Assessment of response to Neoadjuvant chemotherapy in locally advanced breast cancer by Dynamic Contrast Enhanced MR Mammogram and comparison of result with pathologic results –a

Prospective study

DISSERTATION SUBMITTED FOR

M.D. DEGREE IN RADIODIAGNOSIS
BRANCH VIII
MADRAS MEDICAL COLLEGE
CHENNAI.

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CHENNAI, TAMILNADU
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MARCH -2009

CERTIFICATE

This is to certify that **DR. C.SUBHASHREE** has been a post graduate student during the period May 2006 to March 2009 at Department of Radiodiagnosis, Madras Medical College and Research Institute, Government General Hospital, Chennai.

This Dissertation titled "Assessment of response to Neoadjuvant Chemotherapy by Dynamic Contrast Enhanced MR Mammogram in locally advanced breast cancer and comparison of result with pathologic results **"** is a bonafide work done by her during the study period and is being submitted to the Tamilnadu Dr.M.G.R. Medical University in Partial fulfillment of the M.D. Branch VIII RadioDiagnosis Examination.

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ACKNOWLEDGEMENT

I express my profound gratitude to **Dr. T. P KALANITI, M.D**., Dean Madras Medical College, Government General Hospital, Chennai who with his vast knowledge and experience has been a great source of inspiration. I am grateful to him for permitting me to utilize the facilities of this institution for conducting this study.

I profoundly thank **Prof.N.KULASEKARAN, M.D., DMRD, DIRECTOR I/C Barnard Institute of Radiology,** for his continuous guidance and prompt support in completing the thesis work, without his unparalleled support this work would not have been possible.

I express my heartfelt gratitude to **Prof. T.S.SWAMINATHAN M.D, DMRD, FICR-former Director of Barnard Institute of Radiology**, for the able guidance throughout the work and the prompt help rendered whenever approached.

I wish to express my sincere thanks to **Dr.V.CHANDRASEKHAR** former Director I/C, for his encouragement and guidance.

I wish to express my gratitude to all the Assistant Professors in our Department, **Dr.P.UMAPATHY, DR.SUNDARESHWARAN, DR.NESAMMANIVANNAN, DR.KALPANA, DR.S.BABUPETER, DR.S.RAMESH and DR.C.AMARNATH** who helped me immensely with their timely advice and guidance during the study.

I am indebted to the Professor of Radiation Physics of our Department **Prof. K. THAYALAN,** for giving me his time and help.

I wish to thank all my Post Graduate colleagues who co-operated with me and helped me during this study.

I wish to thank our Department radiographers for their kind co-operation during the study.

Last but not least, I wish to thank all the patients without whose kind co-operation, this study would not have been possible.

CONTENTS

Introduction

Breast cancer is the leading cancer in women . 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[18]. Worldwide, nearly 1 million cases are seen annually. Epidemiologists have calculated that a woman born today in the United States has a 1 in 8 chance of developing breast cancer in her life time and the life risk of dying from breast cancer is 3.3% or 1 in 30 women.

In India, breast cancer is second most common cancer among women next to cervical cancer. In Chennai, according to 2004 statistics, the most common cancer among women is breast cancer 26.5%, the next common is cervical cancer 21.2% and the others are ovary, stomach, and oral cancers. The crude ratio and age adjusted ratio per 100000 population for developing breast cancer is 24.4 and 26.6[19].

Most patients presented with locally advanced breast carcinoma. Ratio of locally advanced breast cancer (LABC) to early breast cancer, in our centre, is 70:30,as 0pposed to Western statistics where LABC accounts to less than 20%.

Neoadjuvantchemotherapy (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.

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).

Assessing response to neoadjuvant chemotherapy in breast cancer is important, because a nonreponsive 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. A complete tumour response to neoadjuvant chemotherapy increases the disease-free interval and patient survival. Hence assessing the response also prognosticates the patient's disease- free survival.

Physical examination is often unsatisfactory for assessment of the response of Locally advanced breast cancer to primary medical treatment.

Feldman *et al.* [1] reported That 45% of complete clinical responders had macroscopic tumour at histological examination; inversely, 60% of patients without any histological gross residual tumour had an incomplete clinical response. In the series of 49 patients studied by Cocconi *et al.* [2].

Physical examination overestimated tumour regression in 23% of cases and underestimated the response in 9%. The accuracy of physical examination is mediocre because palpation of a fibrotic and necrotic mass may mimic a residual tumour mass. In other cases, the apparent clinical regression is due to resolution of post-biopsy phenomena such as haemorrhage and oedema. Tumours in a progressive phase are difficult to assess by physical examination; regression of inflammatory phenomena is often the sole objective parameter as the tumour mass itself changes very little.

In the series of Balu-Maestro *et al.* ,(3) ultrasound has been found to be poorly reliable, evaluating the size of residual tumour after chemotherapy only in 43% of cases. In other series ultrasound was found to be superior to physical examination and mammography especially when the tumour was hypoechoic. Modification of tumoral echogenicity induced by chemotherapy limits the reproducibility of the measurements after treatment.

During the treatment the tumoral density decreases on successive mammograms. This density diminution cannot be measured and may even interfere with the

measurements because of the decreased contrast ratio between tumoral and normal tissue. Ultrasound may then be more reliable.

