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Combined use of digital mammography and magnetic resonance mammography in detecting ductal carcinoma in-situ breast

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ABSTRACT:
Introduction: Even though many studies have shown beneficial diagnostic implications of MR mammography, the outcomes of extensive and mandatory use of pre-operative MR mammography remains controversial. the objective of the present study was to check whether combination of magnetic resonance MR mammography with digital mammography will be beneficial for evaluation of non-invasive breast disease as in ductal carcinoma in-situ (DCIS).
Methodology: In a prospective study, 68 patients who came for screening diagnostic mammogram and who had breast lesions of Breast Imaging Reporting and Data System (BIRADS) category 3 and more were evaluated. All patients underwent bilateral digital mammography. Those patients who were thought to possibly have breast cancer and to be candidates for surgical management were offered bilateral contrast-enhanced breast magnetic resonance mammography (MRM).
Results: In this prospective study, we included 68 patients (mean age 50.6 years, range 30-73 years). A total of 74 lesions were evaluated. In detecting these lesions, digital mammography had a sensitivity of 40%, specificity of 100% and diagnostic accuracy of 63.5%. MRM sensitivity was found to be 71.7%, specificity 96.6% and diagnostic accuracy of 83.7%. Combined utilization of both DM and MRM modalities to detect DCIS resulted in 77.2% sensitivity, 96.6% specificity, 97.1% positive predictive value (PPV), 74.3% negative predictive value (NPV) and 85.1% of diagnostic accuracy (DA) with McNemar test significance value at 0.002.
Conclusions: combining digital mammography and MR mammography results in a significant improvement in sensitivity than digital mammography alone in detecting DCIS.

KEYWORDS:screening; breast cancer; contrast enhanced MR mammography; digital mammography.

I. INTRODUCTION

DCIS is the most common type of non-invasive breast cancer.1 It refers to an uncontrolled growth of cells that are confined to the breast duct. Frequently it is a single lesion, however, there is higher risk of developing lesions in the opposite breast. Very few cases of DCIS present as a palpable mass. Most are diagnosed by mammography, usually as clustered microcalcifications.2 DCIS may also present as pathologic nipple discharge, with or without a mass.3 The frequency of diagnosis of DCIS has greatly increased with greater use of mammography.4 DCIS shows varied appearance on MRI: linear, spotty enhancement; gathering of linear enhancement; enhanced area or mass without distortion of the surrounding tissue or well-circumscribed mass mimicking intraductal papilloma. MRI was useful in providing more precise information on the disease extent of DCIS, and it is considered useful in planning the type of surgery.5

Even though many studies have shown beneficial diagnostic implications of MR mammography, the outcomes of extensive and mandatory use of pre-operative MR mammography remains controversial.5 Non-mass enhancement depiction of a lesion is the most common presentation of DCIS.6 MR mammography is prone to under-estimate DCIS especially in high-risk screening studies.7 However, it is more sensitive than digital mammography and sonomammography in detecting invasive breast cancers. Adding to these inconsistencies, the ability to detect DCIS in MR mammography increases with experience of

radiologist.7 Ductal enhancement, clumped enhancement and segmental enhancement are some of the described features of DCIS during MR mammography.8 Mass like presentation of DCIS in MR mammography is not rare.9 Studies have shown that MR mammography do not change the operative course of a invasive breast disease and therefore, routine pre-operative evaluation is not recommended.10

With this background, the present study was considered to check whether combination of MR mammography with digital mammography will be beneficial for evaluation of non-invasive breast disease as in DCIS. As there was minimum sensitivity, specificity and predictive value of combination of digital mammography and MR mammography, the present study was designed to evaluate the diagnostic accuracy of these two modalities.

II. METHODOLOGY

In a prospective study, patients presenting to Out Patient Departments of General Surgery, Oncology and Gynecology with clinical symptoms of breast cancer or for screening of the breast neoplasia are evaluated through digital mammography and sonomammography. Institutional Ethics Committee approved the study at the beginning. Written informed consent was obtained for diagnostic procedures was obtained from each patient and were counselled as to the possibility of MRI detecting other suspicious lesions resulting in additional imaging studies and procedures before inducting into the study.

Study center: this study was carried at Department of Radiology of a multi-specialty hospital with comprehensive cancer center and a separate dedicated breast center which is headed by radiologist having experience in breast imaging of more than 5 years. The study was done from October 2012 to October 2014.

