

Diagnostic Accuracy of MRI in Breast Cancer-A Study of 156 Cases.

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ABSTRACT

Background: Background- MRI helps in detection of multicentric and multifocal disease in the same breast as well as in identification of synchronous lesions in contralateral breast. MRI imaging done with dedicated breast coil and thin section imaging of the axilla is an effective tool in determining the axillary lymph node metastasis in newly diagnosed cases of breast cancer. Aims-To study those interpretation criteria of MRI that serve to increase the sensitivity and specificity of identifying non-mass like enhancement, multi centricity and nodal characteristics in breast cancer patients undergoing breast conservation surgery. **Methods:** Retrospective analysis of 156 patients was conducted in the Department of Radio diagnosis; Max Hospital, New Delhi, from September 2011 to June 2014. Both were correlated for tumor size, multifocality, multicentricity, extension of DCIS, nodal characteristics, extension to nipple and contralateral breast lesions. **Results:** In our study, detection of NMLE on MRI had a sensitivity of 89% and specificity of 78%. Lymph nodes with cortical thickening had a higher sensitivity (86% vs 65%) but lower specificity (69 % vs 89 %) than fatty hilum. Sensitivity was high for post lumpectomy with positive surgical margins and post NACT patients (100%). **Conclusion:** MRI has a high sensitivity in detection of breast cancer lesions. The detection of multicentric/ multifocal lesions in the same as well as contralateral breast and non-mass like enhancements is critical in deciding breast conservation surgery.

Keywords: Breast cancer, breast conservation surgery, MRI.

INTRODUCTION

Breast cancer is the second most common cause of cancer deaths among women exceeded only by lung cancer. However the number of deaths reported have been decreasing mainly contributed by earlier detection through screening mammography and improved treatment strategies.^[1] Accurate staging of breast cancer is important in treatment planning and radiological findings are being incorporated into clinical staging as a routine protocol.^[2-5] Screening mammography is used for early detection of breast cancer and Ultrasound is mainly used as a diagnostic modality and for guided biopsies. Contrast enhanced MRI along with Diffusion weighted imaging has come up to play a pivotal role in breast cancer staging in conjunction with mammography and ultrasound and can be used as a roadmap in treatment planning.^[6,7]

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DCE-MRI helps in detection of multicentric and multifocal disease in the same breast as well as in identification of synchronous lesions in contralateral breast. Involvement of the chest wall or pectoral muscle and the skin is better demonstrated by MRI which upgrades the disease to T4.^[8-10] Identification of non mass like enhancement along with the index lesion increases the total span of the disease in the breast as compared with the clinical examination and may be a predictor of the presence of extratumoral DCIS or extensive intraductal component. DCE MR also helps in the nodal staging of breast cancer by showing the levels of suspicious axillary nodes as well as in detection of internal mammary nodes and supraclavicular nodes. The metastatic involvement of the axillary nodes is suggested by certain features such as rounding of shape, eccentric cortical thickening, compression or partial or complete effacement of fatty hilum. This information is necessary for treatment decision in choosing between breast conservation and mastectomy, preoperative and post-operative chemotherapy or hormonal therapy, sentinel lymph node biopsy and axillary lymph node dissection.^[1] However with all its capabilities and high sensitivity to identify and stage breast cancer, studies have shown that MRI has

a low specificity in terms of high false positive rates and in identifying and specifically characterizing the extratumoral and non-mass forming DCIS.

Aim

- To study those interpretation criteria of MRI that serve to increase its specificity in patients with non mass like enhancement and therefore bring down false positive results.
- To determine the accuracy of MRI in evaluating the multicentric / multifocal breast cancer and its significance as a roadmap in treatment planning.
- To study its role in predicting the nodal status in patients diagnosed with breast cancer.

MATERIALS AND METHODS

This is a retrospective study, conducted in the Department of Radiodiagnosis; Max Super Speciality Hospital, New Delhi, from September 2011 to June 2014.