When the tumour is fractionated, plurifocal, or when it is larger than the field of the probe, the ultrasound measurements are not so reliable. In multifocal disease, the advantage of ultrasound is controversial. Infra-clinical or infra-mammographic lesions may be found that will change the therapeutic strategy but will not be characterized with certainty by this method. Ultrasound is able to measure the skin thickness and oedema and to follow their evolution. Ultrasound is the best modality for examining lymph nodes (sensitivity 72%–84%, specificity up to 97% with high frequencies probes) [5,6]. Controversial results about ultrasound in the literature emphasize the importance of parameters that interfere with the accuracy of the method. The main one is operator dependence. However, the technique is changing and must not remain only morphological especially in monitoring treatment of cancers.

An early decrease or disappearance of tumour vascularity evaluated by **Doppler ultrasonography** may reflect the efficiency of chemotherapy before any decrease in tumour volume. On the contrary, an increase in tumour vascularity reflects tumour progression.

MRI allows morphological analysis of tumours and kinetic study of the contrast enhancement reflecting the richness of the vascularization. It is the most reliable method

for appreciating multifocality. Its role is essential in pre-therapeutic staging and in the assessment of chemotherapy efficacy.

Most authors find an excellent correlation between the macroscopic tumour size and the tumour established by MRI.

In the series of Abraham *et al.* [8], in 97% of the cases, the results of MRI after treatment correlated with the pathological findings.

During or after neoadjuvant chemotherapy, role of MRI is to (a) monitor early response to treatment (b)identify possible residual disease.

To avoid harm and costs due to inefficient treatment it is desirable to predict response to Neoadjuvant chemotherapy as early as possible, ideally immediately after the first cycle. Imaging at this stage is aimed at demonstrating a metabolic response to treatment ,like change in contrast enhancement and time activity curve ,rather than change in tumor size. Since assessing response to chemotherapy shall have substantial impact on clinical decision –making, it may emerge as one of the important indications of breast MRI.[17].

To obtain more and higher level evidence for this indication The American College of Radiology imaging network(ACRIN) has sponsored a multiinstitutional prospective trial (ACRIN 6657) to evaluate the role of MR in predicting response to treatment.[17]

In our study we have studied the response of neoadjuvant chemotherapy to locally advanced breast cancer by dynamic contrast enhanced MR mammogram and compared its efficacy with post surgical histopathology results.

MR MAMMOGRAM–HISTORY OF DEVELOPMENT AND TECHNIQUES

Limitations of conventional breast assessment

- Includes the combination of screen-film X-ray mammography, high-resolution breast ultrasonography (US), and clinical breast examination leads to the detection of approximately 85-90% of breast malignancies, and it forms the foundation of modern strategies for breast cancer detection. The results of this assessment also serve as the final arbiter for the use of breast biopsy in breast screening programs worldwide.

Limitations of conventional breast assessment

- Despite cases in which conventional assessment fails to depict a breast malignancy accurately, as in 1 of the following scenarios.

- Palpable lesion without a focal imaging correlate.

- So-called interval cancers that are missed or not visible on initial images.

- Understaging of the extent of the lesion or multifocality in the same or opposite breast.

- Patient presenting with distant or axillary breast cancer metastasis with no breast lesion

found on mammograms or sonograms.

•Chest wall invasion that is not detected.

•Inaccurate clinical assessment of large tumors that are treated with neoadjuvant chemotherapy.

Development of breast MRI

•Combination of rapid 2D gradient-echo (GRE) imaging with a dedicated breast coil, coupled with the bolus injection of gadolinium dimeglumine (Kaiser, 1989) that created the technique of dynamic contrast-enhanced breast MRI.

•This technique showed an extremely high sensitivity for breast malignancy, which in some cases exceeded that of conventional imaging.

Although this technique was initially limited to a single section location, it was soon modified with newly developed multisection spoiled GRE sequences, with no loss of sensitivity. This still forms the foundation of modern breast MRI. Indications for MR MAMMOGRAM

- **As a screening tool**:

High risk screening

Screening women with dense breast tissue

❖ **As a diagnostic tool**:

To look for occult lesion

To look for multicentricity

❖ **As a staging tool**:

To assess chest wall invasion

❖ As a prognostic tool:

Assess neoadjuvant chemotherapy response

To look for residual disease if tumor margins are not free

To diff scar from recurrence

❖ **Contraindications to MRM**

●Contraindication to gadolinium-based contrast media (eg, allergy, pregnancy, renal failure etc)

●Patient's inability to lie prone

●Marked kyphosis or kyphoscoliosis

●Marked obesity

●Extremely large breasts

●Severe claustrophobia

EQUIPMENT

MRI with field strength with more than 1 tesla

Low-field-strength magnets lack the gradient subsystems required for high-speed, high-resolution volumetric (3D) images, which are now considered essential for the detection of small lesions and for architectural evaluation.

BREAST COIL

A dedicated double breast surface coil is essential because it permits simultaneous high-resolution, high-quality imaging of 1 or both breasts. With patients lying prone with both breasts freely suspended in these coils. Such breastcoils should have excellent homogeneity with minimal image shading and hot spots; otherwise some regions show low signal intensity and poor enhancement, and fat suppression may be unpredictable.

