Evaluation of Non-Palpable Benign Breast Lesion in High Risk Women by Using Contrast MR Mammography

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Abstract: Background: Breast cancer is the most common female cancer worldwide and its incidence has surpassed that of cervical cancer in most urban cancer registries in India. If breast cancer screening is to be successful, the majority of cancers among screened women must be detected when tumors are small and before the occurrence of distant or nodal metastases.

Material and Methods: A prospective study was carried out at study the efficacy of Contrast MR Mammography in evaluating non-palpable probably benign breast lesions (BIRADS 3) and to characterize probably benign lesions detected on digital mammography and breast sonography in 50 high risk women more than 35 years old. Patients referred to the Radiology department for routine screening mammography or with history of risk factors from the period of Feb 2009 to July 2010 were included in this study.

Results: In the Digital Mammography examination 54 probable benign lesions were indentified out of 50 patients. These patients were further subjected to MRI study, in which total 61 lesions were indentified. Total of 5 patients showed evidence of malignancy on MRI. Out of these 5 cases of malignancy, 4 cases were suspected for malignancy on MRI but one case was diagnosed as benign lesion. The fifth case suspected for malignancy on MRI, was false positive and turned out to be benign on histopathology.

Conclusion: In case of doubtful probable benign breast lesions, MRI with dynamic contrast enhancement helps detect additional cancers that are overlooked on mammography.

Keywords: Benign breast lesions, high risk women, magnetic resonance mammography, digital mammography, breast sonography.

1. INTRODUCTION

Breast cancer is the most frequently occurring malignant disease in women with a lifetime risk of 1 in every 8-9 women [1-3]. It is the leading cause of cancer death in female’s worldwide, accounting for 23% (1.38 million) of the total new cancer cases and 14% (458,400) of the total cancer deaths in 2008. Female breast cancer is a complex multifactorial disease, the etiology of which involves a strong interplay between environmental and genetic factors. Although high penetrance cancer genes, BRCA1 and BRCA2, have been identified, these account for only 5-10% of cases.

The others high risk groups are (i) Family history of breast cancer. (ii) Previous personal history of breast cancer and other breast diseases such as fibrocystic disease. (iii) Excessive exposure to ionizing radiation (iv) History of cancer of the endometrium, ovary or colon. Early menarche, late menopause, nulliparity, elderly primigravida, diminished lactation and high breast density are also associated with breast cancer [4-6].

An early accurate diagnosis of breast cancer has a favorable prognosis than that of late detection. The present challenge for the clinicians and the radiologists remain to distinguish between the probable benign lesions from the probable malignant lesions. If breast cancer screening is to be successful, the majority of
cancers among screened women must be detected when tumors are small and before the occurrence of distant or nodal metastases. Currently, conventional X-ray mammography and sonography are the techniques most widely used for the detection and localization of breast abnormalities. However, these techniques have limited sensitivity and specificity for the detection and diagnosis of breast lesions, particularly in patients with dense breast parenchyma or in patients with breast implants or postsurgical scars or deformity. As a possible alternative to these conventional techniques, contrast enhanced magnetic resonance (MR) mammography has emerged as a viable clinical tool for the detection, diagnosis, staging, and management of breast cancer. Advantageous attributes of MR imaging for diagnostic evaluation of breast cancer include high soft-tissue contrast; multiplanar sectioning, which permits the acquisition of contiguous thin sections that enable a full three-dimensional representation of one or both breasts; and the absence of ionizing radiation. A principal limitation of contrast-enhanced MR mammography at present is its use in the detection and accurate characterization of small carcinomas with poor neoangiogenesis [7,8]. MRI is recommended as an adjunct to mammography for women with lifetime risk of 20-25% or greater, which include women with a strong family history of breast or ovarian cancer and women who had been treated for Hodgkin’s disease [5].