The study was conducted after the approval of Institutional Review board. The Institutional Ethics committee waived informed consent, this being a retrospective study. 156 female patients with breast cancer, who underwent MRI in our department for assessment of the disease prior to treatment planning and subsequently underwent treatment in the hospital's Cancer centre, were included in our study. These also included 14 post lumpectomy patients operated elsewhere who either had positive surgical margins or were detected with breast cancer on lumpectomy specimen and MRI was conducted for assessment of presence of residual disease and its extent for further treatment planning. There were 14 post neoadjuvant chemotherapy patients in whom MRI was done to take a decision for wide excision or mastectomy depending upon the response.

Imaging

Magnetic resonance imaging

Equipment

MR imaging of the breast was performed on 3.0 Tesla MRI unit (Discovery 750 by GE Healthcare USA). All patients were imaged in the prone position using dedicated 8 channel bilateral breast coils and providing adequate compression.

Protocol For Breast MRI

After adequate positioning of patient on a dedicated phased array breast coil on a 3T scanner, following sequences were acquired -

- Non fat suppressed Axial T1
- Fat suppressed axial T2
- Axial Diffusion-1000B/value
- Axial Diffusion-1500B/value
- Axial T1/Supraclavicular
- Non fat suppressed axial T2

- Sagittal VIBRANT

Following this a dynamic transverse 3D fat suppressed spoiled gradient echo volume acquisition was acquired through both the breasts prior to and six times sequentially following intravenous administration of 0.1 mmol/kg Gd-DTPA. This was followed by a delayed high resolution contrast enhanced sagittal sequence. These images were then subtracted and reconstructed in multiple planes. Kinetic analysis was done in region of interest. Colour maps were also viewed on the work station using specialized software.

Interpretation Of MRI

Evaluation was done using ACR MRI BIRADS Lexicon

1. Focus/foci – tiny spot of enhancement, < 5 mm
2. Mass lesion- assessed for its size, morphology in terms of margins, shape signal characteristics, ADC value and enhancement characteristics (homogenous/ internal enhancing or nonenhancing septation/ heterogeneous/ clustered rim enhancement) and kinetic curves. Number of lesions (> 2 lesions taken as multiple) were also assessed.
3. Non mass like enhancement- assessed for its pattern and distribution (linear ductal/ clumped nodular/ clumped linear in focal/ductal/ segmental/ regional distribution).
4. Lymph nodes - assessed for eccentric cortical thickening/ partial or complete effacement of fatty hilum/ rounding of shape and perinodal fat stranding.

These patients eventually underwent mastectomy of wide decision with sentinel lymph node biopsy or axillary lymph node dissection. The final specimen pathology report was correlated with MRI findings and variables studied were number of lesions reported, size of the largest single tumor reported, intratumoral DCIS present/ absent, extratumoral DCIS/ LCIS, extensive intraductal component and nodal metastasis.

RESULTS & DISCUSSION

In our study of 156 patients, who were ranged between 25 and 70 yrs. The size of the primary lesion as measured on MRI correlated well with the histopathological size with correlation coefficient of $r = 0.91$. We compared the maximum dimension measured on MRI with the maximum dimension on pathology, although some studies have suggested that comparing the average size or the tumor volume gives more accurate results especially in patients on neoadjuvant chemotherapy.

Detection of additional lesions on MRI with or without nonmass like enhancement (NMLE)- In our study, Clinically and mammographically occult additional lesions were detected in 66/156 patients

(42.3%). Of these 34/66 (51.5%) with nonmass like enhancement were associated with the index lesion thereby increasing the total span of involvement on MRI. 25/34 (73.5%) of these lesions were confirmed on histopathology as extratumoral DCIS/LCIS or extensive intraductal component. 27/34 patients underwent mastectomy and 4/34 had wide local excision on the basis of MRI findings. In 9/34(26.4%) patients, pathology did not show any evidence of extratumoral DCIS or EIC. Of the rest 32 patients with additional disease, 22 patients had multifocal/multicentric disease with nonmass like enhancement and 10 patients had multifocal/multicentric disease without any associated nonmass like enhancement. 26/32 (81.2%) patients underwent mastectomy, 3 patients had wide excision while 3 patients had breast conservation surgery. In 27/32 (84.3%) patients, MRI results corroborated with the final histopathology results and in 5/32 patients, there were false positive results.

