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Assessment of Response to Neoadjuvant Chemotherapy by Dynamic Contrast Enhanced Magnetic Resonance Mammogram in Locally Advanced Breast Cancer

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Abstract:
Objective: *To assess response of the tumour mass to neoadjuvant chemotherapy in locally advanced breast cancer by dynamic contrast enhanced MR mammogram using longest tumor diameter and volume as parameters.*
Materials and methods: *Twenty patients with locally advanced breast cancer were subjected to dynamic contrast enhanced MR mammogram before and after 3 cycles of chemotherapy. Longest tumor diameter and volume in MR mammogram was the criteria used to assess response to NAC. These results were correlated with pathological response in post mastectomy specimen.*
Results*: Of the 20 cases, 15 cases were morphologic partial responders (mPR), 2 cases had morphologic stable disease (mSD) and 3 cases showed morphologic complete response (mCR). Of the 15 partial responders, all of them correlated with histopathology which showed residual tumor. Of the 3 morphological complete responders, 2 cases showed complete response in pathologic specimen (pCR) and one showed residual disease in pathologic specimen. Hence MRI was found to be 94 % sensitive in diagnosing residual tumor. The positive predictive value of MRI was 100%. Negative predictive value was 66%.*
Conclusion: *MRI has a definite role in assessing response to Neoadjuvant chemotherapy in locally advanced breast cancers. Longest tumor diameter and tumour volume are the simplest and most useful parameters in assessing the response.*
Keywords*: Locally advanced breast cancer, neoadjuvant chemotherapy, and dynamic contrast enhanced MR mammogram.*

I. Introduction

Breast cancer is the most common cancer in women, accounting for a total of 215,990 cases and 39,800 deaths per year in United States [1]. Worldwide, nearly 1 million cases are seen annually. In India, breast cancer is second most common cancer among women next to cervical cancer. In Chennai, according to The Madras Metropolitan Tumour Registry (MMTR) 2004 statistics, the most common cancer among women was breast cancer (26.5%), the next common was cervical cancer (21.2%) and the other common cancers were ovary, stomach, and oral cancers. The crude ratio and age adjusted ratios per 100000 population for developing breast cancer were 24.4 and 26.6 respectively [2].

Most patients presented with locally advanced breast carcinoma (LABC) in Coimbatore Medical College hospital during the study period. Ratio of locally advanced breast cancer to early breast cancer, in our hospital was 70:30. Recent guidelines from the U.S. National Comprehensive Cancer Network describe LABC as AJCC stage III breast cancer; the definition includes breast cancer that fulfils any of the following criteria in the absence of distant metastasis.

- Tumours more than 5 cm in size with regional lymphadenopathy (N1–3)
- Tumours of any size with direct extension to the chest wall or skin, or both (including ulcer or satellite nodules), regardless of regional lymphadenopathy
- Presence of regional lymphadenopathy (clinically fixed or matted axillary lymph nodes, or any of infraclavicular, supraclavicular, or internal mammary lymphadenopathy) regardless of tumour stage.

Neoadjuvant chemotherapy (Adjuvant/Basal/Induction/Primary/Preoperative Chemotherapy) is given preoperatively in LABCs to give a tumor size reduction and a better surgical approximation. The role of imaging for patients treated with neoadjuvant therapy for breast cancer is not only to evaluate the therapeutic response in terms of tumour shrinkage, but also to predict the histological response to chemotherapy, which is correlated to survival. Surgery and histopathological analysis after neoadjuvant therapy allow for an objective assessment of the accuracy of imaging techniques in evaluating response. A complete tumour response to neoadjuvant chemotherapy increases the disease-free interval and patient survival. [3,4,5]

Assessing response to neoadjuvant chemotherapy in breast cancer is important, because a nonresponsive tumor can be combatted with a higher or different set of chemotherapeutic agents, thereby preventing adverse effects of chemotherapy regimen and saving time by timely change of regimen and getting a response to treatment. Hence assessing the response also prognosticates the patient's disease- free survival.

