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Original article

Non Invasive Evaluation of Residual Disease in Women of Locally Advanced Breast Cancer after Neoadjuvant Chemotherapy

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ABSTRACT

Background: The aim of this study was to evaluate the role of Neoadjuvant Chemotherapy (NACT) in Locally Advanced Breast Cancers (LABC) by correlating the clinical and radiological findings before and after NACT.**Methods:** A prospective study conducted over a 2yr period, enrolled patients with LABC. All patients were evaluated clinically and radiologically before and after completion of NACT. Breast lump size, axillary nodal metastasis and features of locoregional involvement were recorded. The incidence of complications and locoregional recurrence were also noted.**Results:** Out of total 100 patients, maximum(n= 72) showed partial response (PR) and 02 showed no response. There was a decrease in mean tumor size (4.91cm vs 2.74 cm, p=<0.001) on clinical examination and (4.14cm vs 2.24cm, p= <0.001) on radiological evaluation. Mean lymph node size decreased to (1.34cm vs 0.04 cm, p= <0.001) on clinical examination and (9.95mm vs 0.52m, p=<0.001) on radiological evaluation. There was no case of locoregional recurrence on follow up.**Conclusions:** The implication of this study is that NACT helps in down staging of the tumors and for better clinical evaluation, both physical examination and radiological evaluation should be routinely used in the patients of LABC undergoing NACT.

KEYWORDS:Locally Advanced Breast Cancer, Mammography, Neoadjuvant Chemotherapy

INTRODUCTION

Cancer of the breast is the second most prevalent neoplasm in India and the commonest female malignancy. Due to the lack of diagnostic facilities, ignorance & other social factors, it most commonly presents in a locoregionally advanced stage in our country. Surgery has remained the mainstay of treatment. This used to entail a gruesome operation which left the often middle aged patient, a physical and most importantly a psychological cripple. Also the survival rates after surgery alone were dismal.

In the last four decades, enormous strides have been made in the understanding of the natural history of breast cancer. It has been understood that cancer of the breast when locoregionally advanced has already given rise to systemic micrometastasis.[1] So the modern therapy for locoregionally advanced cancer of the breast entails a two pronged attack ,one for effective local control and the second for a systemic treatment. This includes surgery, chemotherapy,radiotherapy and hormonal therapy. These therapies have been used in various permutations and combinations to obtain optimum results.

Neoadjuvant chemotherapy (NACT), now-a days is commonly used in patients of locally advanced breast cancer (LABC). Preoperative chemotherapy protocols have revolutionized LABC care. All the early concerns were based on the negative effects of preoperative chemotherapy on surgical complication rates, the prognostic value of the axillary staging and overall survival after delayed surgery.

Preoperative versus postoperative chemotherapy have been directly compared in women with LABC. Many clinical trials have demonstrated that overall survival rate is equal in both the groups, which confirms the oncologic safety of the neoadjuvant therapy. Since NACT helps in downstaging the tumor and improves respectability in LABC patients,this has now become the preferred approach.[2]

Considering the efficacy of NACT, the present study is being conducted to evaluate the residual disease by clinical and radiological examination.

MATERIALS AND METHODS

Therapeutic Protocols

This study was conducted in a tertiary care centre.100 patients of LABC treated in this centre were reviewed. All patients were evaluated which included clinical examination and Sono- mammogram of the breast before NACT and within 02 weeks of completion of NACT to detect evidence of residual disease. All patients were given three cycles of chemotherapy as per NCCN specified every three weeks. Patients were monitored for toxicity in the form of myelosuppression, nausea, vomiting and alopecia. All patients after completion were offered definitive surgery. All patients were followed up with a three monthly clinical examination and a six monthly ultrasonography (USG) / mammogram of the breast. Research ethics approval for this study was taken from institutional ethical committee.

Inclusion criteria

Locally Advanced Breast Cancers, Those who have given consent for study & follow up

Exclusion criteria

Early Breast Cancers
Previously received chemotherapy or undergone surgery
Metastatic Breast Cancers
Those who have not given consent for the study & follow up

Clinical examination

Breast lump size, axillary nodal metastasis and features of locoregional involvement were recorded. The longest diameter of the lump size was taken as the reference before NACT and comparison was done after chemotherapy.

Sono-mammographic Evaluation

Mammography was done in all the patients before and after chemotherapy. The findings of mammography were collaborated with the USG findings. In most patients two views of the breast were obtained, the craniocaudal (CC) view and the mediolateral oblique (MLO) view. Categorization of the lump was done using Breast Imaging Reporting and Data System (BI-RADS).[3,4] Evaluation was done using the longest diameter before NACT including the involved quadrant of the breast and comparison was done after the completion of chemotherapy.