In various studies done by Lee et al, Mumtaz et al, Liberman et al, Boetes et al and Fischer et al,^[7,8,10-12] the sensitivity of MRI in detection of additional lesions was shown to be 33.3%, 11.8%, 27.1 %, 13.3% and 16.1% respectively. These variations are mainly contributed by the patient population as seen in the study by Rodenko et al all the 20 patients studied had Invasive lobular carcinoma and had multifocal/multicentric disease.^[13] In our study, 5/66 patients had ILC, 11/66 had predominant DCIS.

Sardanelli et al compared MRI and Mammography in detection of multifocal,^[14] multicentric cancer foci and found that the overall sensitivity was 66% (124/188) for mammography and 81% (152/188) for MRI ($p < 0.001$); 72% (113/158) and 89% (140/158) for invasive foci ($p < 0.001$); and 37% (11/30) and 40% (12/30) for in situ foci.

One of the main goals of our study was to optimally characterise nonmass like enhancement as benign and malignant according to their pattern and distribution, mainly based on BIRADs descriptors.

Our study showed Sn: 79%, Sp: 86%, PPV: 76%, NPV: 88% for NMLE versus extratumoral DCIS, while Sn: 74%, Sp: 76, PPV: 52%, NPV: 89% for NMLE versus extensive intraductal component (EIC) on histopathology.

In our study 26 patients were such who had NMLE and on histopathology they had both EIC and Extratumoral DCIS. There were 20 patients where there was no NMLE however on histopathology Extratumoral DCIS and/or EIC were present.

In practice various studies show different criteria and characteristics of NMLE to characterize it as benign and malignant. These criteria are morphological pattern (clumped nodular, linear nodular or linear spicular), kinetic curve (type 1,2,3) and signal enhancement ratio (SER).^[15] In our study we used morphological pattern and kinetics to grade the NMLE as malignant or benign.

Our analysis on the morphological characteristic of NMLE showed the most common pattern of NMLE associated with extratumoral DCIS and/or EIC was clumped nodular in ductal/segmental and regional distribution followed by linear nodular. The linear spicular pattern showed least number of malignant cases. Linear nodular pattern was most common in cases of Infiltrating Lobular carcinoma.

Hiramatsu et al found that linear and/or spotty enhancement on MRI suggested the presence of DCIS or intraductal spread in the area surrounding the invasive cancer.^[16] In their study of 72 patients, 50 showed linear and/or spotty enhancement on MRI and 41 of those 50 patients had DCIS or intraductal spread. The sensitivity, specificity and accuracy for detecting intraductal spread on MRI were 89%, 82% and 81%, respectively. The surgical decision of MRM purely on the basis of MRI findings was present in 48 patients

NMLE pattern correlation with extratumoral DCIS and/or EIC on Histopathology

	True positive	False Positive
Clumped nodular	33/66(50%)	3/66(4.5%)
Linear spiculated	3/66(4.5%)	5/66(7.5%)
Linear nodular	5/66(7.5%)	1/66(1.5%)
Clumped linear	1/66(1.5%)	15/66(22%)

Studies conducted by

Study	MRI changed decision to mastectomy	Mastectomy done with false positive findings
Bagley et al	Mastectomy 6/27 (22.2%)	Mastectomy 3/27 (11.1%)
Berg et al	Mastectomy 6/96 (6.3%)	Mastectomy 5/96 (5.2%)
Zhang et al	Mastectomy 5/54 (9.3%)	Mastectomy (none reported)
Godinez et al	Mastectomy 8/79 (10.1%)	Mastectomy 2/79 (2.5%)
Our study	Mastectomy 42/156 (26.9%)	Mastectomy 11/56 (0.07%)

The current treatment guidelines recommend wide excision or mastectomy for multifocal disease and mastectomy for multicentric disease, therefore identification of additional lesions on MRI does impact clinical treatment decisions. Although how much this extends into clinical and long term survival benefit is still a matter of debate. Clinical trials exist for both invasive and in situ carcinoma in which no significant difference in survival was found in patients treated with BCT or mastectomy. Both radiation therapy and adjuvant systemic chemotherapy contribute to low rates of cancer recurrence in treated breast. However MRI does play an important clinical role in patients newly diagnosed with breast cancer in aiding to plan a single definitive surgical procedure for management. In such cases even negative findings on MRI play a significant role. Identification of multicentric disease/ characteristic NMLE pointing towards

presence of extratumoral in situ disease and extensive residual disease help in identifying the patients who would benefit from mastectomy rather than breast conservation surgery.