CONTRAST AGENT

Any ECF contrast agent-Gd meglumine, gadodiamide, gadoteric acid agents. Given contrast agents as rapid bolus injection at 2ml/sec followed by 20ml NS flush a dose of 0.16 mmol/kg appears to provide better sensitivity for lesion detection compared with the standard dose of 0.1 mmol/kg at field strengths less than 1.0 T (Heywang-Kˆbrunner, 1994).

Injection timing is important for MRM.Aim to acquire post contrast data within 1-2 min.

AXIAL, SAGITTAL, CORONAL-The acquisition plane has a significant impact on the pulse sequence. Phase-direction motion artifacts due to breathing and heart motion are minimized by ensuring that the frequency-encoding direction is in the anteroposterior direction for axial and sagittal imaging.

ACTIVE FAT SATURATION OR SUBTRACTION?[20]

Active fat suppression or fat suppression means the signal from fatty Tissue is specifically eliminated('knocked out') by additional Radio frequency pulses or by choosing water selective acquisition. Both types take extra acquisition time, therefore difficult to reconcile with dynamic protocols.

Subtraction does not require extra acquisition time and is not influenced By magnetic field inhomogeneities, which is why it is the preferred type of fat suppression for bilateral imaging. The main disadvantage of subtraction is that it may suffer from patient motion. Subtraction errors occur if precontrast images are not entirely congruent with post contrast images, even due to subtle patient motion. Breast immobilization is achieved by gently fixating (not compressing) the breast in the section encoding direction. This is mediolateral direction for sagittal protocols and craniocaudal direction for transverse protocols. Compression should be avoided because it may reduce

enhancement of breast cancers.[21].

●**BIRADS MRI imaging lexicon**

All suspicious areas are defined as:

●***Focus/foci*** - <5mm

●***Mass*** - 3D space occupying lesion with convex margin

●**Non mass enhancement**

- ❖ Further characterisation of mass

●Shape (round/oval/lobular/irregular)

●Margin (smooth/irregular/spiculated)

●Internal enhancement pattern (homogeneous/ heterogeneous/ rimlike/ central/septal)

- ❖ **Further characterisation of non-mass lesion**

●Distribution (focal/ multifocal/ linear/ ductal/ regional/ segmental)

●Internal enhancement (homogeneous/ heterogeneous/ stippled/ clumped/ reticular)

- ❖ **Morphologic criteria for malignant processes**

●Irregular margin

●Spiculated

●Thick irregular rim enhancement

●Segmental non mass enhancement

●Lacelike/dendritic pattern of enhancement in inflammatory Carcinoma

●Other features: focal perilesional edema & architectural distortion

- ❖ **Enhancement kinetics**

●3 types

●**Type 1 curve**: progressive enhancement (80% associated with benignity)

●**Type 2 curve**: plateau pattern-initial increase followed by flattening (suspicious for malignancy)

●**Type 3 cur**ve: washout pattern-brisk increase followed by rapid washout(80% associated with malignancy)

- If early rapid enhancement due to neovascularity were unique to malignant tissues, MRM would be the standard in clinical practice today!

  Unfortunately, such enhancement is not specific, and several benign conditions

may enhance in a fashion similar to cancer. Conversely, a small percentage of malignancies either enhance identically to benign breast parenchyma, or rarely, they do not enhance at all.

Nonmalignant mimics of malignant enhancement

Cyclical parenchymal enhancement-in the secretory phase of menstrual cycle

Fibroadenoma

Sclerosing adenosis

Florid epithelial hyperplasia

Infection

Fat necrosis

Post treatment scarring and/or granulation tissue.

Hence MR mammogram is always done in the proliferative phase preferably First 10 days of menstrual cycle to minimize the normal parenchymal enhancement.

Malignancy that may show benign-type enhancement

Common - Low-grade DCIS

Uncommon –

High-grade DCIS

Highly scirrhous IDC

Invasive lobular carcinoma

Mucinous carcinoma

Papillary carcinoma

Tubular carcinoma

ANATOMY OVERVIEW

Anatomy of breast[10]

The breast is a modified skin gland that develops from the mammary ridge in the embryo. It generally lies on the chest wall between the clavicle and the sixth to eighth ribs. Breast tissue can be found as far medially as the sternum and laterally to the midaxillary line.

Breast tissue is frequently found high in the axilla, occasionally reaching to its apex. The breast lies on top of and lateral to the pectoralis major muscle, whose muscle fibers course obliquely from the ribs to the humerus. Since breast tissue frequently wraps around the lateral margin of the pectoralis major muscle, imaging the breast is best accomplished using the mediolateral oblique projection. The best way to image the most tissue is by positioning the breast such that the plane of compression is parallel to the oblique fibers of the free margin of the muscle. This permits maximum traction on the breast so that it can be fully positioned over the detector and comfortably compressed. It also permits evaluation of the portion of the breast that lies lateral to the muscle and extends up into the axilla.