Radiologic Measurement

To evaluate the response of NACT, the response evaluation criteria in solid tumours (RECIST) criteria was used.[5] It is based on uni-dimensional measurement of the largest tumour diameter. Each patient's tumour response was classified as complete response (CR), partial response (PR), stable disease(SD) or progressive disease(PD) according to the RECIST guidelines on the basis of tumour measurements made on clinical examination and during the imaging studies.

Statistical Analysis

Comparison between the lump size, nodal metastases and other features pre and post NACT was done using Wilcoxon sign rank test ,McNemar's test and paired t- test. P – value< 0.05 considered significant.

RESULTS

During the study period 100 patients of LABC diagnosed by clinical examination and radiological investigation were included in the study after their due consent. All 100 patients presented with history of lump in the breast. Patients in the study had age ranging from 30 to 70 years, with maximum patients in age group of 41- 50 years. More than half of patients presented to hospital within 1 to 6 months of development of symptoms and maximum duration of presentation was 14 months. Left side was involved in 43 and Right side in 57 patients. Maximum patients had tumor size > 5cm at the time of presentation. All the patients in the study were given NACT and evaluation was done after 03 cycles of chemotherapy. FAC (5-Fluorouracil, Adriamycin, Cyclophosphamide) was the primary chemotherapy regimen used in maximum i.e.52 patients. Taxane based regimens TAC (Paclitaxel, Adriamycin, Cyclophosphamide) and AC→T were used in 8 and 29 patients respectively, while remaining 11 patients received CEF regimen (Cyclophosphamide, Epirubicin , 5-Fluorouracil). (Table1)

Table1: Patient and tumour characteristics

Characteristics	Number of patients		Percentage (%)
Age group (years)	≤ 40	13	13.0
	41 – 50	58	58.0
	51 – 60	17	17.0
	61 ≤ 70	12	12.0
Duration of presentation(mths)	2 – 4	34	34.0
	4 – 6	27	27.0
	6 – 8	13	13.0
	8 – 10	9	9.0
	> 10	17	17.0
Maximum Size of tumor (cm)	≤ 2	0	0.0
	>2 – ≤ 5	46	46.0
	> 5	54	54.0
Type of Chemotherapy given	FAC	52	52.0
	AC –T	29	29.0

	CEF	11	11.0
	TAC	8	8.0
Primary Tumor Status (T)	T1	0	0.0
	T2	13	13.0
	T3	25	25.0
	T4	62	62.0
Lymph node Status(N)	N0	13	13.0
	N1	61	61.0
	N2	21	21.0
	N3	05	5.0

Table 2: Distribution of patients according to NACT response

Response	No of patients	Percentage (%)
Complete Response(CR)	26	26.0
Partial Response(PR)	72	72.0
Stable Disease(SD)	02	2.0
Progressive Disease(PD)	00	0.0
TOTAL	100	100.0

Out of 100 patients who received NACT, 26 patients showed complete response (CR), 72 partial response (PR) and 02 showed no response with NACT. Progression of the disease was not seen in any of the patients included in this study.(Table 2) 57 patients were placed in Stage IIIB (T4N0 /N1/N2 M0) followed by 31 patients in Stage IIIA (T2N2M0/T3N1/N2M0).07 patients had tumor of size > 5 cm with no axillary lymph node involvement. (Table 3)

Table 3: Distribution of patients as per TNM stage

TNM Stage	Number of patients	Percentage (%)
IIB		
T3N0M0	07	7.0
IIIA		
T2N2M0	13	13.0
T3N1M0	15	15.0
T3N2M0	03	3.0
IIIB		
T4N0M0	04	4.0
T4N1M0	48	48.0
T4N2M0	05	5.0
IIIC		
T4N3M0	05	5.0
TOTAL	100	100.0

As shown in Table 4 , maximum patients had tumor size of > 5 cm and pectoralis or skin involvement in the form of puckering/ peaud orange at the initial presentation(n=87 patients). After completion of chemotherapy > 90 % of patients had tumor size of <5cm with P- value < 0.05. Lymph nodes were present in maximum patients (n=87) at the initial presentation. After chemotherapy 94 patients had no lymph nodes on evaluation, significant with P- value < 0.05.

84 patients had mobile tumor before NACT. After chemotherapy 97 patients had mobile residual tumor which is considered significant.(P- value <0.001) Before chemotherapy 18 patients had nipple retraction but after NACT only 01 patient had nipple retraction, significant with P- value < 0.001. 52 patients had skin involvement in the form of puckering and peaud ‘orange but after chemotherapy only 1 patient showed no response with significant P- value <0.001. On examination 87 patients had palpable axillary lymph node at the initial presentation. After chemotherapy lymph node was palpable in only 04 patients with P-value < 0.001. All the patients were evaluated radiologically before receiving NACT and after 03 cycles of completed NACT.