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy or preoperative chemotherapy is increasingly used in patients with locally advanced breast cancer to downstage the disease making the initially unresectable tumors more amenable to resection. This increases the chances of breast conservation surgery over mastectomy in these patients.^[17] Accurate assessment of residual disease is important so that the surgical approach is optimised to ensure negative margins and reduce morbidity with optimum cosmetic effect.

Our study included 14 patients on NACT who underwent MRI for assessment of residual disease prior to surgical management. On MRI there were 12 partial responders, 1 complete responder and 1 nonresponder. On comparison with histopathology on final surgical specimen, one of the cases with PR on MRI had no residual disease in the mastectomy specimen giving a sensitivity of 100%, specificity of 50%, PPV of 92.31% and NPV of 100 % in our study.

In agreement with the study by Partridge et al,^[18] we considered any amount of enhancement more than the normal in the initial tumor bed as residual disease regardless of the enhancement kinetics. Residual tumor was indentified in 11/11 partial responders in our study. This is in correlation with studies by Partridge at Al [44/44],^[18] Gilles et al [17/18],^[19] Weatherall et al [20/20] and by Abraham et al [30/31],^[20,21] However, with this consideration we had 1/14 false positive case in which the tumor showed nonfocal enhancement with type 2 kinetics, thereby reducing our specificity. In a systematic review done by Lobbes et al,^[22] in which the authors studied 35 studies, the reported sensitivity, specificity, PPV and NPV for predicting pCR with MRI ranged from 25 to 100%, 50 – 07%, 47 -73% and 71 – 100% respectively.

In our study, the maximum residual tumor size on MRI had a good correlation with maximum size on histopathology with correlation coefficient of $r=0.87$. This was well in correlation with studies done by Partridge et al ($r=0.89$) and weatherall et al ($r=0.93$),^[18,20] However study by Reiber et al showed less favourable association and a high false negative rate in residual disease assessment in post chemotherapy patients.^[23] This was mainly attributed to the reduced contrast uptake by the tumor after treatment resulting in inaccurate assessemtn of tumor size as shown in study by Hayes et al.^[24]

Different studies have shown underestimation as well as overestimation of the tumor size on MRI. In our study MRI overestimated the tumor size in 4/12 (33%) patients and in all these patients there was

nonmass like enhancement seen either alone or in association with the focal mass. This result is similar to the findings by Rosen et al who found overestimation in 11/21 patients which was due to high % of nonfocal lesions in their study (17/21) and also by Partridge et al.^[17,18]

The overestimation of tumor size has also been explained by that the standard histological examination may not accurately estimate the tumor size and intraductal tumor size assessment is rarely done in mastectomy specimen number of microscopic sections needed is prohibitive and the information does not affect clinical management.^[17]

Post lumpectomy

Patients who have undergone lumpectomy or excision biopsy, where the pathological specimen shows positive surgical margins, require re-excision, either in the form of wide excision or mastectomy. The treatment offered is determined by the presence and extent of the residual disease. The assessment of residual disease after the initial surgical procedure is difficult to be determined by clinical assessment, mammography or ultrasound examination due to the presence of scarring, skin thickening and breast edema. Some of the earlier studies have shown that MRI cannot distinguish between residual/ recurrent tumor from postoperative scarring when done within 9 months of initial surgery.^[25,26]