Inclusion criteria: all female patients who came for screening diagnostic mammogram and who had breast lesions of Breast Imaging Reporting and Data System (BIRADS) category 3 and above were taken into the study. Patients who had underwent all three modalities (digital mammography, sonomammography and MR mammography) are included in this study.

Exclusion criteria: women who were diagnosed to have BIRADS 1 / 2 in digital and sonomammography, those who were already treated with surgery / chemotherapy / radiotherapy and those with no histopathological evaluation were excluded from the study. Those were unable to undergo MR imaging because of a pacemaker, an aneurysm clip, or a metallic foreign body in or near the eye were also excluded. Women who were not willing for consent were excluded.

Study setting: All patients initially underwent bilateral digital mammography with spot and magnification views as indicated. Targeted high-frequency sonography of the primary lesion was used to further characterize the morphology, size, and extent. Sonography was routinely used to evaluate for other suspicious lesions within either breast and additionally detected lesions were recorded. Those patients who were thought to possibly have breast cancer and to be candidates for surgical management were offered bilateral contrast-enhanced breast MRI. Each patient and each individual lesion were initially assessed by one of two qualified radiologists who has experience of more than five years.

Breast MRI technique

All positive cases are subjected to MR imaging performed within 2 weeks of the initial lesion detection. MRI were performed with a SKYRA 3-T MR imaging unit by using a dedicated, four channel bilateral breast coil, with subjects resting in the prone position.

After the initial pre-contrast sequences, five series of dynamic contrast enhanced axial T1-weighted 3D fat-suppressed fast-spoiled gradient echo were acquired; (each series -120 sections; each section - 1.3mm interpolated to 0.2mm intervals; matrix – 416 x 416; 360mm field of view; flip angle - 10°; and 1 acquisition). The initial pre-contrast sequences were acquired before contrast administration. During a subsequent pause of 20 sec, a single dose of gadopentetate dimeglumine (0.1 mmol/kg, Magnevist) was injected at a rate of 1.5 mL/sec and was immediately followed by a 20-mL normal saline flush injected at same rate with a power injector. Series 2–5 were then acquired sequentially with no inter scan delays. Centric spatial encoding was used for all sequences. Reconstruction is done in coronal and sagittal planes once post contrast images were acquired. Subtraction images generated were used for interpretation. Delayed contrast-enhanced axial with high resolution T1-weighted 3D fat-suppressed fast-spoiled gradient echo were acquired. Single voxel spectroscopy of suspicious lesion is done.

The presence or absence of areas of abnormal enhancement was classified according to the BI-RADS MRI lexicon.11–14 Bilateral breast

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imaging is done to include the usefulness of assessing symmetry and screening of the contralateral breast in patients with newly diagnosed breast carcinoma.

The evaluation of CE-MRM images was performed by one of two qualified radiologists who has experience in interpreting breast MRI for more than 5years. If CE-MRM revealed more extensive breast disease other than the index cancer, the patients would return for a second look examination with ultrasound. More extensive disease included larger size of index cancer, additional foci of cancer in the same or in other breast quadrants and contra lateral lesions.

The second look ultrasonography was performed by the same radiologists who interpreted the CE-MRM images. If a lesion was confirmed as suspicious, a new ultrasound guided needle biopsy was performed. If the patients refused to undergo a core biopsy, surgical removal was strongly suggested. If the lesion was not seen on second look ultrasound, the patient was counselled for surgical removal of it if the image was suspicious on CE-MRM, or to have 6-month follow-up CE-MRM if the lesion was less concerning in opinion of the attending breast radiologist. After surgery, all radiographic and pathologic results were examined.

Discrete variables are analysed for the mean, median, standard deviation (SD), range etc. The categorical variables are analysed using cross tabulations – Chi square test and Fischer's exact analysis. P value < 0.05 is considered statistically significant. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy are calculated from the results of the observation.

III. RESULTS

In this prospective study, we included 68 patients (mean age 50.6 years, range 30-73 years). Fourteen patients had family history of breast cancer. The patient related attributes, clinical presentations are tabulated in table 1. A total of 74 lesions were evaluated.