A prospective study was carried out at a tertiary care hospital of AFMS to study the efficacy of Contrast MR Mammography in evaluating non-palpable probably benign breast lesions (BIRADS III) and to characterise probably benign lesions detected on digital mammography and breast sonography in high risk women more than 35 years old.

2. MATERIALS AND METHODS

All the patients in the age group of 35 to 50yrs, who had come to the Radiodiagnosis department for screening mammogram and patients who are having high risk factors for malignancy were taken into the study. A total of fifty patients with probable benign breast lesions on digital mammogram and also having high risk factors for malignancy were further evaluated by MRI. Ultrasonography was done in all patients followed by USG guided FNAC. The patients with high risk for malignancy included: patients with family history of breast cancer; previous personal history of breast cancer and diseases like fibrocystic disease; history of excessive exposure to ionizing radiation; and history of cancer endometrium, ovary or colon. A woman with a past history of unilateral breast cancer who satisfied the criteria was also eligible if her contra lateral breast had not been removed. Pregnant or lactating women, moribund patients are not included in this study. Women with pacemaker and history of claustrophobia were excluded. The above mentioned patients reported for the study were followed up over a period of 24 months (Feb 2009-Jan 2011). A detailed clinical history was taken and physical examination was done for all patients included in the study. Routine Screening Mammography was done. After the Mammogram was studied, 50 patients with probable benign breast lesions and having high risk factors were selected for further evaluation. Ultrasonography was done in all patients as an adjunct to Digital Mammography. All the patients underwent MRI mammogram followed by ultrasound guided FNAC of the lesions. The pathology reports were collected and results were analyzed. The mammography was done on Novation DR Siemens machine. Conventional Cranio caudal (CC) and Medio lateral oblique (MLO) view of both breasts were taken. Further views were done case to case basis. These mammogram images were reviewed by using the American College of Radiology’s Breast Imaging Reporting and Data System (BI-RADS) category. The patients were divided according to the findings into five groups. BIRADS: 1 to 5 [9]. The specific type of BIRADS III lesions are, clustered round calcifications, a noncalcified circumscribed solid mass lesions, a focal symmetry, multiple cluster of tiny calcifications, scattered tiny calcifications, and multiple solid circumscribed mass lesions. MRI mammography was done using Siemens Magnetom 1 Tesla machine with dedicated breast coils. The coil support apparatus was designed to provide breast immobilization with gentle medial-lateral compression, thereby optimizing coil coupling to each breast. Following sequences were taken for all patients: T1 Weighted and T2 Weighted axial, coronal and sagittal and STIR sagittal, T2 Fat Saturated coronal and 3 D Flash pre and post contrast sequences. Gadolinium-DTPA was given at a dose of 0.1mmol/kg and the uptake of contrast by the lesions was assessed. The precontrast images were subtracted from the contrast-enhanced images to improve visualization of the enhancing structures. In cases where a potentially suspicious area of enhancement (anything other than an obvious benign structure such as a blood vessel or scar) was detected, time intensity curve of these lesions were obtained and analyzed. These images were used to further track tracer kinetics and to help characterize the lesion for
clinical management. MRI results were analyzed in a pattern similar to the BI-RADS classification using a combination of morphology and enhancement kinetics. The various criteria that were considered for evaluation of lesions on MRI were: Number of lesions, Architectural Distortion, Overall lesion configuration, lesion margins, internal architecture (e.g., internal septations or central clearing), and the time course of signal intensity changes.

3. RESULTS

The percentage of various pathological lesions is given in Figure 1. Invasive ductal carcinoma was seen in 6% cases while fibroadenoma was seen in 36% cases. Out of fifty patients who participated in the study, digital mammography detected 54 lesions and MRI mammography detected 61 lesions. 37 patients (74%) were in 5th decade of life. The distribution of risk factors is given in Table 1. In our study most common risk factor was history of benign breast disease and significant percentage were without risk factors.