Recent work at the MGH by Jennifer Rusby, MD, suggests that there are usually more than 20 lobes or segments that are defined by the major lactiferous ducts that open on the nipple. A lobe (segment) can be thought of as a tree whose trunk, branches, and

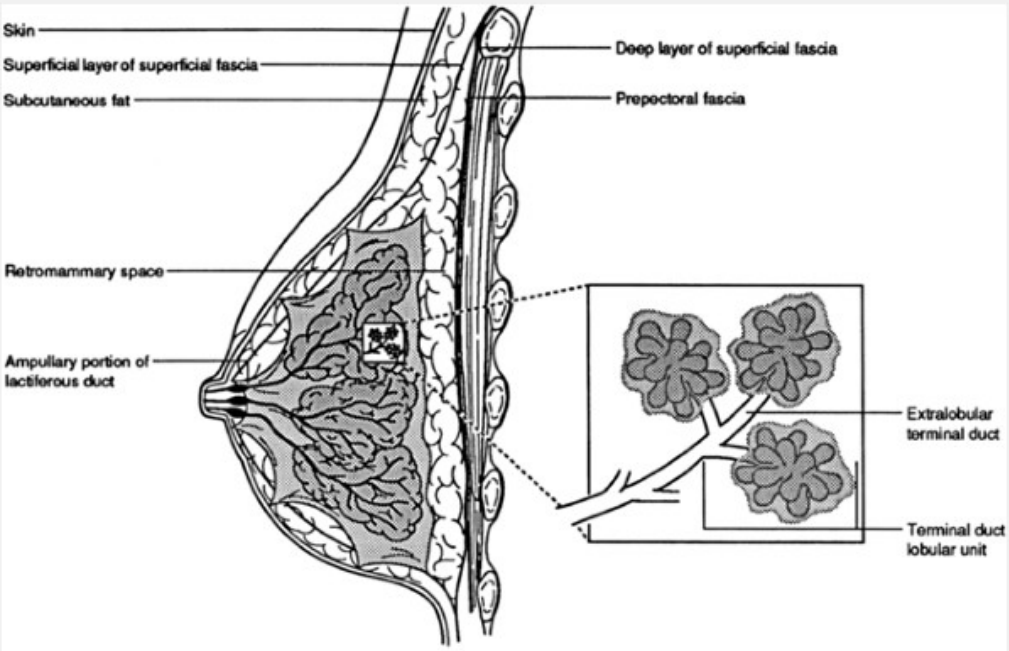
leaves are hollow. These arborizing networks conduct milk from the lobules (the true glands of the breast) to the nipple. The lobule is actually the most proximal of the structures if direction is the flow of breast secretions (milk), but it is called the terminal portion of the duct system. The lobule consists of multiple blunt-ending ductules in a cluster like the fingers of a glove. These fingers form the glandular acini of the lobule. They are surrounded by specialized connective tissue that differs histologically from the stromal connective tissue found in the rest of the breast.

The acini and specialized connective tissue together form the lobule. A terminal duct and its lobule are collectively called the terminal duct lobular unit (TDLU) . TDLUs can be found as immediate branches of the major ducts and are not always at the periphery of the ductal networks.

Breast cancer is thought to originate in the terminal duct in the lobule.

One theory is that this is the location of stem cells and that these undifferentiated cells are the most likely to develop malignant transformations.

The breast is held together by varying amounts of connective tissue that form varying volumes of sheets of tissue known as Cooper's ligaments. Fat is interspersed throughout the breast and surrounds it as subcutaneous and retromammary adipose deposits.


Skin
Superficial layer of superficial fascia
Subcutaneous fat
Retromammary space
Ampullary portion of lactiferous duct
Deep layer of superficial fascia
Prepectoral fascia
Extralobular terminal duct
Terminal duct lobular unit

The Vascular Supply of the Breast

Arterial blood flows from the axillary artery through the lateral thoracic artery to supply the upper outer quadrant of the breast. The central and medial portions of the breast are supplied from perforating branches of the internal mammary artery, which lies adjacent to and beneath the sternal border. Branches of the intercostal arteries provide blood to the lateral breast tissues, with some blood coming from the subscapular and thoracodorsal arteries.Venous drainage is back through the axillary, internal mammary, and intercostal veins, providing three major routes for hematogenous metastasis.

Enervation

Nerves supplying the breast originate primarily from the anterior and lateral cutaneous branches of the thoracic intercostal nerves, with some enervation from the cervical plexus to the upper breast. The deep pain sensors in the breast appear to be variable.

The Lymphatics of the Breast

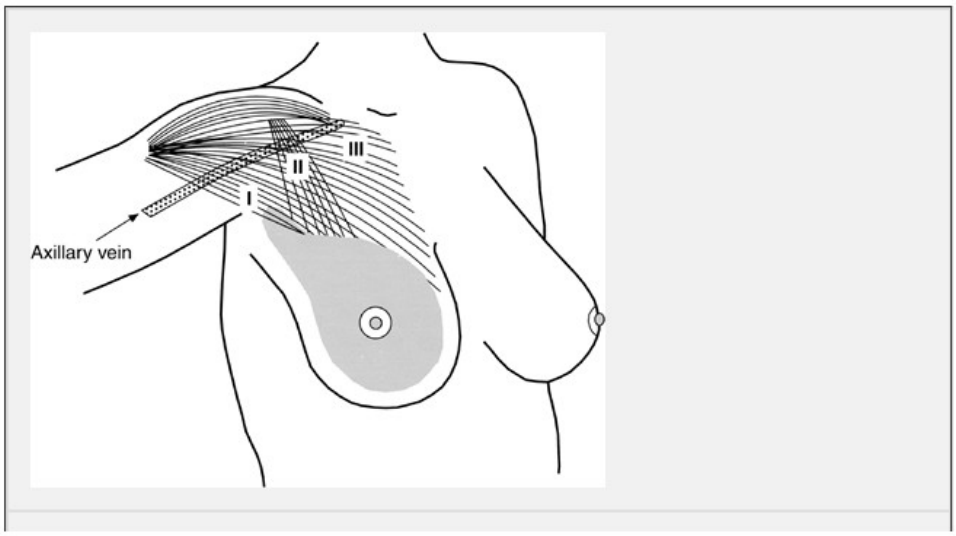
For staging purposes and prognostication, axillary lymph nodes are divided into three levels.