Among them 41 patients underwent modified radical mastectomy (MRM, unilateral in 38 patients and bilateral in 3 patients); 1 patient underwent MRM of one breast and breast conservative therapy (BCT) of other breast; and 26 patients underwent BCT (unilateral in 24 patients and bilateral in 2 patients). Out of 41 patients who underwent MRM, 26 patients no additional foci were detected in MRI. These patients had undergone MRM either due to size of the lesion, multicentricity detected by either mammography or ultrasonography or by choice. The remaining 15 patients who underwent MRM were diagnosed to have additional suspicious lesions on MRI. Among these 15 patients in 7 patients, additional lesions were also seen on second look ultrasound which were biopsied and proved to be malignant. 3 patients were already diagnosed to have multifocal disease on mammography or ultrasound. Detecting additional foci in MRI in these patients did not alter the treatment plan.

3 patients preferred to undergo MRM as their choice before performing MRI. In 2 patients additional lesion detected on MRI was not seen on second look ultrasound and these patients were referred for MR guided biopsy.

In the remaining 27 patients no additional lesions in different quadrant were detected on MRI and hence these patients underwent BCT.

Table 1: Tabulation of patient related parameters and clinical presentations among patients (n=68) included in the study

Parameters	n
Patient age	
30 – 40 years	13
41 – 50 years	22
51 – 60 years	20
More than 61 years	13
Clinical presentations	
Painless lump	51
Painful lump	3
Screening	3
Painless lump with nipple discharge	2
Only pain	2
Only nipple discharge	2
Skin dimpling	2

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Women less than 50 years of age had extremely dense breast when compared to women of more than 50 years of the age ($p<0.001$).

MR mammography detection of DCIS

MR mammography (figure 1A and 1B) showed a 71.7 % sensitivity 96.6 % specificity, 97 % positive predictive value (PPV), 69 % negative predictive value (NPV), 83.7 % diagnostic accuracy (DA) and 1.4% false positive with a McNemar test significance of < 0.001 in detecting DCIS lesions (table 2).

Table 2: DCIS in magnetic resonance mammography (MRM) vs DCIS in histopathological evaluation: cross tabulation

		DCIS in HPE		Total
		Detected	Not Detected	
DCIS in MRM	Detected	32	1	33
	Not Detected	13	28	41
Total		45	29	74

In detecting these lesions, digital mammography had a sensitivity of 40%, specificity of 100% and diagnostic accuracy of 63.5%.

Digital mammography with MR mammography detection of DCIS

Combined utilization of both DM and MRM modalities to detect DCIS resulted in 77.2% sensitivity, 96.6% specificity, 97.1% positive predictive value (PPV), 74.3% negative predictive value (NPV) and 85.1% of diagnostic accuracy (DA) with McNemar test significance value at 0.002 (table 3).

Table 3: DCIS in combined Digital mammography (DM) and magnetic resonance mammography (MRM) vs DCIS in histopathological evaluation (HPE) cross tabulation

		DCIS in HPE		Total
		Detected	Not Detected	
DCIS in DM and MR M	Detected	34	1	35
	Not Detected	10	29	39
Total		44	30	74

From above data we found that MR mammography is more sensitive in detecting noncalcified DCIS which were not detected in digital mammography. In one patient with significant pleomorphic calcification detected in digital mammography there was no evidence of non-mass like enhancement in corresponding area in MRI. In 29 breasts DCIS was not detected in any modality and in all these cases are low grade DCIS by histopathology.

IV. DISCUSSION:

Historically, MR mammography was not considered a choice of investigation for evaluation of suspected DCIS.5 As more and more centers are opting screening MR mammography, incidence of DCIS is increasing.15,16 As there are no uniformity in enhancement of lesions, radiologists could miss many of DCIS during MR mammography.17 Such false-negatives may also be due to poor conspicuity, subtle or atypical appearance, stable disease or even radiologist bias.17 Therefore, even today, MR mammography even though a powerful tool to detect invasive breast conditions, it continues to be supplementary to digital mammography and sonomammography in screening breast cancers.

In the similar lines, a combined MR mammography and digital mammography has detected two additional lesions that were not detected through MR mammography alone. DCIS in MR mammography is appreciated as segmental, focal, diffuse, linear and regional enhancement patterns.15 We also noted all these enhancement patterns but not quantified as it was not the objective of the study. In a study of 220 cases of

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histopathologically proven DCIS, Akiko et al., noted 7 occult lesions on detected through MR mammography.18 However, in the same study, authors also note, 2 patients where MR mammographically suspicious of breast cancer and biopsy showed no sign of cancer.18 Therefore, extensive and routine pre-operative MR mammography is not recommended by many guidelines.