Table 4: T and N stage of patients pre and post NACT (Wilcoxon Sign rank test used)

		Pre NACT	Percentage (%)	Post NACT	Percentage (%)
Primary Tumor Status (T)	T1	0	0.0	55	55.0
	T2	13	13.0	38	38.0
	T3	25	25.0	05	5.0

	T4	62	62.0	02	2.0
	Total	100	100.0	100	100.0
Lymph node Status(N)	N0	13	13.0	94	94.0
	N1	61	61.0	04	4.0
	N2	21	21.0	01	1.0
	N3	5	5.0	01	1.0
	Total	100	100.0	100	100.0

On sonomammography maximum patients had lesion with irregular margins and calcification. While skin involvement was seen in 62 patients before NACT and after chemotherapy only 04 patients showed skin involvement, considered significant with P- value <0.001. Pectoralis involvement was seen in 05 patients at the initial presentation but after chemotherapy no patient had involvement. 89 patients showed the presence of lymph node in sonomammography at the presentation. After completion of chemotherapy repeat sonomammography showed lymph nodes in only 06 patients , with significant P-value <0.001.(Table 5)

Table 5: Distribution of patients on evaluation with different methods (Using McNemar's test)

		NACT(Number of patients)		P-value
		Pre	Post	
Clinical Examination	Mobile	84	97	< 0.001
	Nipple Retraction	18	01	< 0.001
	Skin Involvement	52	01	< 0.001
	Axillary lymphnode	87	04	< 0.001
Sono- mammography	Skin Involvement	62	04	< 0.001
	Pectoralis Involvement	05	00	-
	Axillary lymphnode	89	06	< 0.001

100 LABC patients had pre NACT tumor size of mean 4.91cm, ranging from 3-10 cm. After chemotherapy there was down staging in tumor size to a mean of 2.74 cm, considered significant while there was pre NACT tumor size of mean 4.14 cm , ranging from 1.4-11.2 cm on radiological evaluation. After chemotherapy there was down staging in tumor size to a mean of 2.24cm, considered significant.(Table 6)

Table 6 :Tumor response to NACT on evaluation with different methods (Using paired t-test)

Tumor Size (cm)		Pre NACT	Post NACT	P-value
Clinical	Mean	4.91	2.74	<0.001
	SD	1.24	1.17	
	Range (Min-Max)	3-10	1-8	
Sono-mammography	Mean	4.14	2.24	<0.001
	SD	1.37	1.33	
	Range (Min-Max)	1.4-11.2	0.6-10	

Among 87 patients with palpable axillary lymph nodes , the mean size of lymph node calculated was 1.34 cm with SD of 0.86 cm at the initial presentation. After chemotherapy the mean size decreased to 0.04 cm with SD 0.20 cm , statistically significant with P-value <0.001. Among 89 patients with axillary lymph nodes on sono-mammography ,the mean size of lymph node calculated was 9.95mm with SD of 6.05 mm at the initial presentation. After chemotherapy the mean size decreased to 0.52 mm with SD 2.11mm , statistically significant with P-value <0.001.(Table 7)

Table 7: Lymph node response to NACT on evaluation with different methods (Using paired t-test)

Lymph Node Size		Pre NACT	Post NACT	P-value
Clinical (cm)	Mean	1.34	0.04	<0.001
	SD	0.86	0.20	
Sono-mammography (mm)	Mean	9.95	0.52	<0.001
	SD	6.05	2.11	

DISCUSSION

The goal of this study was to evaluate the outcome of NACT in LABC by correlating the clinical and radiological findings before and after NACT and its efficacy in downstaging inoperable cases. A total of 100 patients were included in this study with varying age groups. All the

patients in the study were given NACT and evaluation was done after 03 cycles of chemotherapy. The effects of NACT on the primary breast tumor and lymph node were evaluated in those patients who had clinically evident breast tumors and lymph node at the time of diagnosis of LABC.

All patients had clinical tumor size and lymph node measurements by at least one modality (Physical examination and Sonomammography). In this study on initial presentation the mean size of the breast lump was 4.91 cm as measured by clinical examination and 4.14 cm by sonomammographic evaluation.