Monitoring response to neoadjuvant chemotherapy was traditionally done with clinical examination, ultrasonogram and mammogram. However these techniques were found to be of unsatisfactory accuracy [4,5,6,7,8,9,10].Dynamic contrast-enhanced MRI allows assessment of morphologic properties such as tumor size and in addition also allows assessment of functional properties, such as those associated with neoangiogenesis [10]. Several studies have found that MRI is the most accurate technique for evaluating the extent of residual disease after systemic treatment in vivo [11–15]. MRI may even allow assessment of the pathophysiologic response to chemotherapy, which occurs before volume changes [16, 17]. Moreover, it has been suggested that application of MRI may improve the complete remission rate [17–19]. It is the most reliable method for appreciating multifocality. Its role is essential in pre-therapeutic staging and in the assessment of chemotherapy efficacy.

During or after neoadjuvant chemotherapy, role of MRI is to monitor early response to treatment and identify possible residual disease [15,16]. The parameter with the greatest predictive value is the absence of any gross residual tumour. Limited microscopic residual tumour does not play any significant role, and is found nearly constantly (95% of complete responses). Most authors find an excellent correlation between the macroscopic tumour size and the tumour established by MRI.

However, the clinical value of dynamic MRI for predicting the efficacy of neoadjuvant chemotherapy during treatment has not been fully assessed. Hence we set out, in our study to assess response of neoadjuvant chemotherapy in locally advanced breast cancers by dynamic contrast enhanced MR mammogram.

II. Objective

To assess response of neoadjuvant chemotherapy in locally advanced breast cancers by dynamic contrast enhanced MR mammogram and to compare its efficacy with postsurgical histopathology results by considering largest tumor diameter and tumor volume as parameters.

III. Materials And Methods

3.1 Period of study:

September 2012 to October 2013. Institutional ethical committee clearance was obtained for the study.

3.2 Patient population:

20 Patients were selected for the study with median age 48 years with stage IIB to stage IIIC breast carcinoma. Lumps small enough for the surgeon to give good tumor clearance and cancers with metastasis (stage 4) were excluded from study.

3.3 Inclusion criteria:

Patients with locally advanced invasive ductal carcinoma of breast –with stage IIB to stage IIIC.

3.4 Exclusion criteria:

1. All patients with stage less than IIB, or stage IV.
2. Patients with renal failure (not fit for MR contrast study)
3. Patients with claustrophobia
4. Patients with other contraindications –pacemaker, implants etc.

3.5 Pretreatment evaluation:

Pretreatment evaluation was as done for all patients which included complete blood counts, renal function test, Chest radiographs.

3.6 Chemotherapy regimen:

All patients received 3cycles of chemotherapy consisting of 5-flourouracil 600mg/m^2, adriamycin 60mg/m^2, cyclophosphamide 600mg/m^2 (FAC). All patients received chemotherapy within 1week of 1st MR study. 3cycles of chemotherapy regimen lasted for 63 days with FAC regimen. Follow up MRI was done in the range of 12 to 18 days following completion of third cycle of chemotherapy.

3.7 MR Mammogram technique:

All patients selected for study were subjected to dynamic CE MR mammogram before the start of first cycle of chemotherapy (with 5 flourouracil-600mg/m^2,adriamycin-60mg/m^2, cyclophosphamide-600mg/m^2)-using SIEMENS Magnetom 1.5 Tesla MRI machine with breast coil with patient in prone position and using MR contrast (gadodiamide) in the dose of 0.16mmol/kg.

Dynamic CE MR Mammogram was repeated after the third cycle of chemotherapy (after 2 weeks of completion of 3rd cycle). Response to neo adjuvant chemotherapy was assessed in terms of longest tumor diameter and tumor volume.

