Original Article

DOI: 10.7860/IJARS/2016/23252:2217

Radiology Section

A Prospective Study on the Role of Diffusion Weighted MR Imaging in Charcterisation of Breast Masses

RAJALAKSHMI PREETHI G, MARIAPPAN MURUGAN, MAHESH K MITTTAL, BRIJ BHUSHAN THUKRAL

ABSTRACT

Introduction: Breast MRI has been widely used for the detection, diagnosis and staging of breast cancer. Even though lower ADC, which is the objective measure of the diffusivity has been proved too strongly associated with malignant tumours, the threshold ADC value which best differentiates these lesions is not yet standardized.

Aim: To identify the appropriate cut-off value for ADC value to diagnose malignant breast lesions in Indian women.

Materials and Methods: A total of 55 lesions, in patients presenting with clinically palpable breast lump, mammographically or sonographically detected breast masses, were included in the study. MRI was done, using dedicated phased-array breast coil. Routine MRI sequences and dynamic contrast enhanced MRI was done in addition to the DWI sequence (b- values of 0 & 1000 s/mm^2). ADC value of each of the breast lump was acquired. Histological confirmation was done by trucut biopsy/ excision biopsy of the lumps and was considered to be the gold standard.

Results: The area under ROC curve was close to highest possible value of 1 (AUC=0.997, 95% CI 0.98 to 1, p value < 0.001), indicating high predictive validity of ADC. The best sensitivity (96.2%) and specificity (100%) were observed for an ADC cut off value of 1.31 in study population. When slightly lower cut off value of 1.15 is considered the sensitivity remained at 96.2 but specificity has declined to 99.97%. When slightly higher cut off of 1.42 is considered, the sensitivity has declined to 93% with specificity remaining at 100%.

Conclusion: DWI using cut-off ADC value is a promising MRI technique which could improve the diagnostic accuracy of the breast MRI in lesion characterization. It could prove to be an useful adjunct to the established DCE-MRI. More validated studies are required to standardize the DWI protocol, optimize the b-values and to determine the optimum cut-off ADC values.

Keywords: ADC, Benign, DWI, Malignant breast mass

INTRODUCTION

Breast MRI has been widely used for the detection, diagnosis and staging of breast cancer. Contrast enhanced MRI of the breast is known for high sensitivity of 70 – 100 %. However, variable specificity (75–98%) may lead to unnecessary biopsies [1-3]. The specificity of breast MR imaging has been increased by applying diffusion weighted imaging (DWI). Several studies have shown good results supporting the role of DWI using apparent diffusion co-efficient (ADC) threshold levels, in differentiating benign and malignant lesions [4-11]. Malignant lesions have lower ADC values than benign lesions. Yet, a standard threshold ADC value which best differentiates benign and malignant lesions is yet to be established, justifying the need for further studies.

DWI reflects the local micro structural characteristics of water diffusion in the lesions. ADC is the objective measure of the diffusivity [4-6,12,13]. In the presence of diffusion-hindering obstacles such as membranes, tight junctions, fibres, macromolecules, and cell organelles, the mobility of water protons is hindered, resulting in reduced diffusivity and decreased ADC. Increased intracellular tissue, either due to swelling or due to increased cellular density, leads to diffusion restriction on DWI and low ADC values. Accordingly, malignant tumour tissue will show restricted diffusion and hence, low ADC because of the densely packed malignant cells. Whereas, in tissues which are less densely packed (i.e. non-neoplastic tissue/ benign lesions) the ADC values is expected to be high. Hence, the ADC values are useful to distinguish malignant tumour from benign lesions. DWI also has the unique advantage over all other techniques in being quantitative [14,15].

Previous published studies have evaluated the role of DWI

and ADC measurement in differentiating benign and malignant lesions [14-20]. However, the threshold ADC value which best differentiates these lesions is not yet standardized and the need for more studies has also been highlighted by meta-analysis by Tsushima et al.,[20]. Hence, the current study was planned with an objective of identifying the appropriate cut off value for ADC value to diagnose malignant breast lesions in Indian women.

MATERIALS AND METHODS

This was a cross sectional study conducted in the Department of Radiology of Safdarjung Hospital, which is a tertiary care teaching hospital in North India, after obtaining ethical committee approval. The study was conducted between the period of January 2010 to May 2011 for the duration of 1 year 5 months.

The study population included women presenting with clinically palpable breast lump, mammographically or sonographically detected breast masses, were included in the study after obtaining written consent from the subjects. In case of women presenting with mass on both sides, each mass was considered as one study unit.

Purely cystic lesions or sub centimetric lesions were excluded and remaining 50 patients who satisfied our inclusion criteria were taken up in our study.

MRI was performed on a 1.5 Tesla PHILIPS Intera Achieva MRI system, using dedicated phased-array breast coil. Routine axial T1W, T2W, sagittal and coronal STIR sequences and dynamic contrast enhanced MRI were done in addition to the DWI sequence.

Diffusion weighted imaging was acquired using single shot echo planar imaging (EPI) sequence in axial plane using b-values of 0 & 1000s/mm^2. ADC value of each of the breast lump was acquired.

Histological confirmation was done by Tru-cut biopsy/ excision biopsy of the lumps and was considered to be the gold standard.

