20 patients in each group. If age <40 years USG b/l breast with axilla or histopathology size will be a guide to assess size of tumour12. If age > 40 mammography or histopathology size will be a guide for tumour size.The staging of the patient was done using TNM classification.All female patients of stage III carcinoma breast with histopathological negative margins (R0 resections) in their surgical interventions, and who gave consent to participate in study were included in the study.*
Results: *Distribution of patients according to presence of lymphovascular Invasion was done which was statistically non-significant. However, when disease recurrence or disease metastasis/mortality was compared with lymphovascular invasion in neo-adjuvant group, it was found to be statistically significant (p value=0.022) In the adjuvant group 90 % of patients belonged to stage IIIA while in neo-adjuvant group only 50 % patients belonged to stage IIIA. Rest patients in both group belonged to stage IIIB. This difference in adjuvant and neo-adjuvant group was statistically significant. (p=0.022) In comparison of outcome in both adjuvant and neo-adjuvant chemotherapy, 5% patients of adjuvant group developed metastasis and died succumbing to it while another 5 % developed recurrence during follow up. In the neo-adjuvant group 35% patients developed distant metastasis or died due to disease while another 5 % patient developed local recurrence in axilla for the disease. This difference in the outcome of two groups was statistically significant with p value of 0.013.*
Conclusion: *In our study we found that for a locally advanced breast cancer patient (stage IIIA &B) with an operable breast lump, adjuvant chemotherapy is superior than neo-adjuvant chemotherapy with a significant p value of 0.013. Superior in terms of lesser distant metastasis/recurrence when we followed up the patient for 1 year after the completion of treatment.*
Key Words: *Carcinoma breast, TNM, lymphovascular Invasion, USG.*

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I. Introduction

Carcinoma breast accounts for 26% of all newly diagnosed cancers in females and are responsible for 15% of the cancer related death in women. It is seen rarely before the age of 30. Thereafter, its incidence rises rapidly.[1] In developing countries, it accounts for 1% -3% deaths. It causes 5,19,000 deaths in a year world wide about 9,00,000 women are diagnosed per year. Incidence of breast cancer is 0.26/1,00,000 in males and 20.01/1,00,00 in females.[2] While mortality associated with breast cancer is 1.20/1,00,000 in males and 4.32/1,00,000 in females. Deaths from breast cancer have increased during the past 60 years in every country.[3]

Neoadjuvant chemotherapy [NACT] also known as primary systemic therapy or induction therapy has become an integral part in the management of LABC. Many inoperable tumours reduce in size after

chemotherapy (down staging) making the tumour operable.[4]The response to neoadjuvant chemotherapy influences surgical management and also facilitates to plan about the further adjuvant chemotherapy.[5] The reduction in tumour size also makes breast conservation surgery feasible in certain cases. All the tumours do not respond in the same manner. Response is assessed by tumour size measurement before and after chemotherapy.[6]

We wanted to study the outcome,assess the local recurrence,determine systemic metastasisand compare the outcome of chemotherapy as well asresponse in terms of recurrence and metastasis,of adjuvant and neoadjuvant chemotherapy of stage III carcinoma breast.

II. Materials And Methods

This is a comparative observational study conducted at Rajendra Institute of Medical Sciences, Ranchi from January 2018 to December 2019,which included patients of TNM stage IIIA and IIIB breast carcinoma, half of whom were treated with adjuvant chemotherapy and other half were treated with neoadjuvant chemotherapy along with standard surgical procedure like MRM/toilet mastectomy. Thereafter parameters required for evaluation of outcome were studied.Data wascollected throughpreformed proformas.Patients aged less than 70 years with clinically palpable, primary breast cancer confirmed by Tru-Cut biopsy/FNAC with hormonal status and Her2 neu status and fit for treatment with surgery, cytotoxic chemotherapy, were considered eligible for the study.The total sample size 40 cases (stage 3 breast cancer) 20 patients in each group.If age <40 years USG b/l breast with axilla or histopathology size will be a guide to assess size of tumour12. If age > 40 mammography or histopathology size will be a guide for tumour size.The staging of the patient was done using TNM classification.All female patients of stage III carcinoma breast with histopathological negative margins (R0 resections) in their surgical interventions, and who gave consent to participate in studywere included in the study.

