Int. J. Curr. Res. Med. Sci. (2017). 3(5): 111-121

International Journal of Current Research in Medical Sciences

ISSN: 2454-5716

P-ISJN: A4372-3064, E -ISJN: A4372-3061

www.ijcrims.com

Original Research Article

Volume 3, Issue 5 -2017

DOI: http://dx.doi.org/10.22192/ijcrms.2017.03.05.016

The impact of preoperative breast MRI on the surgical management of newly diagnosed non metastatic breast cancers

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Abstract

Background: Preoperative MRI (magnetic resonance imaging) of the breast is likely to accurately stage the disease and thereby influence the surgical decision making in newly diagnosed non metastatic breast cancers. We assessed the impact of preoperative contrast-enhanced MRI in surgical management of women with early breast cancer.

Design: Prospective retrospective study of 48 cases of newly detected non metastatic breast cancers in an Oncology unit of a tertiary care teaching hospital. Enrolled patients were assessed with preoperative MRI of breasts and findings were compared with standard sonomammography findings. Appropriate stage wise treatment plan was devised in conjunction with MRI findings and were corroborated with histopathological examination results.

Outcomes: Primary outcome was assessment of changes in the surgical management of newly detected non metastatic breast cancer as a result of findings revealed in the preoperative MRI of breasts. The agreement of assessment between new MRI findings vis-à-vis histopathology of new lesion was also analyzed

Conclusions: Addition of preoperative MRI to routine mammography did not have a statistically significant impact on surgical management of newly detected non metastatic breast cancers. No statistically significant difference was noted in the number of lesions detected by sonomammography and MRI.There was significant difference between histologically proven and unproven cases in patients where the treatment plan was changed, i.e. 37.5% (3/8) vs 62.5% (5/8) amongst 08 cases where treatment plan was changed following MRI. Changes in treatment plan accrued higher percentage of negative results on histopathological examination.

Keywords: MRI, breast cancer, histopathological examination.

Introduction

Breast cancer is the second leading cause of cancer death in women after lung cancer worldwide. As per the SEER Cancer Statistics Review(1), approximately 12.4 percent of women will be diagnosed with female breast cancer at some point during their lifetime.

In India, breast cancer is the most common cancer among women in urban population and is the second commonest among rural population(2, 3). Agarwal G et al(4) observed that breast cancer patients are about one decade younger in developing countries than their counterparts in developed nations. Further, the proportions of young patients (< 35 years) vary from about 10% in developed to up to 25% in developing Asian countries, which carry a poorer prognosis(4).

World over, mammography is the imaging of choice for breast cancer diagnosis. Mammography has several shortcomings like its decreased sensitivity in patients with elevated lifetime risk of breast cancer and BRCA carriers, in patients with dense breasts, overlapping of tissues when interpreted on a 2D format and patient discomfort due to compression of breast during imaging. There has been a significant reduction in breast cancer mortality amounting to a realistic estimate of 10-15 percent following the implementation of screening mammography(5).

The search for newer modalities for imaging breast led to the introduction of MRI for screening as well as evaluation of breast cancer patients in early 2000s. However, significant controversies still exist regarding its use as a preoperative tool. Preoperative MRI in assessment of response to NAC had superior sensitivity compared to mammography and ultrasound in invasive breast cancers (6), however had no effect on rates of reoperation(7). In view of lack of guidelines on indications of preoperative MR imaging of early invasive breast cancers, we conducted a study to determine the impact of preoperative breast magnetic resonance imaging on the surgical management of newly diagnosed non metastatic breast cancers.

Materials and Methods

The study was conducted in a tertiary care oncology centre over a period of 24 months (April 2013 to March 2015). The study was approved by institutional ethics committee and written informed consent was obtained from all enrolled subjects.

Patients

48 women with newly diagnosed non metastatic breast cancers were included in the study population. Patients with history of prior needle aspiration or biopsy of the breast within four weeks, personal history of breast cancer or metastatic breast cancer, all pregnant and lactating females, those with contraindications to undergo MRI, patients with end stage renal disease and poor general conditions precluding MR study were excluded from the study population. Appropriate patients, as per the inclusion and exclusion criteria, underwent a standardized protocol evaluation and subsequent treatment.