![Figure 1: Pathological Distribution of lesions.](image)

4. ANALYSIS OF FINDINGS ON DIGITAL MAMMOGRAPHY

54 lesions were picked up in these 50 patients on digital mammography. Most of the lesions (36%) were in Supero lateral quadrant, while the least common quadrant is Superomedial (17%). The parenchymal density was classified as per ACR criteria. 22 patients (44%) had Type II pattern followed by Type-I pattern in 28% cases. The breast parenchymal density pattern was noted as per ACR criteria in 50 patients (Table 2).

Out of 54 lesions picked up on digital mammography, 31 (57.4%) showed iso-density to slightly high density lesions; 12 showed high density while the remaining 11 lesions showed low to iso density lesions. 23 lesions show sharp well defined margin. Of the 31 lesions showing iso to slightly high density lesions, 18 lesions show lobulated margins and remaining 13 lesions show indistinct margins. 19 lesions out of 54 show calcification within; of which 11 lesions show clustered round calcification and 8 lesions show scattered calcification. Rest of 35 lesions shows no evidence of calcification.

Out of 54 lesions 11 lesions presented as non calcified solitary mass lesions, 22 lesions presented as asymmetrical breast density, 11 lesions presented with round smooth clustered micro calcification. 2 Patients present with multiple mass lesions. In our study, the most common lesions are those with asymmetrical breast density.

5. ANALYSIS OF FINDINGS ON MR MAMMOGRAPHY

The total numbers of lesions detected in MR mammography in all 50 patients were 61. Thus MRI detected 7 more lesions than the digital mammography. These lesions are analyzed on the basis of margin of the lesions, shape, area of necrosis, lymph node involvement, and enhancement pattern and time intensity curve. Most of the lesions are in Supero lateral quadrant (22 lesions or 36%) while least common quadrant is Superomedial quadrant comprising 11 (17%) lesions. Out of 61 lesions, 25 lesions show well circumscribed margin, 19 lesions show lobulated

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>No of Patients</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Benign breast disease</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>Family history of breast cancer</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Previous history of breast cancer</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Early menarche</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Late menopause</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>No risk factors</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>
margin and 17 lesions show irregular margins. 16 lesions show areas of necrosis within. Rests of 45 lesions show no necrosis. 2 lesions show ipsilateral enlarged axillary lymphadenopathy.

In this study, out of 61 lesions, 09 lesions show architectural distortion and 52 lesions show no architectural distortion. During analysis of time intensity curve, five lesions show Type III curve which means rapid uptake and early washout. Rest of the lesions show Type I (28 lesions) or Type II curve (19 lesions); as depicted in Figure 2. On MRI, based on time intensity curve, five patients with probable benign lesions (having Type III intensity curve) on mammography were suggested to be malignant. The specific suspicious finding of each of the index cases in terms of enhancement, morphology, internal architecture and enhancement kinetics is given in Table 3.

### Table 2: The Breast Parenchymal Density Pattern as Per ACR Criteria (No of Patients = 50)

<table>
<thead>
<tr>
<th>Type of Breast Parenchymal Pattern</th>
<th>Number of Patients</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>Type II</td>
<td>22</td>
<td>44</td>
</tr>
<tr>
<td>Type III</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Type IV</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table 3: Findings in Type III Curve (n=5)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Margins</th>
<th>Enhancement</th>
<th>Internal Architect</th>
<th>Kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Smooth</td>
<td>Intense</td>
<td>No distortion</td>
<td>Type III</td>
</tr>
<tr>
<td>2</td>
<td>Irregular</td>
<td>Intense</td>
<td>Distortion noted</td>
<td>Type III</td>
</tr>
<tr>
<td>3</td>
<td>Irregular</td>
<td>Intense</td>
<td>Distortion noted</td>
<td>Type III</td>
</tr>
<tr>
<td>4</td>
<td>Irregular</td>
<td>Intense</td>
<td>Distortion noted</td>
<td>Type III</td>
</tr>
<tr>
<td>5</td>
<td>Irregular</td>
<td>Intense</td>
<td>Distortion noted</td>
<td>Type III</td>
</tr>
</tbody>
</table>