Level I lymph nodes are lateral to the lateral margin of the pectoralis major

muscle and extend down into the tail of the breast. Mammography can frequently demonstrate the lowest lymph nodes in this portion of the lymphatic chain.

Level II lymph nodes are beneath the pectoralis minor muscle. When an axillary dissection is performed, the free margin of the pectoralis major muscle is retracted out of the way and preserved, and the pectoralis minor muscle is transected to remove these lymph nodes. This is also performed when a modified radical mastectomy is used to treat breast cancer.

The level III lymph nodes are medial and superior to the pectoralis minor muscle, up to the clavicle. Data suggest that the higher the level of nodal involvement with cancer, the worse the prognosis.



Levels of Axillary lymph nodes

Literature review

Conventional imaging methods (mammography and USG) are not very useful in assessment of response to pretreatment or neoadjuvant chemotherapy.

MRI has an established role in assessment of response of breast cancer to neoadjuvant Chemotherapy.Dynamic contrast enhanced (DCE) MRI and FDG PET serve as biomarkers in functional assessment of tumor post chemotherapy.

Retrospective analysis of conventional imaging and physical examination was done at MD Anderson chemotherapy trials[11].

	Correlation Between Measurements*	
Comparison	**Preneoadjuvant Chemotherapy**	**Postneoadjuvant Chemotherapy**
PE vs. US	0.45	0.28
PE vs. M	0.40	0.26
US vs. M	0.58	0.35
PE vs. pathology	--	**0.42**
US vs. pathology	--	**0.42**
M vs. pathology	--	**0.41**

*Spearman rank correlation coefficients.
PE indicates physical examination; US, ultrasonography; M, mammography

Table :1 -Correlation of tumor measurements

Table 2: Correlation with pathologic tumor size among published studies.

Study	n	Physical Exam	Ultrasound	Mammography
Fourouhi et al (1994)	35	0.88	0.96	0.94
Gawne-Caine et al (1995)	16	0.74	0.85	0.61
Herrada et al (1997)	100	0.73	0.60	0.65
Akashi-Tanaka et al (2001)	57	0.57	0.56	0.55
Fiorentino et al (2001)	141	0.68	0.29	0.33
Chagpar et al (2006)	189	0.42	0.42	0.41

MRI prior to chemotherapy is accurate than USG or mammogram in assessing especially multifocal disease and DCIS (ductal carcinoma in situ). MRI following chemotherapy performs equally accurately in assessing the response to treatment compared to USG and mammography.

Table 3- Review of studies

Study	n	MRI	Physical Exam	Mammo	US
Weatherall et al (2001)*	20	0.93	0.72	0.63	--
Rosen et al (2003)*	21	0.75	0.61	--	--
Akazawa et al (2006)*	38	0.89	--	--	0.48
Montemurro et al (2005)*	21	0.82	--	--	0.71
Balu-Maestro et al (2002)†	51	63%	52%	38%	43%
Yeh et al (2005)†	31	71%	19%	26%	35%

*Comparison given by correlation coefficient.
†Comparison by concurrence criteria.

MRI is effective for measuring the degree of tumor response, but can miss residual disease ,particularly for good responders.[12,13,14,15]

Complete response to chemotherapy does not preclude surgery at any cost.

MRI for monitoring accuracy has led to increased interest in using MRI to assess response to treatment. DCE MRI used as part of functional imaging.

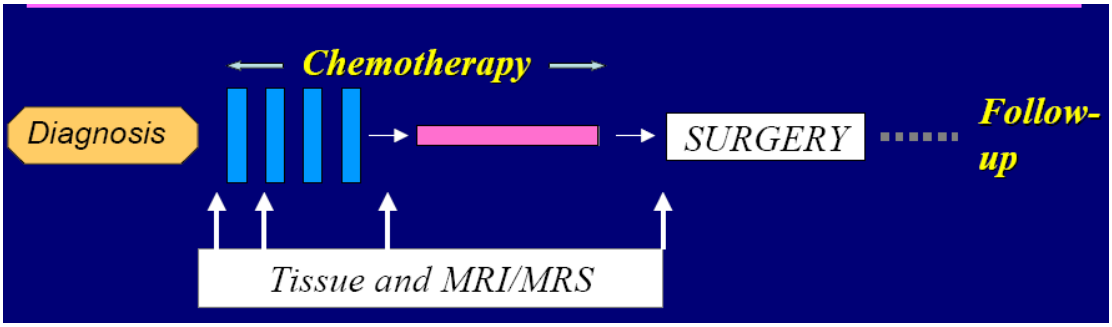
Measurements made to assess response in MRI-tumor volume, tumor morphology, vascular heterogeneity.