Exclusion Criteria:

- Patients who have already taken neoadjuvant therapy prior to admission.
- Patients with positive surgical margin.
- Patient not tolerating chemotherapy.
- Stage I breast cancer, Stage II breast cancer, Stage IIIc breast cancer, Stage IV breast cancer, patients with distant metastasis.

Patients in whom primary defect closure was possible were directly subjected to MRM followed by adjuvant chemotherapy.Patients in whom primary defect closure was not possible, they first underwent neoadjuvant first line of chemotherapy.In case of response, patient underwent completion of chemotherapy neoadjuvantly. Patients who had partial response or clinical progressive disease to first line chemotherapy at the end of 3 cycles were subjected to 2ndline of chemotherapy with paclitaxel.On completion of chemotherapy, Responders (clinical size decrement of more than 50 %) underwent modified radical mastectomy followed by adjuvant therapy. Non-responders/partial responders/progressive responders underwent palliative mastectomy followed by adjuvant chemotherapy. Patients were followed for 1 year once every3months. At every follow-up we examined local site, axilla, supraclavicular region, USG abdomen, and required investigations if symptoms of systemic metastasis were present.

Statistical Analysis: Statistical analysis was done by using descriptive and inferential statistics using chi square test, student's unpaired t test and Multiple Regression Analysis and software used in the analysis were SPSS 24.0 version and GraphPad Prism 7.0 version and $p<0.05$ is considered as level of significance.

III. Results

Distribution of patients according to presence of lymphovascular Invasion was done which was statistically non-significant. However, when disease recurrence or disease metastasis/mortality was compared with lymphovascular invasion in neo-adjuvant group, it was found to be statistically significant (p value=0.022) In the adjuvant group 90 % of patients belonged to stage IIIA while in neo-adjuvant group only 50 % patients belonged to stage IIIA. Rest patients in both group belonged to stage IIIB. This difference in adjuvant and neo-adjuvant group was statistically significant. (p=0.022) In comparison of outcome in both adjuvant and neo-adjuvant chemotherapy, 5% patients of adjuvant group developed metastasis and died succumbing to it while another 5 % developed recurrence during follow up. In the neo-adjuvant group 35% patients developed distant metastasis or died due to disease while another 5 % patient developed local recurrence in axilla for the disease. This difference in the outcome of two groups was statistically significant with p value of 0.013.

S.No	Lymphovascular Invasion	Adjuvant	Neo- Adjuvant	X^2 Value
1	Yes	18 (90%)	14 (70%)	
2	No	2 (10%)	6 (30%)	2.50
3	Total	20 (100%)	20 (100%)	P=0.11

Table 1: Distribution of Patients in to Two Groups According to Lymphovascular Invasion

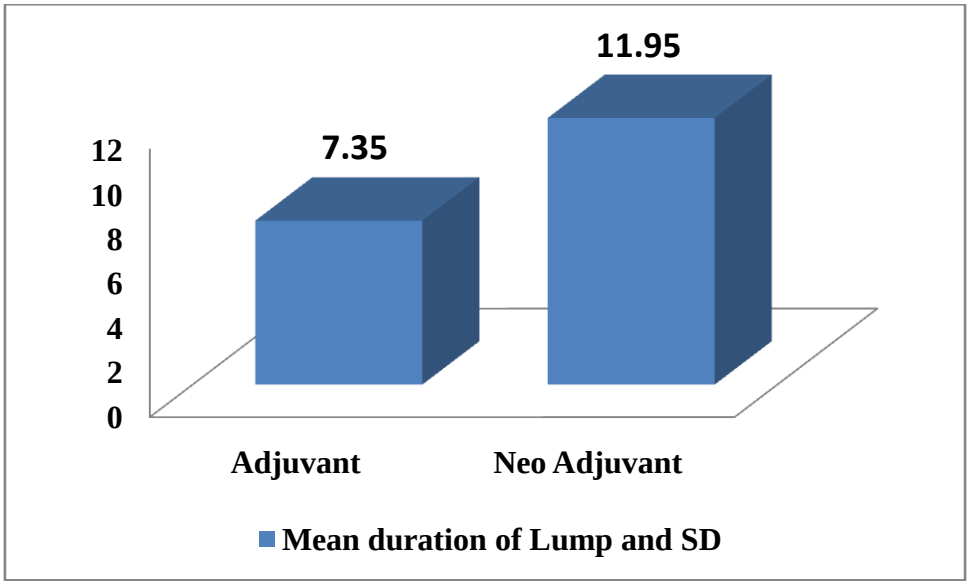

Figure 1: Distribution of Patients in to Two Groups According to the Duration of Lump