In our study, we had 14 patients who had positive/ close (within 2mm) surgical margins after initial lumpectomy and underwent MRI for assessment of residual disease. All these patients had surgery done outside our institution and had MRI within 4-6 wks of surgery. In our institution, all lumpectomy specimens are sent for frozen section for margins as a routine clinical practise and reexcision if required is done in the same setting. Of these 14 patients, 1 patient had close margin and 13/14 had positive margins. Classifying the MRI findings into true positive, true negative, false positive and false negative in accordance with the study by Soderstorm et al,^[27] MRI showed sensitivity of 100%, sp of 66.67%, PPV of 91.67% and NPV of 100% in detection of residual disease either in the form of focal enhancing lesion or nonfocal enhancing abnormality. Our specificity is similar to that of Lee et al,^[28] who showed sensitivity and specificity of 61.2% and 69.7%. Clumped nodular nonmass like enhancement around the cavity, in the surrounding breast or even in the different quadrant was considered significant. Besides the pattern and distribution, low ADC value (cut off of 1.2×10^{-3} mm²/sec) and enhancement kinetics (wash out type 3 and plateau type 2) were considered as significant. 5/14 patients had focal nodular enhancing lesions which were proven as residual IDC on pathology specimen. 1/5 patients had BCS, 2/5 had wide local excision and 2/5 underwent mastectomy (by patients choice). Residual disease was seen as multiple

enhancing nodules in 3/14 patients. All 3 underwent mastectomy and final histopathology showed residual IDC with multiple foci in 2 patients while benign findings were present in one patient. In 4/14 patients, there was clumped nodular nonmass like enhancement, all 4 underwent mastectomy and specimen histopathology showed residual DCIS in 2 patients, residual IDC with DCIS in 1 and 1 patient had residual IDC with DCIS with ILC and LCIS. 2/14 patients had true negative result in which no residual disease was reported on MRI, 1 had wide excision and 1 patient had mastectomy and no residual disease was seen on the final histopathology.

Soderstrom et al in their study showed that MR imaging with 3D RODEO technique,^[27] could identify the residual tumor and determine its extent in 84% of patients while Orel et al,^[29] in their study of 47 patients had PPV of 82% and NPV of 61%. They showed that false positive findings were predominantly due to granulation tissue and benign breast tissue and false negative findings due to post-surgical changes.

Frei et al,^[30] found that greatest specificity (75%) is achieved when MRI is performed between 28-35 postoperative days. The mean imaging interval in our study was 5 weeks and we achieved almost comparable specificity. The clinical role of MRI in detection of residual disease in this subset of patients was proven to be significant in subsequent surgical management.

Axillary lymphadenopathy

Our study showed that MRI imaging done with dedicated breast coil and thin section imaging of the axilla is an effective tool in determining the axillary lymph node metastasis in newly diagnosed cases of

breast cancer. MRI provides visualization and comparison of bilateral axillae without any appreciable increase in scan time. Unenhanced T1W images without fat suppression help in identification of axillary nodes with their abnormal characteristics in metastasis. The major criteria we studied in classifying a node as suspicious for metastasis were eccentric cortical thickening, effacement of fatty hilum, change in the shape of the enlarged nodes and perinodal fat stranding. Our study showed that if only complete effacement of fatty hilum was included MRI had sensitivity of 69.4%, specificity of 90.9%, PPV of 86.27% and NPV of 78.65%. Inclusion of eccentric cortical thickening with cut off of 3mm. increased the sensitivity of 93.94%, specificity to 72.9% and NPV and PPV to 93.10% and 75.61% respectively.

Scaranelo et al,^[31] in their study achieved sensitivity and specificity of 88% and 82% respectively when studying the T1W imaging characteristics of involved nodes. Their study however also included the ADC value of metastatic nodes and showed significant difference between the ADC of malignant and benign nodes. This was also seen in our study but ADC could not be considered as a reliable criteria in clinical context since even reactive or inflamed nodes also at times showed low ADC value. Perinodal fat stranding when present was seen as a highly sensitive criteria of nodal involvement with extra capsular extension of disease.

Mortellaro et al,^[32] in their study concluded that presence of any axillary lymph node with no fatty hilum and the number of nodes with no fatty hilum on MR significantly correlated with pathologic node positivity ($P = 0.04$); while kinetics, node number, and node size did not correlate. This is also well in correlation with our study.