At the outset we defined **a morphologic partial responder** as one who exhibits 1.>50% reduction in actual tumor size 2. decrease in maximal contrast enhancement & 3. flattening of time-activity curve.

A morphologic complete responder as one who showed no residual tumor in MRI after 3 cycles of chemotherapy.

A patient with **Stable disease** as one who showed decrease in tumor volume less than 50%

A patient with **Progressive disease** as one who showed increase of >25% in tumor volume.



Functional measurements by MRI (DCE-MRI, diffusion weighted MRI, MR Spectroscopy) can be used to make quantitative measurements of tumor biology (microvascular permeability ,water diffusion and choline concentration).

TABLE :4
AMERICAN JOINT COMMITTEE ON CANCER STAGING OF BREAST CANCER

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
Tis DCIS)	Ductal carcinoma *in situ*
Tis LCIS)	Lobular carcinoma *in situ*
Tis (Pagets)	Pagets disease of the nipple with no tumor
T1	Tumor 2 cm or less in greatest dimension
T1mic	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	More than 1 cm but not more than 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to chest wall or skin, only as described below

Definition of locally advanced breast carcinoma by stage grouping –AJCC 6th edition

TABLE:5- Definition of LABC

Stage Grouping			
0	Tis	N0	M0
I	T1[7]	N0	M0
IIA	T0	N1	M0
	T1[7]	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1[7]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Contd.

_ T3	Tumor more than 5 cm in greatest dimension
_ T4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below.
_ T4a	Extension to chest wall, not including pectoralis muscle
_ T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
_ T4c	Both T4a and T4b
_ T4d	Inflammatory carcinoma

AIM OF THE STUDY

AIM OF THE STUDY

Assessing the response to neo-adjuvant chemotherapy with dynamic contrast enhanced MR mammogram using

- Tumor size,
- Contrast enhancement pattern and
- Time–activity curve as parameters, in locally advanced breast cancer.

MATERIALS AND METHODS

Period of study: September 2007 to October 2008.

Patient population: Patients selected for the study would be from stage IIB to stage IIIC breast carcinoma. Lumps small enough for the surgeon to give good tumor clearance and cancers with metastasis (stage 4) would be excluded from study.

Inclusion criteria

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

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.

PRE MRI WORK UP:

Clinical assessment of tumor & lymph nodes by

- Physical examination,
- X-ray mammogram,
- Sonomammogram and Doppler.

- Assessment of renal function –blood urea and serum creatinine values. Institutional ethical committee clearance was obtained before the start of the study and informed consent was obtained from every patient for use of MRI contrast medium.

MR MAMMOGRAM:

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 phased array body coil and using MR contrast (gadodiamide) in the dose of 0.16mmol/kg. Core biopsy of lesion would be done and sent for HPE.

Dynamic CE MR mammogram was repeated after the third cycle of chemotherapy (after 2weeks of completion of 3rd cycle). Response to neo adjuvant chemotherapy was assessed in terms of tumor size (tumor volume, longest tumor diameter), maximal contrast enhancement and change in time-activity curve.

MRI SEQUENCES:

- T1 axial, sagittal T2,TIRM axial
- 3D GRE sequence –axial
- 3D GRE Sequence with fat saturation(pre contrast)- axial
- 3D GRE sequence with fat saturation –post contrast

With dynamic study, MR contrast agent (gadodiamide) was given at the dose of 0.1 mmol/kg of bolus Intravenously into a cannula in the antecubital vein fixed before the MRI the contrast was given by hand injection over time of 10 seconds by a single radiologist[17], 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 earlypost contrast phase with acquisition beginning within 60 seconds of start of contrast injection, scan was repeated at 2,4,6 & 8 minutes. Comparison of pre & post neoadjuvant chemotherapy MR mammogram images was done.

Change in tumor size-percentage of reduction in tumor volume & longest diameter were assessed. Change in maximal contrast enhancement and change in the time activity curve were assessed. After 3 cycles of chemotherapy, core biopsy/mastectomy specimen was subjected to pathologic study. The results in MR mammogram were compared with pathologic results.

All 20 were followed up till surgery with histopathological correlation. As per the morphologic and enhancement kinetics response criteria the images were analysed by a radiologist experienced in breast imaging.

IMAGE REVIEW AND ANALYSIS

The images were analysed by 2 radiologists with more than 3 years experience in breast MR imaging.

Tumor volume was calculated in dynamic contrast enhanced MR image at 120 sec of the study using volume assessment software. Tumor volume reduction was assessed in the study done after 3 cycles of chemotherapy.

At the outset we defined

- **A morphologic partial responder** as one who exhibits

    1. >50% reduction in actual tumor size
    2. Decrease in maximal contrast enhancement &
    3. Flattening of time-activity curve.

- **A morphologic complete responder** as one who showed no residual tumor in MRI after 3 cycles of chemotherapy.

- A patient with **Stable disease** as one who showed decrease in tumor volume less than 50%.

- A patient with **Progressive disease** as one who showed increase of >25% in tumor volume.

For the **time –activity curve,** ROI was drawn on the first image of the batch. Care was taken no non tumoral area came under the ROI and that entire area of interest was within the tumor. The area of interest taken was to 0.4 square cm.