3.7.1 MRI sequences:

Sequences	TR/TE in ms	Slice Number / Thickness in mm	Flip Angle deg	Pixel in mm	Field of view in cm	Total scan Time in min	Number of Acquisitions
Axial TIRM	5750 / 67 TI 160	34 / 4	170	1*0.9*4	340*100	4.15	1
Axial T2	4000 / 107	28 / 4	160	1*0.8*4	340*100	2.5	1
Axial T1 NonFS	8.4 / 4.7	104 / 1.6	20	1*0.9*1.6	340*100	1.20	1
3D GRE FS Pre Contrast	4.3 / 1.5	160 / 1	8	1.1*0.7*1	320*100	1.25	1
3D GRE FS Post Contrast	4.3 / 1.5	160 / 1	8	1.1*0.7*1	320*100	5.01	4

With dynamic study, MR contrast agent (gadodiamide) was given at the dose of 0.16 mmol/kg of bolus intravenously into a cannula in the antecubital vein fixed just before the MRI. The contrast was given by pressure injector at the rate of 2 to 3 ml per second, followed by 20 ml flush of normal saline; the patient would not be moved in or out of magnet for injection to prevent motion and unnecessary time losses in early post contrast phase. Four acquisitions were performed following contrast injection with acquisition beginning immediately after contrast injection. Comparison of pre & post neoadjuvant chemotherapy MR mammogram images was done. Changes in longest tumor diameter and tumor volume were assessed.

3.7.2 Image review and analysis:

The images were analyzed by two radiologists with more than three years of experience in breast MR imaging. Longest tumor diameter and tumor volume were calculated in dynamic contrast enhanced MR image at 120 sec of the study. Tumor diameter and volume reduction were assessed in the study done after 3 cycles of chemotherapy. Longest tumor diameter was always measured in axial plane, in the first and follow up MRI. Three orthogonal diameters were measured to calculate volume by ellipsoidal formula:

Volume (V) = d [cc] x d [ap] x d [l] x $\pi/6$ (d-diameter; cc-cephalocaudal; ap-anteroposterior; l-length)

At the outset we defined (based on the Revised RECIST criteria for tumor response) [17,18].

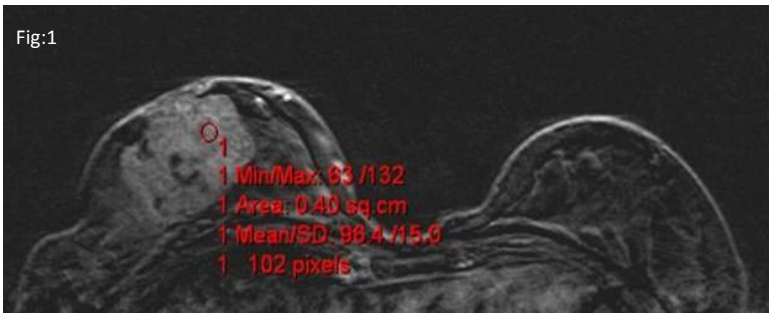
1. A morphologic partial responder as one who exhibits >30% reduction in longest tumor diameter.
2. A morphologic complete responder as one who showed no residual tumor in MRI after 3 cycles of chemotherapy.
3. A patient with Stable disease as one who showed neither sufficient decrease to qualify for Partial response nor sufficient increase to qualify for Progressive disease.
4. A patient with Progressive disease as one who showed increase of >20% in longest tumor diameter.

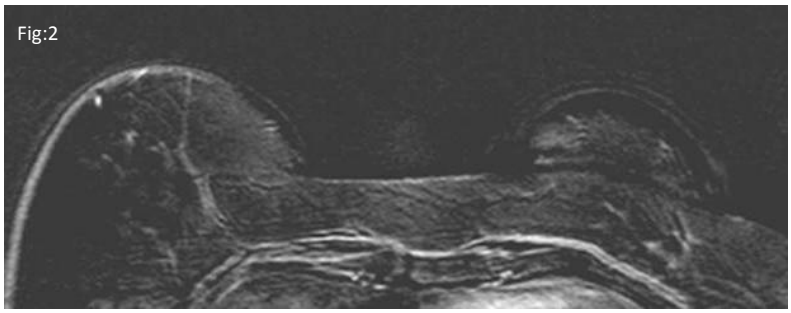
After 3 cycles of chemotherapy, patients underwent mastectomy and the mastectomy specimen was subjected to pathologic study. The results in MR mammogram were compared with pathologic results. Patients were followed up till surgery with histopathological correlation.