Evaluation protocol

Patients with history and clinical features suspicious of malignancy underwent a diagnostic mammography on Mammomat Fusion, Siemens Healthcare with standard CC and MLO views per breast. Results were reported in accordance with Breast Imaging Reporting and Data System® (BI-RADS®) initiative, instituted by the ACR(8) and corroborated with ultrasonography of the breast and axillary region on Philips 5000 ultrasound system using multi-frequency linear transducer (4-11 Hz). Clinical staging (AJCC Cancer Staging Manual, 7th edition(9)) was done after staging workup, following core needle biopsy (22 G Bard Max-core) of the suspicious lesions and a protocol based treatment was planned.

Thereafter, patients underwent contrast enhanced MRI performed with 1.5T (Avanto, Siemens Medical Systems) of bilateral breasts with dedicated twin breast phased array coils (8 channels) for optimal signal reception, including bilateral dynamic scanning with axial acquisition and kinetic analysis. Gadolinium chelate as a

contrast agent was administered after the pre-contrast sequence. Gradient Echo (GRE) sequence was used for image acquisition protocol. Images so obtained were processed and regions of interest (ROIs) were analyzed to obtain the kinetic curves. Images were reported according to BI-RADS descriptors for MR imaging, including morphologic and kinetic features(10). Subjects with new breast lesions detected on MR were subjected to a "relook" mammogram or USG and representative image guided (US or MR) biopsies were taken.

Reassessment of the disease was done in all subjects post MRI where new findings were revealed. Appropriate changes in treatment protocol based on the post MR clinical staging were made on approval of multidisciplinary team of our institute. Definitive treatment in the form of surgery or NACT was instituted within two weeks of the assessment of post MR clinical staging of the disease.

Statistical analysis

Retrospective analysis of the data was undertaken to find out the impact of MRI findings on surgical decision making and treatment protocol. A total of 48 women who met the inclusion criteria were enrolled in the study. Two subjects were later excluded from the study as they were lost to follow-up. Various characteristics of the study population and the distribution of change in surgical management following preoperative MRI were analyzed. Further, the agreement of assessment between MRI vis-à-vis histopathology of the lesion was also analyzed and conclusions were drawn. Chi-square test was used to compare the difference in surgical treatment plan following MRI and the distribution of change in surgical management following MRI was assessed. A P value <0.001 was considered significant.

Results

The mean age of the study population was 52.6 years. Cohort characteristics are tabulated in table 1.1.

Table 1.1 – Comparison of characteristics of cohort.

Cohort Characteristics		Frequency(percentage)
Age(in yrs)	35-44	7(15.2%)
	45-54	20(43.4%)
	55-64	15(32.6%)
	>65	4(8.6%)
Family history		2(4.3%)
Obstetric history	Early menarche (<12 yrs)	-
	Menarche (12-15 yrs)	46(100%)
	Nulliparity	-
Clinical Features		
Pain		1(2.17%)
Axillary LN	N0	31(67.3%)
	Ipsilateral	15(32.6%)
	Bilateral	-
Local skin changes		3(6.5%)
Nipple retraction/Discharge		-
Lump		
Number	One	45(97.8%)
	More than one	1(2.17%)
Location	UOQ	26(56.5%)
	UIQ	8(17.3%)
	LOQ	6(13%)
	LIQ	6(13%)

Almost 90% of the study population had a single irregular lump with length/AP ration < 1.4 on diagnostic mammography (Table 1.2). A total of 53 mammographically suspicious lesions were picked up. However, contralateral breast and axilla were normal in all subjects. Mammography features of the lesions are as described below.

Table 1.2 Comparison of findings on Mammography.

Findings on Mammography	Frequency(percentage)	
Number of lesions	One	41(89.1%)
	Two	4(8.7%)
	Four	1(2.17%)
Total no of lesions		53
Characteristics		
Length/AP ratio	<1.4	37(80.4%)
	>1.4	9(19.5%)
Micro-calcifications		9(19.5%)
Macro-calcifications		3(6.52%)
Architectural distortion		33(71.7%)
Skin thickening		4(8.7%)
Lymph node status	No axillary nodes	24(52.1%)
	Single ipsilateral node	12(26%)
	Multiple ipsilateral nodes	10(21.7%)
	Bilateral nodes	-
BIRADS stage	I	-
	II	-
	III	-
	IV	10(21.7%)
	V	36(78.2%)

Following staging workup, around 67.3 % of the subjects were diagnosed as Early Breast Cancers (EBC). 23.91% cases were Locally Advanced Breast Cancers (LABC) and the rest were Advanced Breast Cancers (ABC) (Table 1.3& 1.6). Based on clinical, mammographic and histological characteristics of the lesion, 54.5% of the study population was provisionally scheduled to undergo Breast Conservation Therapy (BCT), the remaining, Modified Radical Mastectomy.