RESULTS

Results

5 patients could not be followed up beyond the first cycle of chemotherapy, we are excluding them at the outset. Attrition in our study was 20%. The remaining 20 women in our study, were in the age range of 33 to 60 years.

The mean age of our patients was 48.2years. Of the 25, 12 were of stage $T_{4b}N_1M_{0.}$ 3 members were T_{4a} N_1 $M_{0.}$ 9 members were of stage $T_3N_1M_{0.}$ 1 person was of stage $T_2N_1M_0$.

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 were partial responders (75%).3 out of 20 were morphologic complete responders (15%).2 out of 20 had stable disease (10%). Out of 20,17,patients had Type 3 time activity curve before chemotherapy and 3 had indeterminate or type 2 curve.

Following chemotherapy 14 out of 15 with partial response showed flattening of time –activity curve to Type 2 curve, Whereas 1 partial responder showed persistent

type 3 curve whereas 1 patient with stable disease showed persistent type 3 curve and another showed flattening to type 2 curve.

Statistical analysis was done using **Student paired test**.

Overall tumor volume reduction was 88% on the average. In **responders** the tumor volume reduced by a mean 91.5+/-135ml.

In **non-responders** the tumor volume reduction was mean 6.6ml+/-12.6ml. **P value =0.03-significant.**

Regarding time-activity curve, 93% (14 out of 15 partial responders) showed a change of malignant type (type 3) of curve to indeterminate or benign morphology (type 2 or 1) following 3 cycles of chemotherapy. 1 of the 2 non-responders showed a persistent malignant morphology of curve. The other showed a response to type 2 curve.

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

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 33%.

There were no patient characteristics including patient age and menstrual state or tumor stage that predicted response.

In both **non-responders** there was no significant change in tumor size. All the **responders** a decrease in tumor size was noted **Thus decrease in tumor size is the best early predictor of tumor response**.

The morphology of time-activity curve is a semi-quantitative , non-cumbersome method to know about reduction of neoangiogenesis of tumor in response to neoadjuvant chemotherapy. However the more complex quantitative kinetic analyses like the transfer constant are the only the most reliable parameters to assess neoangiogenesis, which was not done in our study.

With time-activity curve, 93% (14 out of 15 partial responders) showed a change of malignant type (type 3) of curve to indeterminate or benign morphology (type 2 or 1) following 3 cycles of chemotherapy.1 of the 2 non-responders showed a persistent malignant morphology of curve. The other showed a response to type 2 curve.

Hence the time activity curve showed 93% sensitivity in our study to detect tumor response. Whether time activity curve showed functional tumor response before reduction in tumor size, we were not able to tell from this study, because imaging was not done during the early cycles of chemotherapy (eg after the first cycle of chemotherapy).

TABLE 6: Chemotherapy regimen, Tumor volume, Morphologic response & Pathologic findings.

S. No.	Age	Stage	Chemo therapy regimen	Pre chemotherapy Tumor volume(ml)	Post chemotherapy Tumor volume(ml)	Morphologic response	Pathologic Findings
1	47	T4bN1M0	FAC	1575	200	m PR	IDC
2	50	T4b N1 M0	FAC	605	42	m PR	IDC
3	45	T4b N1 M0	FAC	52	18	mPR	IDC
4	55	T4b N1 M0	FAC	198	25	mPR	IDC
5	55	T4b N1 M0	FAC	240	30	mPR	IDC,DCIS
6	45	T2N1M0	FAC	8.7	6	mSD	IDC,DCIS
7	35	T3 N1 M0	FAC	182	0	mCR	IDC
8	70	T4b N1M0	FAC	46	25.4	mSD	IDC,DCIS
9	33	T4b N1 M0	FAC	48	4	mPR	IDC
10	45	T3N1M0	FAC	2	0	mCR	IDC
11	39	T3N1M0	FAC	250	15	mPR	IDC
12	42	T3N1M0	FAC	56	0	mCR	IDC
13	55	T4b N1M0	FAC	40	3	mPR	IDC
14	65	T4b N1 M0	FAC	42.5	6	mPR	IDC
15	42	T4b N1M0	FAC	56	14	mPR	IDC
16	45	T4b N1 M0	FAC	177	20	mPR	IDC
17	52	T3 N1M0	FAC	180	1.5	mPR	IDC
18	30	T4a N1 M0	FAC	535	50	m PR	IDC

19	45	T4a N1 M0	FAC	190	13	mPR	IDC
20	43	T3N1M0	FAC	217	20	mPR	IDC

F-5=Flourouracil, A=Adriamycin, C=Cyclophophamide, DCIS=Ductal carcinoma in situ, IDC=Infiltrating ductal carcinoma, mCR=Morphologic complete response, m PR =Morphologic partial response, m SD = Morphologic stable disease

DISCUSSION

DISCUSSION

Assessment of response to locally advanced breast cancers done in our Centre where the ratio of Locally advanced breast cancer (LABC) to Early breast cancer is 70%: 30% patients presented with huge masses-T4 category.

Maximum tumor diameter encountered was 16cm, maximum tumor Volume encountered was 1575ml (prechemotherapy).