**Figure 2:** Distribution of intensity curve on contrast enhanced MRI.

In our study total 61 lesions were analyzed pathologically. Out of sixtyone, 5 malignant lesions were detected in fine needle aspiration cytology (FNAC) report. All 5 were invasive ductal carcinoma. Fibro adenomas were found in 34 lesions and 22 lesions were fibroadenosis.

**Figure 3(a):** X-ray digital mammography shows small ill-defined hyper dense mass lesion with irregular margin in retroareolar region of left breast (red arrow), likely BIRADS III (Probable benign lesion). (b): MR mammography (FS T2W coronal section) shows hyperintense small mass lesion with irregular margin (red arrow). Time intensity curve for this lesion shows Type III Curve, likely malignancy. (c): Time intensity curve shows type III curve. Histopathological examination confirmed invasive ductal carcinoma.
The relative characteristics of malignant lesions on digital mammogram, MRI breast image and MRI time intensity curve are shown in Figure 3 and Figure 4; while those of benign breast lesions are shown in Figure 5 respectively.

Out of 56 lesions diagnosed as benign on MR mammograms, one was malignant while 55 were truly negatives. MR mammogram had a positive predictive value of 80% and a negative predictive value of 98% in this study. It had a sensitivity of 80% and a specificity of 98%. The sensitivity and specificity calculation of Contrast MR Mammography for benign and malignant lesions is tabulated as Table 4.

6. DISCUSSION

In recent years there has been an increasing interest in MRI as a non-invasive diagnostic modality for further characterizing suspicious breast lesions detected with mammography or ultrasound [9,10]. In a recent meta-analysis, Peters NH [9] et al. found that the sensitivity and specificity of MRI to diagnose breast cancer is 0.90 and 0.72 respectively. The authors concluded that the additional value of MRI of the breast lies mainly in its capacity to detect multicentric, multifocal and bilateral disease, to detect invasive components in ductal carcinoma in situ (DCIS) lesions, to depict the tumor in a 3-dimensional image and to depict breast cancer in dense breast tissue.

Figure 4(a): Digital MMG shows small hyper dense mass lesion with irregular margin. Few calcified foci noted in the periphery of the lesion. Likely BIRADS III (probable benign lesion). (b): Post contrast Axial MR section show intensely enhancing small mass lesion with ill-defined margin. (c): Intensely enhancing small mass lesion with ill-defined margin. Time intensity curve show Type III Curve. Likely malignant. Histopathological examination: Invasive ductal cell carcinoma (NOS).

Figure 5: The relative characteristics of benign breast lesions on digital mammogram, MRI breast image and MRI time intensity curve.

Table 4: Sensitivity and Specificity Calculation of Contrast MR Mammography

<table>
<thead>
<tr>
<th>Nature of Lesion</th>
<th>Malignant on MRI</th>
<th>Benign on MRI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant on FNAC</td>
<td>04</td>
<td>01</td>
<td>05</td>
</tr>
<tr>
<td>Benign on FNAC</td>
<td>01</td>
<td>55</td>
<td>56</td>
</tr>
<tr>
<td>Total</td>
<td>05</td>
<td>56</td>
<td>61</td>
</tr>
</tbody>
</table>
In our study, the Digital Mammography examination identified 54 probable benign lesions out of 50 patients. These patients were further subjected to MRI study, in which total 61 lesions were identified. All 50 patients were subjected to histopathological examination. Total of 5 patients showed evidence of malignancy. Retrospectively out of these 5 cases of malignancy, 4 cases were suspected for malignancy on MRI but one case was diagnosed as benign lesion. The fifth case suspected for malignancy on MRI, turned out to be benign on histopathology. The false positive rate in our study is 20% (one case out of five). The false negative rate in our study is also 20%.