IV. Results

Total number of patients included in the study was 20. These women in our study group were in the age range of 33 to 60 years. The median age of our patients was 48 years. All 20 cases were infiltrating ductal carcinoma. Of the 20 cases, 11 were of stage $T_{4b}N_1M_0$, 2 members were T_{4a} N_1 M_0 stage, 6 members were of stage $T_3N_1M_0$ and 1 person was of stage $T_2N_2M_0$. All patients received chemotherapy within 1 week of 1st MR study.

Chemotherapy regimen lasted for 63 days with FAC regimen. Follow up MRI was done in the range of 12 to 18 days following completion of third cycle of chemotherapy. The interval between follow up MRI and surgery was 7 to 14 days. 15 out of 20 patients showed a partial response (75%) in MRI as assessed by longest tumor diameter and morphologic tumor volume. 3 out of 20 patients were morphologic complete responders (15%) as evidenced by no demonstrable mass in follow up MRI. Two out of 20 patients had stable disease (10%).





Pre and Post NAC MRI of breasts of same patient;
Fig.1 Left breast mass, prechemotherapy tumor volume 190 ml;
Fig.2 Complete resolution of left breast mass following 3 cycles of FAC regimen suggesting morphologic complete response.

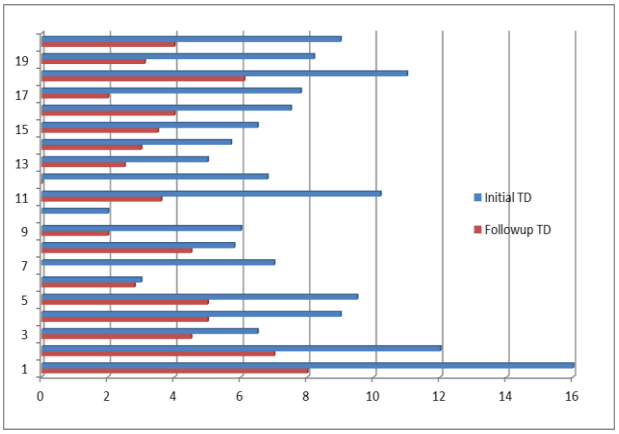


Chart 1: Relation between initial and follow up longest tumor diameter

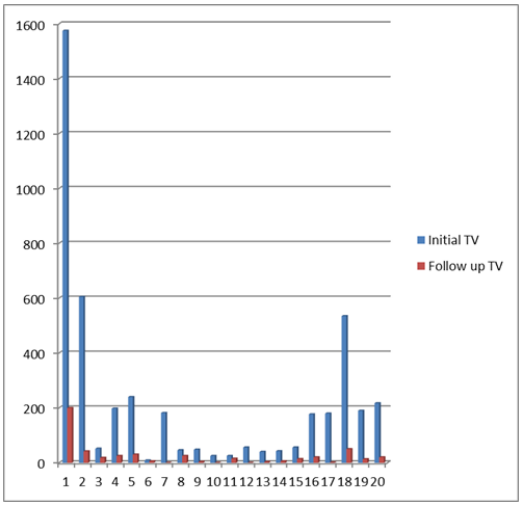


Chart 2: Relation between initial and follow up tumor volume

Statistical analysis was done using Student paired test. Overall tumor volume reduction was 88% on the average. In partial responders longest tumor diameter reduced by a mean of 3.0ml +/- 5.01 ml. P value =0.02, significant. P value =0.01, significant. In partial responders the tumor volume reduced by a mean of 46 +/- 393.1ml. P value =0.02, significant.

Out of 3 morphologic complete responders in MRI, 2 patients correlated with pathologic CR, while one patient showed pathologic residual disease. All persons with partial response and stable disease correlated with pathology.

Parameters	HPE Positive	HPE Negative
MRI positive	19	0
MRI negative	1	2

Hence tumor volume as assessed by dynamic contrast enhanced MR mammogram was 94% sensitive in detecting residual tumor. The measurement of tumor volume had a positive predictive value of 100% and negative predictive value of 66%. Accuracy of longest tumor diameter in MR assessment of response was the same as tumor volume. In both non-responders there was no significant change in tumor size. All the responders a decrease in tumor volume of more than 65% were noted.