Table 1.3 Composite clinical staging and provisional plan of surgical management.

Composite clinical Stage	Frequency(percentage)	
Breast cancer stage(AJCC 8th edition)	IA	3(6.5%)
	IIA	16(34.7%)
	IIB	16(34.7%)
	IIIA	7(15.2%)
	IIIB	4(8.6%)
Provisional plan of surgical management	Breast conservation therapy	25(54.35%)
	Modified radical mastectomy	21(45.65%)

Following preoperative contrast enhanced MRI of breasts, a total of 60 lesions was identified (58 mass lesions and 2 non mass like enhancing lesions, NMLE) (Table 1.4). 02 cases (4.3%) of nipple retraction were observed in clinically and mammographically normal breasts. 86.9% cases showed a type III Kuhl enhancement kinetic curve and 50% of subjects had ipsilateral axillary lymphadenopathy. However, none had contralateral or bilateral axillary lymph node metastasis. 11 cases underwent a relook sonomammography following MRI due to discrepancy in measured size following MRI or detection on new lesions as per schema in Fig1.

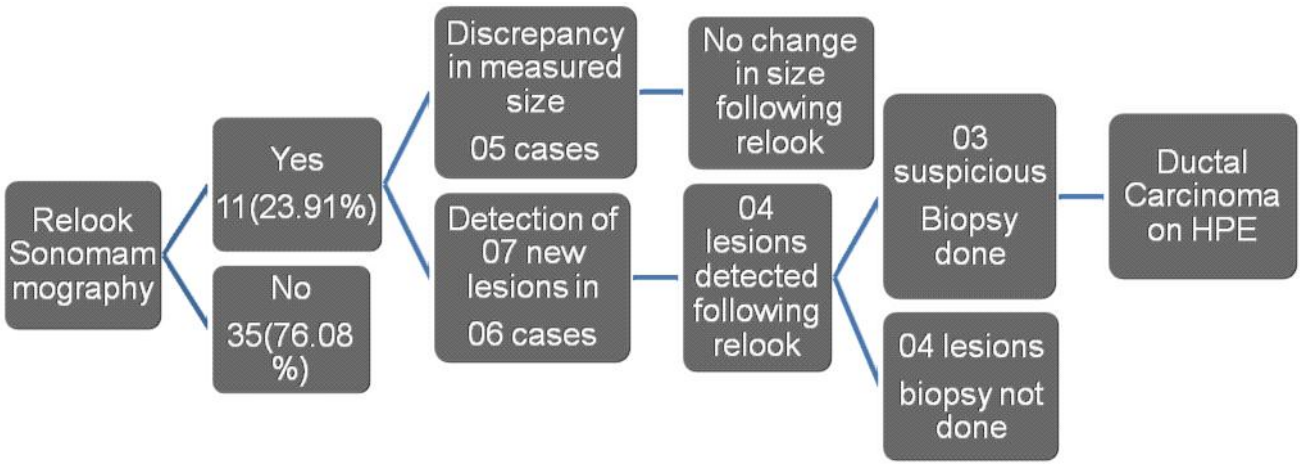

Figure 1 Schema of selection of patients for relook mammography.

Table 1.4 Findings on MR Imaging

Findings on MRI	Frequency(percentage)	
Lesions	Foci or focus	-
	Masses	58
	NMLE	2
Total no of lesions		60
Nipple retraction		2(4.35%)
Skin thickening		4(8.7%)
Number and characteristics of Masses		
Masses	1	38(82.6%)
	2	5(10.8%)
	3	2(4.35%)
	4	1(2.17%)
Characteristics	Irregular	45(97.8%)
	Round	1(2.17%)
Internal enhancement	Heterogeneous	44(95.65%)
	Homogeneous	1(2.17%)
	Rim enhancement	1(2.17%)
Kinetic curve	Inconclusive	1(2.17%)
	Type I	1(2.17%)
	Type II	4(8.7%)
	Type III	40(86.9)
Lymph Node status	No axillary lymph nodes	23(50.0%)
	Single ipsilateral node	11(23.9%)
	Mulitple ipsilateral node	12(26.)%)
	Bilateral nodes	-

Out of these 11 cases (23.91%), 05 cases showed lesions which were larger than 1.5 cms from their initial size on sonomammography. 06 cases showed 07 newly detected lesions on MRI. 04 newly detected lesions were identified on relook sonomammography and image(US/MR) guided biopsy of those amenable lesions (03 suspicious lesions) were undertaken. Four new lesions were not biopsied as either size of lesion was not amenable for biopsy or benign appearance or lesions were in already image proven multicentric disease.