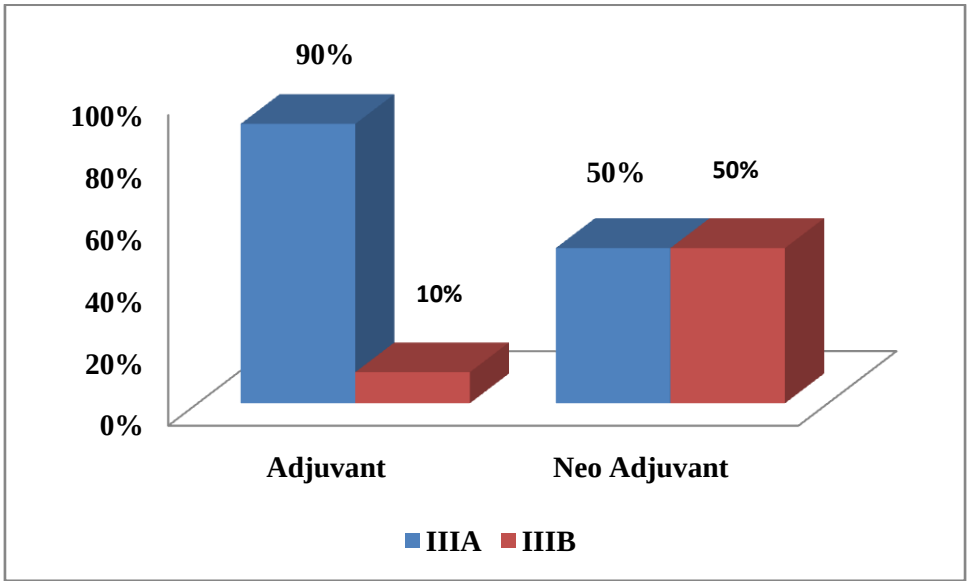

Figure 2: Distribution of Patients in toTwo Groups According to TNM Stage

Model	Unstandardized coefficients		Standardized coefficients	t	P Value
	B	Std.Error	Beta		
Mortality/ Recurrence/Metastasis	-2.625	1.420			
Type of malignancy	-	-	-	-	-
Lymphovascular invasion	2.375	0.891	0.618	2.665	0.022, S
BR grading	0.437	0.446	0.228	0.982	0.347, NS

Table 2: Multivariate Analysis of Mortality/Recurrence with Type of Malignancy, Lymphovascular Invasion and BR Grading in Neoadjuvant Group

In comparison of outcome in both adjuvant and neo-adjuvant chemotherapy, 5% patients of adjuvant group developed metastasis and died succumbing to it while another 5 % developed recurrence during follow up. In the neoadjuvant group 35% patients developed distant metastasis or died due to disease while another 5 % patient developed local recurrence in axilla for the disease. This difference in the outcome of two groups was statistically significant with p value of 0.013.The mean follow-up in neoadjuvant was 5.3 months whereas mean follow up of adjuvant group was 10.65 months. There is statistical significance in follow-up between neo-adjuvant and adjuvant chemotherapy.