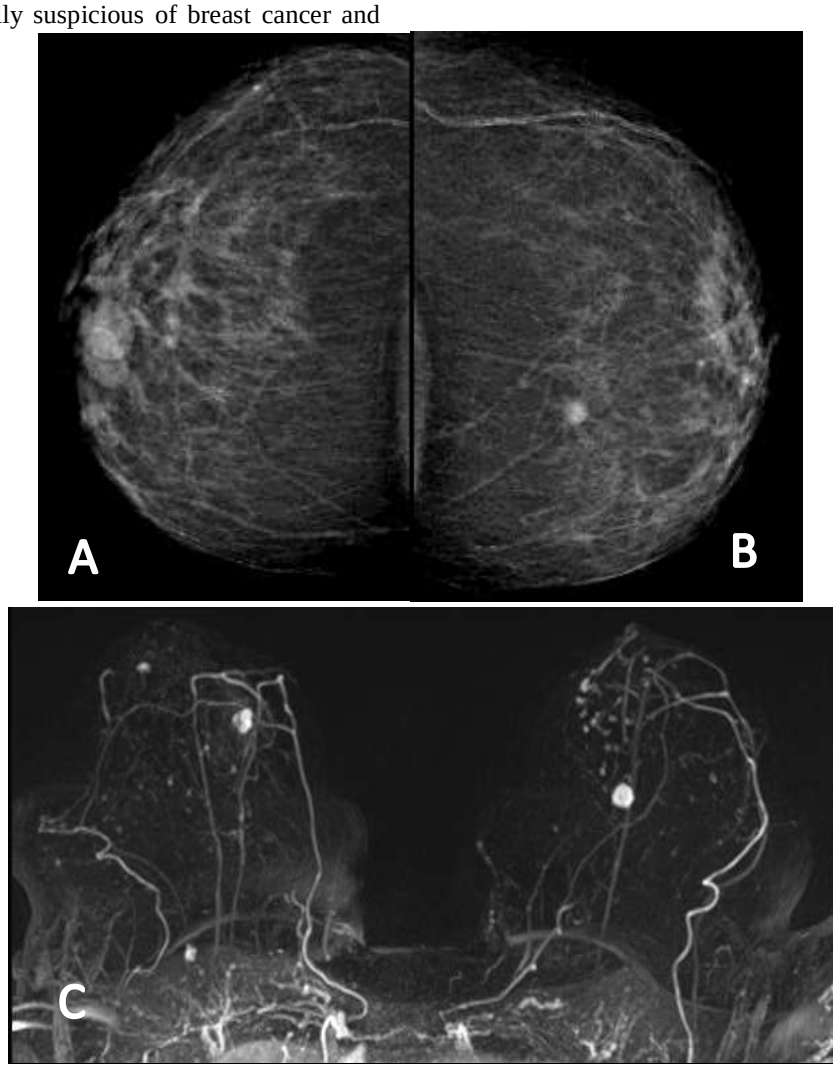

Figure 1A: 69-year-old women with history of painless lump felt in right breast since 15 days, the digital mammography (A and B) shows well-defined oval shaped iso-dense lesion in subareolar region of right breast and another well-defined macro lobulated lesion medial to the above mentioned lesions. Incident spiculated hyper dense lesion is seen in left breast. MR mammography (C) in addition to above mentioned index lesions in both breasts shows non mass like enhancement with internal clumped enhancement in lower inner quadrant of left breast and proven as intraductal carcinoma of cribriform type in histopathology.

V. CONCLUSION:

Combining digital mammography and MR mammography results in a significant improvement in sensitivity than digital mammography alone in detecting DCIS.

As shown in the study, a combination of MR mammography and digital mammography can have better diagnostic accuracy than any single modality alone. Such combinations of digital mammography and breast tomosynthesis has been proven beneficial.19 It reduces recall rates for noncancer cases. Addition of MR mammography to sonomammography modality during screening can yield an additional 1.1 to 7.2 cancers for every 1000 high-risk women screened.20 Advances in radiomics or radiogenomics along with machine learning and artificial intelligence can influence effective detection and treatment of DCIS.5

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