Among 54 probable benign lesions, eleven (20.3%) lesions presented as solitary masses. The most common morphology of probable benign lesions in our study was lesion with asymmetric breast density (41%). In a study of Varas et al. [11] who followed up 544 probable benign breast lesions (BI-RADS III) out of 18,435 asymptomatic women, the commonest form of lesion was a solitary mass which constituted 40% lesions (204 lesions), second commonest was asymmetric breast density constituting 26% lesions (134 lesions). Woods RW et al. [12] retrospectively assessed the data of 348 consecutive breast masses in 328 women who underwent image-guided or surgical biopsy; and found that 70.2% of high-density masses were malignant, and 22.3% of the isodense or low-density masses were malignant (P < 0.0001).

The American College of Radiology breast MR imaging lexicon provides a specific standardized vocabulary for describing the morphologic and kinetic characteristics of breast lesions. All suspicious areas are defined as a focus or foci (with a diameter of less than 5 mm), mass (a three-dimensional space-occupying lesion with a convex margin), or no mass. The description of a mass should include a characterization of its shape (round, oval, lobular, irregular), margin (smooth, irregular, spiculated), and internal enhancement pattern (homogeneous, heterogeneous, rim like, central, septal). The kinetic curve assessment involves a description of both the initial peak (slow, medium, rapid) and the delayed phase (persistent, plateau, or washout) of contrast enhancement [13]. In our study, the malignant lesions which are detected by MRI and later confirmed by histopathological examination, showed irregular margin, heterogeneous intense enhancement on post contrast sequences and Type III time intensity curve.

On Mammography among these lesions two lesions showed high density pattern and other two lesions showed iso to low density as compared with surrounding breast parenchyma. Two of the lesions showed clustered calcification within. All the four lesions showed architectural distortion in both imaging modalities. In our study, out of seventeen lesions which showed irregular margins on MRI, four turned out to be positive for malignancy, constituting 23.3%. All 5 lesions suspicious for malignancy showed heterogeneous enhancement, out of which four turned out to be malignant. 80 percent of the lesions with heterogeneous and intense enhancement were reported to be malignant in our study.

Dynamic contrast-enhanced MRI (DCE-MRI) has been widely used to improve the specificity of MRI in characterizing breast lesions. The most widely used form of DCE-MRI analysis is the assessment of the type of time–signal intensity curve (i.e., kinetic curve) by categorizing the washout pattern of a gadolinium contrast agent. These patterns are classified as type I, persistently enhancing (progressive), which is suggestive of benignity; type II, plateau type, which has an intermediate probability for malignancy; and type III, washout type, which is indicative of malignancy [14].

In our study, all 5 lesions suspicious for malignancy showed Type III time intensity curve pattern. 80 percent lesion with Type III time intensity curve were considered malignant in our study. In a study of Kaiser and Zeitler [15] of 45 patients with 55 MR imaging, the study was done to differentiate benign from malignant breast lesions that had been detected exclusively on MR imaging by analyzing qualitative and quantitative lesion characteristics. This study reported that all carcinomas could be differentiated from benign lesions by early signal enhancement in a series of 25 and 18 dynamic contrast-enhanced breast MR examinations, respectively. All six malignant tumors found in these 25 patients showed enhancement characterized by a sudden increase in signal intensity on the order of 100%. In a study of Stack et al. [16] which had done tissue characterization with Gd-DTPA enhancement profiles of breast lesions, similar findings were also reported of nine malignant and nine benign lesions. Our study is in consensus with study of Kaiser and Zeitler et al. and Stack et al.