Around 67.3 % (31 of 46 cases) of the subjects were diagnosed as Early Breast Cancers (EBC) after peroperative MRI. 23.91% cases were Locally Advanced Breast Cancers (LABC) and the rest were Advanced Breast Cancers (ABC) (Table 1.5& 1.6). A total number of 22 cases underwent BCS (47.82%) and the rest underwent modified radical mastectomy (52.17%) (Table1.5). 05 out of the 22 cases who underwent BCS, had wider excision margin following MRI findings (05/46 i.e. 10.87%). In these 05 cases, breast MRI detected the lesion to be 1.5 cm larger than that measured on sonomammography. 03 out of the 24 cases who underwent MRM had a change of treatment plan from BCS to MRM following MRI findings (03/46 i.e. 6.52%). 02 of them had a new lesion each detected in different quadrant on MRI, making it a multicentric disease. 01 cases had a new lesion detected making it a multifocal disease.

Table 1.5 Composite clinical staging post MRI and plan of surgical management.

Composite clinical Stage(Post MRI)		Frequency(percentage)
Breast cancer stage(AJCC 8th edition)	IA	3(6.5%)
	IIA	15(32.6%)
	IIB	17(36.9%)
	IIIA	7(15.2%)
	IIIB	3(6.5%)
	IIIC	1(2.17%)
Surgical management	BCS (with wider excision post MRI)	22 (05) 47.82 % (10.87%)
	MRM (changed from BCS post MRI)	24 (03) 52.17 % (6.52 %)

Table 1.6 Composite clinical staging pre and post MRI.

Pre MRI Staging			Post MRI staging		
TNM		**Composite (cases)**	**TNM**		**Composite (cases)**
T1N0M0	**Early Breast Cancer(31)**	IA (3)	T1N0M0	**Early Breast Cancer(31)**	IA (3)
T2N0M0		IIA (16)	T2N0M0		IIA (15)
T2N1M0		IIB (12)	T2N1M0		IIB (13)
T3N0M0	**Locally Advanced Breast Cancer(11)**	IIB (4)	T3N0M0	**Locally Advanced Breast Cancer(11)**	IIB (4)
T3N1M0		IIIA (5)	T3N1M0		IIIA (5)
T1N2aM0		IIIA (1)	T1N2aM0		IIIA (1)
T3N2M0		IIIA (1)	T3N2M0		IIIA (1)
T4bN0M0	**Advanced Breast Cancer(4)**	IIIB (1)	T4bN0M0	**Advanced Breast Cancer(4)**	IIIB (1)
T4bN1M0		IIIB (2)	T4bN1M0		IIIB (1)
T4bN2M0		IIIB (1)	T4bN2M0		IIIB (1)
			T4bN3bM0		IIIC (1)

Thus, 08 cases out of 46 who underwent breast MRI had their surgical treatment changed depending upon MRI findings (17.39%). 03 cases had their surgical plan changed from BCS to MRM (Table 1.5). Out of these 03, only 02 had proven lesion on histopathology (Table 1.7). 05 cases underwent BCS with a wider than previously planned margin. However, only one out of these 05 was confirmed beneficial on tumour size evaluation on histopathology. To conclude, only 03 out of 46cases (6.52%), who had their surgical management altered based on MRI findings, were proven beneficial on histopathology (Table 1.8).

Table 1.7 Findings on histopathological examination.

Histopathological examination	Frequency(percentage)	
No of lesions on HPE	One	39(84.7%)
	Two	4(8.69%)
	Three	2(4.34%)
	Four	1(2.17%)
Type	Ductal carcinoma in situ	5(10.86%)
	Infiltrating ductal carcinoma	33(71.7%)
	Infiltrating lobular carcinoma	1(2.17%)
	Medullary carcinoma	1(2.17%)
	IDC with DCIS component	6(13.04%)
Pathological Stage	IA	4(8.69%)
	IB	1(2.17%)
	IIA **Early Breast Cancer**	29(63.04%)
	IIB	10(21.73%)
	IIIA **Locally Advanced**	1(2.17%)
	IIIB **Breast Cancer**	1(2.17%)
Lymphovascular Invasion		2(4.34%)
Perineural Invasion		-
Margins	Involved	4(8.69%)
	Free	42(91.3%)

Table 1.8 Comparison between Imaging and Histopathology.