Response with NACT was evaluated in all the patients. There are many large randomised trials which have proven the safety of NACT in LABC. Most of these showed a good objective response rate of about 60-80%. As seen in National Surgical Adjuvant Breast and Bowel Project B-18 (NSABP B-18) trial, in the neoadjuvant group, the objective clinical response (ORR) rate was 78% with clinical partial response (cPR) in 43% and a clinical complete response (cCR) in 36%.[6] In a randomized trial by Van der Hage et al, only 6.6 % patients showed clinical CR while 42.3% patients showed PR which was low in comparison with the response rates described in the literature.[7]

NACT is being increasingly used in LABC patients for downstaging of the tumors and thus helping in more breast conservative surgeries.[8,9] Physical examination is regarded as a gold standard for evaluating response after NACT. There are two major factors, dense breast tissue and infiltrating nature of the LABC which make the evaluation of the residual tumor size by mammography difficult.[10] It is also of the view that chemotherapy-induced fibrosis is really difficult to differentiate from residual disease on physical examination.[11,12,13] As a result of which residual tumor is potentially overestimated by clinical examination.[14,15] In this study the mean residual tumor size after chemotherapy on clinical examination calculated was 2.74 cm as compared to 2.24 cm by radiological evaluation .

There are many studies in the literature which have come to a contrary conclusion that physical examination is the better modality as compared to USG/ mammogram in evaluating the residual tumor size. According to a study by Herrada et al, for the primary tumor physical examination is the best modality for the evaluation of residual tumor size followed by radiological evaluation.[16]But there is a significant improvement in the evaluation , if it is combined with USG/mammogram of the breast both in pre and post NACT phase. Fiorentinoet. al., in a similar series, also concluded that physical examination is more accurate than either mammography or ultrasound. Lluch et al evaluated 60 patients who underwent NACT to study the role of physical examination and radiological investigations for the primary tumor size. In this study also, it was observed that physical examination had more accuracy as compared to USG/ mammography.[17]

Some mammographic abnormalities cannot be detected by physical examination which include clustered microcalcifications and areas of abnormal density (e.g. architectural distortions). Cox et al conducted a study on 116 LABC patients, the median tumor size was 06 cm, ranging from 01- 20 cm on initial evaluation. After the completion of chemotherapy the median tumor size decreased to 03 cm , ranging from 0- 19 cm.[18] In a study by Croshraw et al , 61 patients were evaluated before and after neoadjuvant therapy by clinical breast examination (CBE), digital mammogram/ breast ultrasound. Overall accuracy ranged from 54% (CBE) to 80% (breast ultrasound).[19] Still there is no consensus in the literature regarding the best method to evaluate the residual size after NACT. Physical examination is often difficult when the residual tumor size is small and also inaccurate due to irregular & poorly defined margins or when neoadjuvant chemotherapy results in residual fibrosis and/or necrosis.

In a prospective study conducted on 98 patients of LABC by Alawad et al, on evaluation by clinical and radiological examination, the overall clinical response rate was 83%.[20] In another study by MJ Beresford et al on 200 breast cancer patients, the clinical response rate was 79%.[21]In the NSABP B-27 trial, the mean tumor size was 4.5 cm and after chemotherapy the overall clinical response rates observed was 87.0% while clinical complete responses were observed in 38.4%.[22]

In this study 87 patients had palpable axillary lymph nodes, with 1 or 2 cm mobile nodes in 61 patients. 13 patients had no palpable axillary lymph nodes at the initial presentation. The mean size of lymph node calculated was 1.34 cm with SD of 0.86 cm. After chemotherapy only 04 patients had palpable axillary lymph nodes and the mean size decreased to 0.04 cm with SD 0.20 cm. While on sono - mammography 89 patients had axillary lymph nodes and the mean size of lymph node calculated was 9.95mm with SD of 6.05 mm at the initial presentation. After chemotherapy the axillary lymph nodes were diagnosed in only 06 patients, mean size decreased to 0.52 mm with SD 2.11mm. A study by Arimappamagan A et al also concludes that ultrasonography of axilla is better than clinical examination in the assessment of axillary nodes and their response to neoadjuvant chemotherapy.[23]

Kuerer et al documented complete axillary conversion in 43 (23%) out of 191 patients who had documented nodal metastasis before receiving NACT.[24]

The implication of this study is that physical examination has more accuracy as compared to USG/ mammography in evaluating the tumor size while USG has a better hand in the assessment of axillary nodes and their response to neoadjuvant chemotherapy. But for better clinical evaluation both physical examination and USG/Mammography should be routinely used in the patients of LABC undergoing NACT which is important to guide the choice of subsequent therapy. Although there has been no recurrence in this study after the definitive treatment post NACT, it cannot be commented upon due to short follow up period.

CONCLUSION

On evaluating the results of this study, it can be concluded that NACT plays a very good role in down staging the tumor in LABC patients. Non-invasive evaluation done before and post chemotherapy gives a good estimate of overall clinical response.

Competing interest: The authors declare that they have no competing interests.

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