Sardanelli F outlined [17] the role of pre-operative breast MRI outlined on the basis of the existing evidence. He concluded that the patients with a potential higher anticipated benefit from pre-operative...
MRI can be identified as those: with mammographically dense breasts; with a unilateral multifocal/multicentric cancer or a synchronous bilateral cancer already diagnosed at mammography and sonography; with a lobular invasive cancer; at high-risk for breast cancer; with a cancer which shows a discrepancy in size of >1 cm between mammography and sonography; or under consideration for partial breast irradiation. He further recommended that results of pre-operative MRI should be interpreted taking into account clinical breast examination, mammography, sonography and verified by percutaneous biopsy; and MRI-only detected lesions require MR-guidance for needle biopsy and pre-surgical localization.

In our study, only two lesions (40%) out of five malignant lesions presented with enlarged lymph node. Mieke Kriege [18] compared the efficacy of MRI with that of mammography in high risk women and concluded that MR is 35% more sensitive than the Mammography. However in our study, MR showed only 14% more sensitive than digital mammography, which is less than the result of Mieke et al. This may be due less number of patients we have studied as compared with the Kriege et al. [18].

Our estimates of sensitivity of the screening modalities were based on only five tumors that were detected during the study. In our study, the results showed four lesions were correctly diagnosed as malignant on MRI. One lesion was missed and one patient was wrongly diagnosed as malignant on MRI. All lesions were diagnosed as probable benign lesion on Digital mammography. We conclude that, MRI showed 80% sensitivity for detecting malignancy with 20% false positives, 20% false negatives. Specificity for MRI in our study is 92.3%. As a result, our estimate of 80% sensitivity for MRI is relatively equal to other study.

Data from the Memorial Sloan-Kettering Cancer Center suggest that MRI can detect mammographically occult breast cancer in high-risk populations. This study evaluated 367 women at high risk (i.e., with a personal history of breast cancer, lobular carcinoma in situ, or atypia, or with a family history of breast cancer). Biopsy was recommended in 64 (17%) of the women on the basis of MRI findings. Biopsy revealed cancer in 14 (24%) of 59 women who underwent biopsy. Subgroup analysis further suggested a 50% positive predictive value of biopsy based on MRI findings in women with both a positive family history and a personal history of breast cancer [19]. Our results indicate that the sensitivity of breast imaging can be increased by complementary use of MRI. Especially for patients in whom the status of breast lesion remains unclear, MRI, though costliest among all other complementary diagnostic modalities, may help to reduce the number of unnecessary biopsies and diagnostic ambiguities. Our results suggest that MRI may be superior to mammography of the breasts for the surveillance of women from age group 35 to 50 yrs.

**CONCLUSION**

Total numbers of 54 probable benign breast lesions and 61 probable benign breast lesions were detected on MR mammography from 50 patients. MR mammography is 14% more sensitive to Digital mammography in detecting breast lesions. In our study the True positive rate for MRI is 80%; false positive rate is 20% and false negative rate is 20% which is comparable to other studies. The correlation of positive predictive value for MR mammography was found to be statistically highly significant (p value < 0.005) MR Mammography is more sensitive than digital mammography in detecting breast lesions, particularly in young women with dense breast. In case of doubtful probable benign breast lesions, MRI with dynamic contrast enhancement has a higher specificity and sensitivity compared to digital mammography in characterizing the lesions as benign or malignant.

**INTELLECTUAL CONTRIBUTION OF AUTHORS**


*Drafting and Manuscript Revision:* Lt. Col. AK Singh, DN Singh, Col. PK Thakur, Lt. Col. Sunita BS


**CONFLICTS OF INTEREST**

None identified.

**FUNDS AND SUPPORT**

This study has been financed by the research grants from the office of the DGAfms as an AFMRC project, Lt. Col. AK Singh being the Principal Worker.

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Evaluation of Non-palpable Benign Breast Lesion in High Risk Women


Received on 25-04-2015
Accepted on 04-05-2015
Published on 30-06-2015

DOI: http://dx.doi.org/10.14205/2309-4419.2015.03.01.2

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