We have used phased array body coil to image the breast in Assessment of residual tumor in such large masses as we have encountered, DCE MR mammogram with phased array body coil correlated well with macroscopic tumor size in pathology.75% of patients showed partial response in MRI, all of which correlated with histopathology.

Out of 3 persons with morphologic complete response, 2 correlated with HPE which showed pathologic complete response.1 person who showed m CR had residual disease in pathology. Non-responders in our study were 10% for whom MRI and pathologic results correlated.

Thus decrease in tumor size is the best early predictor of tumor response. 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 33%.

Results of all research have shown that successful treatment causes decreases in rate and magnitude of contrast enhancement and that poor response results in persistent abnormal enhancement.

With time-activity curve, 17 out initial 20 persons showed type 3 or malignant type of time activity curve (85%). 3 out of 20 (15%) type 2 or indeterminate curve. All the 17 which showed type 3 curve showed early peak of contrast wash-in within the first 120 seconds and showed rapid washout which is typical of malignant contrast enhancement kinetics.

93**%** (14 out of 15 partial responders) showed a change of malignant type (type 3) of curve to indeterminate or benign morphology (type 2 or 1) following 3 cycles of chemotherapy. 1 of the 2 non-responders showed a persistent malignant morphology of curve. The other showed a response to type 2 curve.

Hence the time activity curve showed 93% sensitivity in our study to detect Tumor response. Whether time activity curve showed functional tumor Response before reduction in tumor size, we were not able to tell from this study, because imaging was not done during the early cycles of chemotherapy (eg after the first cycle of chemotherapy).

Hence the time activity curve is an non cumbersome parameter to assess early functional tumor response to neoadjuvant chemotherapy.

More complex contrast kinetics calculations like the transfer constant etc, which are better parameters for reduction in tumor angiogenesis were not assessed in our study.

The causes of the changes in time –activity curve that we observed are likely to be multifactorial, relating to both microvessel density and function.

A possible explanation is that successful chemotherapy causes reductions in tumor-angiogenic factors, including VEGF-vascular endothelial growth factor. VEGF is a strong stimulus of tumor neoangiogenesis and a potent tissue permeability factor in breast cancer [22].

With respect to the vasculature, it is clear that VEGF is also required for vascular homeostasis and maintains the high fraction of immature vessels within most tumors. Immature vessels (those without investing pericytes and/or smooth muscle cells) are highly dependent on exogenous survival factors, including VEGF [23], and these immature vessels are by definition the most permeable.Cytotoxic tumor cell death would result in a reduction of tissue VEGF production and hence apoptosis of endothelial cells in immature vessels. Endothelial cell apoptosis in immature vessels as a response to VEGF withdrawal has been noted in a number of treatments, including antiangiogenicand hormonal treatments [24,25,26].

Drug delivery is best to areas of highest microvessel permeability. With high drug concentration, tumor cell death would result in VEGF withdrawal and apoptosis of immature vessels, leading to a decrease in contrast enhancement and change in time activity curve.

On the other hand, tumor resistance to chemotherapy would result in ongoing production of angiogenic factors that maintain or increase the proportion of immature vessels.

TABLE 7:COMPARISON OF MRI versus HPE

	HPE POSITIVE	***HPE NEGATIVE***
MRI POSITIVE	***19***	***0***
MRI NEGATIVE	***1***	***2***

Study limitations

1. Even though imaging tumor size correlated with pathology, not using a dedicated breast coil is major limitation in our study, where we have used phased array body coil to cater to the economically deprived population.

2. Attrition rate in our study was 20%.

CONCLUSION

CONCLUSION

MR imaging following neoadjuvant chemotherapy is an important Investigation tool to assess early response to neo adjuvant Chemotherapy and to assess residual tumor at the end of neoadjuvant Chemotherapy.

Tumor volume is the best early predictor of tumor response. The time activity curve obtained from the dynamic contrast enhanced MR Mammogram is an early functional parameter in assessing tumor response to neoadjuvant chemotherapy even before any reduction in tumor size occurs.

Hence MR Imaging can be used to assess tumor response to neoadjuvant chemotherapy, which is important for clinical decision making, prevents unnecessary adverse effects to patients and prevent financial loss.

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GLOSSARY

LABC	-	Locally advanced breast cancer
mPR	-	Morphologic partial response
mCR	-	Morphologic complete response
mSD	-	Morphologic stable disease
mPD	-	Morphologic progressive disease
pCR	-	Pathologic complete response
DCIS	-	Ductal carcinoma in situ
IDC	-	Infiltrating ductal carcinoma
MRM	-	MR mammogram
FAC	-	5 flouro uracil, adria mycin, cyclo phosphamide
ROI	-	Region of interest

PROFORMA:

NAME :
AGE:
ONCOLOGY NO:
ADDRESS:

CLINICAL HISTORY:
Marital status
Obstetric details
Pre/postmenopausal
CLINICAL EXAMINATION:
R/L breast lump - Size
Fixity to skin ,chest wall
Axillary nodes-number,fixity
TNM STAGING

PRE MRI WORK UP

Blood urea
Serum creatinine

X ray mammogram-size of lump,lymph nodes
Sonomammogram –size of lump , vascularity,
number of lymph nodes

MR MAMMOGRAM

Size – Dimensions
Tumor volume
Time activity curve
Lymph nodes