V. Discussion

The ratio of locally advanced breast cancer (LABC) to early breast cancer was 70%: 30%, patients presented with huge masses-T4 category, in our hospital. This is contrary to Western statistics where the locally advanced breast cancer constitutes 20% of total breast cancer patients.All cases in our study were of Invasive ductal carcinoma. Morphologic Complete Response was attained in 3 patients who constituted 15% of total, which was comparable to other studies where mCR was 7-17% [19]

Two parameters taken to assess the response were longest tumor diameter – a unidirectional measurement and tumor volume – a 3D measurement. In our study, tumor volume as assessed by MR mammogram was 94% sensitive in detecting residual tumor. This parameter had a positive predictive value of 100% and negative predictive value of 66%. Longest tumor diameter provided similar sensitivity and positive predictive value in assessing the response to NAC, as tumor volume. In our study, the unidimensional measurement of longest tumor diameter gave similar results as the 3D measurement of tumor volume. Hence longest tumor diameter is the simplest as well as reliable parameter to assess response to NAC correlating with RECIST criteria.

In a study of 216 breast cancer patients, Hylton et al, evaluated changes in tumor volume and diameter after first cycle of NAC. They observed that early in treatment, maximum tumor diameter and tumor volume were the best parameters to predict pCR [15].

Apart from morphological assessment of breast tumour by MRI, advanced techniques like Diffusion weighted imaging (DWI), MR Spectroscopy (MRS), and pharmacokinetic modeling are being under evaluation for assessing response to NAC. Diffusion weighted imaging measures the changes in apparent diffusion coefficient (ADC). Following NAC, ADC value increases during tumor destruction, which is used as a parameter to predict pathological response to neoadjuvant chemotherapy in patients with breast cancer [21,22,23,24]. Various studies have proposed ADC cut off values to assess the response to NAC and have found that the ADC values were statistically significant between responders and non-responders [20, 27]. However DWI sequences can vary grossly between vendors and institutions, especially with respect to b values, which influence the ADC values. Hence a comparative study between different study groups for standardization is difficult.

In a study by Jagannathan et al, patients with breast cancer and 16 healthy controls were evaluated using MR spectroscopy. They showed specificity and sensitivity of MRS for detecting choline (tCho) peak in tumors was 78% and 86% respectively [25]. However, the analysis of the MRS data can be time consuming and there are many technical difficulties in assessing the very low concentrations of tCho *in vivo*. Other confounding factors are the variable fat content within the breast, field inhomogeneity caused by air-tissue interfaces and marker clips artifacts (inserted after biopsy).

With respect to early response monitoring in NAC, many parameters of pharmacokinetic modeling have been proposed, such as K trans, K ep etc. For proper measurement of Arterial Input Function (AIF), high temporal resolution is needed and in case of breast, the supplying artery is at a significant distance from the tumor. Hence temporal resolution is reduced when Field of view (FOV) is increased. Moreover dose and type of contrast agent also influence the above values [22, 23, 26]. Until now, these limitations prevented a widespread clinical use of these advanced techniques to monitor the response in patients receiving NAC. Hence from our study and reviewing of recent literature, we found that decrease in tumor size as measured by longest tumor diameter and tumor volume are the best predictors of tumor response.[14]

VI. Conclusion

Magnetic resonance imaging is an important investigation tool to assess response to neo-adjuvant chemotherapy in locally advanced breast cancer. In our study we found that longest tumor diameter and tumor volume are the simplest and reliable parameters for predicting tumor response by MR imaging. In clinical practice, the MRI response prediction test offers the oncologist an objective tool to tailor the chemotherapy for each individual patient.

Abbreviations:
NAC – Neoadjuvant chemotherapy
LABC – Locally advanced breast cancer
DCE MRI –Dynamic contrast enhanced magnetic resonance imaging
GRE – Gradient recalled echo
TIRM – Turbo inversion recovery magnitude
FS – Fat saturated.
RECIST – Response evaluation criteria in solid tumours
mCR – morphologic complete response.
mPR – morphologic partial response
mSD – morphologic stable disease
mPD – morphologic progressive disease
FAC – 5-flourouracil, adriamycin, cyclophosphamide
DWI – Diffusion weighted imaging
ADC – Apparent diffusion coefficient
3D – Three dimensional

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