Comparison between Imaging and Histopathology			
Axillary lymph nodes	Mammography	MRI	Confirmed on HPE
	22(47.8%)	23(50.0%)	13(28.2%)
New lesions on MRI	07		05
Change of treatment plan post MRI	08(17.39%)		03(6.5%)
BCS (with wider excision post MRI)	05		02(4.34%)
MRM (changed from BCS post MRI)	03		01(2.17%)

We studied change in surgical management following preoperative MRI in 3 categories:

(1) A change from breast conservation surgery to mastectomy when the new lesion resulted in multicentric disease or the lesion appeared to be much more extensive on MRI so that breast conservation was not appropriate.
(2) A wider excision when an adjacent lesion or more extensive primary lesion was detected but breast conservation was still possible.
(3) Detection of an otherwise undetected lesion in the opposite breast that resulted in contralateral surgery.

We found that distribution of proportion of change of surgical management differs significantly across HPE proven and non-proven cases (P-value<0.001). There was significant difference between histologically proven and unproven cases in cases where the treatment plan was changed, i.e. 37.5% (3/8) vs 62.5% (5/8) amongst 08 cases where treatment plan was changed following MRI (Table 2.1). Thus, the percentage of cases in which management was changed based upon MRI findings but were proven negative on final HPE analysis was significantly higher than those proven positive on final HPE analysis. Further, there was no statistically significant difference in the number of lesions detected by sonomammography and MRI (Table 2.5).

Table 2.4 The distribution of change in surgical management as per MRI findings. Values are n (% of cases). *Chi-Square value = 26.646, P-value = 0.001*** *(Significant).*

Management Status	**Histopath Proven**		**Histopath Not Proven**		**Total**	
	n	%	n	%	n	%
Management Not changed	38	92.7	0	0.0	38	82.6
Management changed	3	7.3	5	100.0	8	17.4
Total	**41**	**100.0**	**5**	**100.0**	**46**	**100.0**

Table 2.5 The distribution of total number of lesions detected by all three modalities, Values are no. of lesions (% of lesions). NS: Statistically Non-Significant.

Modality	**Total no. of lesions**	**% of lesions (Out of 60)**	**One-Sample Chi-Square test**	
			Chi-Square value	**P-value**
MRI (Gold Std.)	60	100.0%	*Reference*	*Reference*
Histopathology	59	98.3%	0.008	0.927^{NS}
Ultrasound	53	88.3%	0.434	0.510^{NS}

We studied change in surgical management following preoperative MRI in 3 categories:

(4) A change from breast conservation surgery to mastectomy when the new lesion resulted in multicentric disease or the lesion appeared to be much more extensive on MRI so that breast conservation was not appropriate.
(5) A wider excision when an adjacent lesion or more extensive primary lesion was detected but breast conservation was still possible.
(6) Detection of an otherwise undetected lesion in the opposite breast that resulted in contralateral surgery.

We found that distribution of proportion of change of surgical management differs significantly across HPE proven and non-proven cases (P-value<0.001). There was significant difference between histologically proven and unproven cases in cases where the treatment plan was changed, i.e. 37.5% (3/8) vs 62.5% (5/8) amongst 08 cases where treatment plan was changed following MRI (Table 2.1).

Thus, the percentage of cases in which management was changed based upon MRI findings but were proven negative on final HPE analysis was significantly higher than those proven positive on final HPE analysis. Further, there was no statistically significant difference in the number of lesions detected by sonomammography and MRI (Table 2.2).

Table 2.1 The distribution of change in surgical management as per MRI findings. Values are n (% of cases). *Chi-Square value = 26.646, P-value = 0.001*** *(Significant).*

Management Status	**Histopath Proven**		**Histopath Not Proven**		**Total**	
	n	%	n	%	n	%
Management Not changed	38	92.7	0	0.0	38	82.6
Management changed	3	7.3	5	100.0	8	17.4
Total	**41**	**100.0**	**5**	**100.0**	**46**	**100.0**

Table 2.2 The distribution of total number of lesions detected by all three modalities, Values are no. of lesions (% of lesions). NS: Statistically Non-Significant.