Results of our study in nutshell

	Sensitivity	Specificity	PPV	NPV
NMLE with Extratumoral DCIS on HSP	79%	86%	76%	88%
NMLE with EIC	74%	76%	52%	89%
MF/MC with multiple lesions on HSP	86%	89%	60%	97%
NMLE with both Extratumoral DCIS and EIC	89%	78%	50%	97%
Lymph nodes with effaced fatty hila and HSP correlation	65%	89%	86%	73%
Lymphnodes with cortical thickening and HSP correlation	86%	69%	73%	84%
Post lumpectomy with positive surgical margins and MRI correlation for residual disease	100%	66.67%	91.67%	100%
Post NACT and MRI correlation	100%	50%	92.31%	100%

In study by Luciani et al Iso eccentric or regular cortical thickening and nonvisualisation of hila was seen as having a high positive predictive value

for nodal metastasis.^[33] They also showed that irregular nodal margin was correlating well with extracapsular extension.

Murray et al studied nodal enhancement index and nodal area as criteria of nodal involvement and showed that nodal enhancement index of >21% and nodal area of > 0.4 cm had sensitivity of 100% in prediction of axillary nodal metastasis with low specificity of 56%.^[34]

Imaging of the axilla requires thin section imaging of the axilla with patient in prone comfortable position. In our center we used dedicated breast coil at 3Tesla system with 2mm thickness slices of the axilla both precontrast T1W non fat sat and post contrast T1W non fat sat. With optimal thin section imaging of the axilla and following certain criteria of nodal involvement sentinel lymph node biopsy can be avoided and patients can straight away be taken for axillary nodal detection. And in those with negative MRI unnecessary SNLB can be avoided.

CONCLUSION

Our study concluded that MRI has a high sensitivity in detection of breast cancer including the detection of multicentric/ multifocal lesions in the same as well as contralateral breast. It also has a high sensitivity in detection of nonmass like enhancement. This is in concordance with various earlier studies. There was a good correlation seen between the size of the primary tumor detected on MRI and the tumor size on final histopathology. Identification of multiple lesions in different quadrants of the breast helps in treatment decisions in which either the patient is treated with mastectomy or with neoadjuvant chemotherapy. However multiple tumors in the same quadrant within 2cm of the primary lesion can be still treated with wide excision with subsequent whole breast radiation as the protocol followed in our hospital's cancer centre.

In post lumpectomy patients with positive surgical margins MRI is a highly sensitive technique to assess for residual disease seen as enhancing mass/ foci or residual areas of DCIS seen as clumped nodular NMLE. Patients with no residual disease can be treated with wide excision while those with residual disease are treated according to its extent.

Our study showed that nonmass like enhancement in clumped nodular pattern in ductal/ segmental or regional distribution has high specificity in detection of DCIS or extensive intraductal component. Linear spicular enhancement and stippled enhancement along with the tumor had low specificity. Multiple areas of nonmass like enhancement in the same or both breasts is also seen in benign breast disease than in malignancy. Identification of these patterns can help in diagnosing the in situ carcinoma with relatively high specificity. Non mass forming DCIS, Infiltrating Lobular Carcinoma and oestrogen receptor negative invasive ductal carcinoma are the malignant lesions which are more likely to have these patterns on MRI.^[11,12]

MRI has a definite role in detection of metastatic involvement of axillary lymph nodes. The features with high positive predictive value for malignancy are rounding of the shape, eccentric cortical thickening of > 3mm, effacement of fatty hilum and effacement of fatty hilum. It also identifies enlarged internal mammary and supraclavicular nodes.

Given the above mentioned potential of MRI in evaluation of breast cancer, MRI should be added to the preoperative imaging work-up of breast cancer patients as an aid in surgical and definitive treatment. Breast MRI has a definite potential to reduce the number of surgical procedures to obtain negative margins of resection or to convert patients from planned breast-conservation therapy (BCT) to mastectomy.^[13,14] It also has been postulated that the detection of additional areas of cancer in the ipsilateral breast on MRI may result in a lower rate of in-breast recurrence following BCT .

One of the major limitations of MRI of the breast in breast cancer staging is false-positive enhancement as seen in fibroadenomas, fat necrosis and fibrocystic changes resulting in being results on biopsy on the MRI detected suspicious lesions. This may result in increased cost, patient anxiety and increased rate of mastectomies. Balancing the known pitfalls of breast MRI and its false positives with the clinical goal of accurate assessment of extent of disease is a subject of continued investigation.

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