S.No	Outcome	Adjuvant	Neoadjuvant	P
1	Mortality due to disease	0 (0%)	3 (15%)	6.15 P=0.014
2	Distant Metastasis but alive	1 (5%)	4 (20%)	
3	Locoregional recurrence	1 (5%)	1 (5%)	
4	Lost to followup	0 (0%)	1 (5%)	
5	Total	2 (10%)	9 (45%)	

Table 3: Distribution of Patients in the Two Groups According to Mortality/Metastasis/Recurrence

S.No	Stage IIIA Patients in Adjuvant vs Neoadjuvant	Adjuvant Group (n=20)	Neoadjuvant Group (n=20)	P
1	Total no of patients of stage IIIA in	18 (90%)	10 (50%)	0.022
2	Metastasis/mortality/recurrence in stage IIIA patients	2 (10%)	3 (20%)	

Table 4: Distribution of Patients of Only Stage IIIA in Both the Groups with Their Outcome

IV. Discussion

In our study, BR grading, luminal status or triple negative status, laterality of disease, age at presentation, histopathological type of malignancy were a non significant contributing factor in determining prognosis of disease.[7]

In our study, 90% patients in adjuvant group had lymphovascular invasion whereas only 70% patients in neoadjuvant group had lymphovascular invasion. This above data is though statistically nonsignificant.In the adjuvant group out of 18 patients who had lymphovascular invasion present, 2 patients developed either metastasis or recurrence. In the neo-adjuvant group out of 14 patients who had LVI, 7 patients developed recurrence/metastasis/death during treatment or follow up, while 1 patient was lost to follow up in neoadjuvant.In a multivariate analysis between metastasis/local recurrence/mortality vs type of malignancy/LVI/BR grading, the correlation between metastasis/local recurrence/mortality was found to be significant with LVI in neoadjuvant group (p value 0.022).Thus presence of lymphovascular invasion is a sign of poorprognosis.[8] However,the relation was non-significant in the adjuvant group.In the study by Ryu et al,out of 187 patients, 35% patients showed LVI. The LVI group tended to have advanced status in terms of disease burden (clinical stage III) and had statistical significance. In the univariate analysis of association with recurrence (locoregional/distant) LVI (p value <0.001) showed statistically significant differences.Similar results were found with statistically significant differences in the study byLiu et al,15where in the univariate analysis, presence of LVI was significantly associated with worse progression free survival (p value <0.01).[9]

In our study, 3 patients (15%) of neoadjuvant group died due to disease. Metastasis was found in 1 (5%) patient in adjuvant group while 4 (20%) patient in neoadjuvant group. Recurrence was found in 1 (5%) case each in adjuvant and neo-adjuvant group.The death in neoadjuvant group was due to distant metastasis. In the neoadjuvant group, 3 patients developed bony metastasis first, while 2 patients developed liver metastasis first.One patient developed lung metastasis. One patient developed seizures and brain metastasis.1patient in neoadjuvant group was lost to follow-up.The comparison in between the two groups of adjuvant and neoadjuvant in terms of poor prognosis (mortality/metastasis/recurrence) was found to be statistically significant (p value of 0.013) (table 3). Hence our study shows that overall outcome in terms of disease recurrence (distant/local) is poor when neoadjuvant chemotherapy is given as compared to adjuvant therapy in stage IIIA &IIIB carcinoma breast.[10]

In the study of adjuvant chemotherapy only, Casper et alfound 7 of 41 patients (17%) had local recurrence of which 5 patients later developed distant metastasis.Saarto et alin their study of adjuvant regimens in carcinoma breast over a follow-up of 8 years found that distant metastasis occurred in 48 %of patients while 23 % had local recurrence. All local recurrence patients later developed distant metastasis.Marrow et alin their study on effectivity of neoadjuvant chemotherapy found that out of 31 patients, 3 (10%)patient developed metastasis who completed therapy and 4 patients (13%) of them had local recurrence. While 2 patients did not complete their complete course of treatment. There are several factors contributing to poor prognosis (disease

recurrence/mortality) are triple negative status, LVI presence, her2 neu overexpression. Of these, in our study LVI was statistically significantly associated with poor outcome in neoadjuvant group in terms of distant metastasis and locoregional relapse.Other parameters were statistically non-significant in our study. This could be because of low sample size.[11]

V. Conclusion

Adjuvant chemotherapy is better in outcome in terms of locoregional recurrence and distant metastasis for stage IIIA & IIIB carcinoma breast than neoadjuvant chemotherapy, provided surgery with primary skin closure is feasible.Lymphovascular invasion is a marker for poor prognosis in carcinoma breast.

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