Modality	**Total no. of lesions**	**% of lesions (Out of 60)**	**One-Sample Chi-Square test**	
			Chi-Square value	**P-value**
MRI (Gold Std.)	60	100.0%	*Reference*	*Reference*
Histopathology	59	98.3%	0.008	0.927^{NS}
Ultrasound	53	88.3%	0.434	0.510^{NS}

MRI had a sensitivity of 100% in picking up new lesions which were unidentified by sonomammography, but its accuracy and PPV on final comparison with HPE analysis for newly detected lesions was only 85.7% and 85.7% respectively(Table 2.3a & 2.3b).

Table 2.3a The assessment of agreement between MRI and Histopathology for newly found lesions, Values are no. of new lesions (% of new lesions).

New Lesions Status	**Histopath Proven**		**Histopath Not Proven**		**Total**	
	N	%	n	%	n	%
New Lesions on MRI	6	100.0	1	100.0	7	100.0
No New Lesions on MRI	0	0.0	0	0.0	0	0.0
Total	**6**	**100.0**	**1**	**100.0**	**7**	**100.0**

Table 2.3b The assessment of agreement between MRI and Histopathology for newly found lesions (Sensitivity analysis of MRI against Histopathology for detecting new lesions)*PPV: Positive predictive value, NPV: Negative predictive value*.

	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
Values (%)	100.0	--	85.7	--	85.7

Discussion

Our results show that addition of preoperative MRI to routine mammography did not have any statistically significant beneficial effect on surgical management of newly detected non metastatic breast cancers. Further, no statistically significant difference was noted in the number of lesions detected by sonomammography and MRI. Similar results were observed by A Parker etal who concluded that use of MRI in women with newly diagnosed breast cancer does not reduce re-excision rates(7) for positive margins; and does not reduce local recurrence (13).

Further, no statistically significant difference was noted in the number of lesions detected by sonomammography and MRI. Due to lack of concrete guidelines on indications of breast MRI, there has been an increase in its utilisation by

breast surgeons. Personal experience was the most influential factor which guided utilisation of breast MRI among surgeons (11). To date, pre-operative MRI is indicated in defined groups of patients in which a potential benefit of local staging is expected, *i.e.*, women with mammographically heterogeneous or extremely dense breasts, at high risk for breast cancer, diagnosed with invasive lobular carcinoma and/or with multifocal, multicentric or contralateral disease(12).The ACS guidelines state that MRI of breast is not an adjunct to mammography as certain lesion like DCIS are detectable only with mammography and recommends that screening with MRI is inappropriate for women at 15% lifetime risk for breast cancer(13). The MONET trial concluded that breast MRI should not be routinely used as a preoperative tool in patients with non-palpable breast cancers(14).

In our study, we observed that findings on MRI impel surgeon to undertake wider excision margins or contemplate change in surgical management, but with higher percentage of negative results on histopathological examination. Turnbull etal, in a large prospective, multicenter COMICE trial reported a change in management in 7 % of patients based on MRI with a higher mastectomy rate in the MRI group (7 vs. 1 % of women)(15). However, the study concluded that addition of MRI to conventional triple assessment has no benefit on reduction of reoperation rate.

A potential limitation of our study is the fact that ours is a single center study encompassing a study population of only 46 subjects. Further, modest amount of selection bias might be associated with selection of subjects.

There are 2 persistent concerns based on current evidence. Firstly, the technical false positives cause unnecessary diagnostic biopsies. Secondly, and perhaps more importantly, is the concern that although MRI detects previously unrecognized, but pathologically confirmed cancer deposits, these deposits may be biologically and clinically irrelevant in a patient who will undergo standard excision and breast irradiation. Further, Most of the in-breast recurrences occurring after the first 10 years post-breast–conserving therapy are believed to be new primary breast cancers and not cancers recurring as a result of therapeutic failure(16).

To conclude, evidence on preoperative MRI indicates that it is of little benefit for women with newly diagnosed, early stage breast cancer with no personal or family history. It does not appear to improve surgical planning, and there is very limited and inconsistent evidence on its long-term impact on clinical outcomes.

Financial support: Nil

Conflict of Interest : None declared.

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How to cite this article:
Col (Dr.) Puneet Takkar, Surg Lt Cdr (Dr.) Hari JP, Surg Lt Cdr (Dr.) Khushdeep Kaur. (2017). The impact of preoperative breast MRI on the surgical management of newly diagnosed non metastatic breast cancers. Int. J. Curr. Res. Med. Sci. 3(5): 111-121.
DOI: http://dx.doi.org/10.22192/ijcrms.2017.03.05.016