Descriptive analysis of MRI and HPE findings were done using frequency and proportions. The quantitative data like lesion size on MRI and ADC were assessed for normal distribution by visual inspection of histograms, Z value of skewness and kurtosis and p– value of Shapiro Wilk test, with each category of breast lump. Since, the data was not normally distributed it was decided to present median and inter quartile range to summarize them. Non parametric test like Mann Whitney 'U' test and independent sample median test were used for statistical analysis. The predictive validity of ADC in classifying the tumours as beings and malignant was assessed by Receiver Operating curve (ROC) analysis. The area under the curve and its 95% CI and p-value were presented. Based on the ROC analysis best cut off ADC values was identified and their sensitivity, specificity and predictive values were presented.IBM SPSS version 21 was used for statistical analysis.

RESULTS

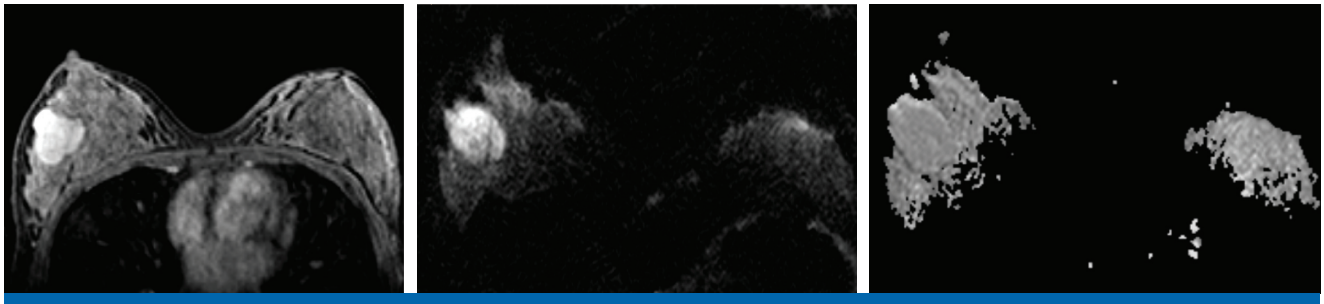
A total of 55 lesions were included in the final analysis. Considering the minimum sensitivity to be documented as 80%, the sensitivity of 92%, with an alpha error of 0.05 and assuming the Wald test to detect the difference between two proportions, the current sample size of 55 in the current study has yielded a power of 90.3%.

Almost all the lesions showed enhancement on MRI, except 1 (1.8%). The tumour margins were irregular in 15 (27.35), smooth in 30(54.55) and spiculated in 10 (18.2%) of the patients [Table/Fig-1a–1c, 2]. On histopathological examination 29 (52.7%) lesions were malignant and 26 (47.3%) were benign [Table/Fig-3,4].

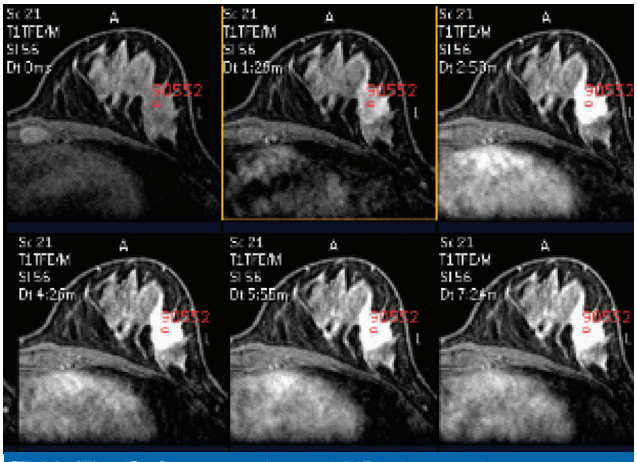
The median ADC values were lower in malignant lesion, compared to benign lesions (0.89 vs 1.53) [Table/Fig-5]. Both the differences in distribution and median values of tumour size and ADC values were statistically significant (p-value < 0.05) [Table/Fig-6,7].

The area under ROC curve was close to highest possible value of 1 (AUC=0.997, 95% CI 0.98 to 1, p-value < 0.001), indicating high predictive validity of ADC [Table/Fig-8].

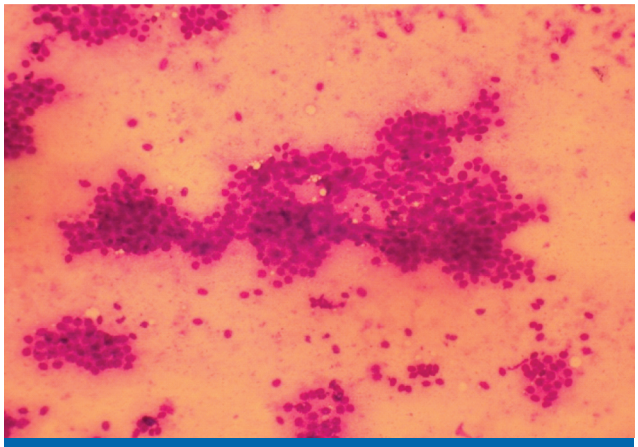
The best sensitivity (96.2%) and specificity (100%) were



[Table/Fig-1]: (1a) Contrast enhanced MRI shows smooth marginated, lobulated, homogeneously enhancing mass. (1b) On MRI – DWI (b- 1000) the mass appears hyperintense. (1c) On ADC map mass is isointense to the surrounding parenchyma with an ADC value of 1.513 x 10^{-3} mm^2/s also s/o benign lesion.



[Table/Fig-2]: Contrast enhanced MRI shows a homogeneously enhancing mass with spiculated margins.



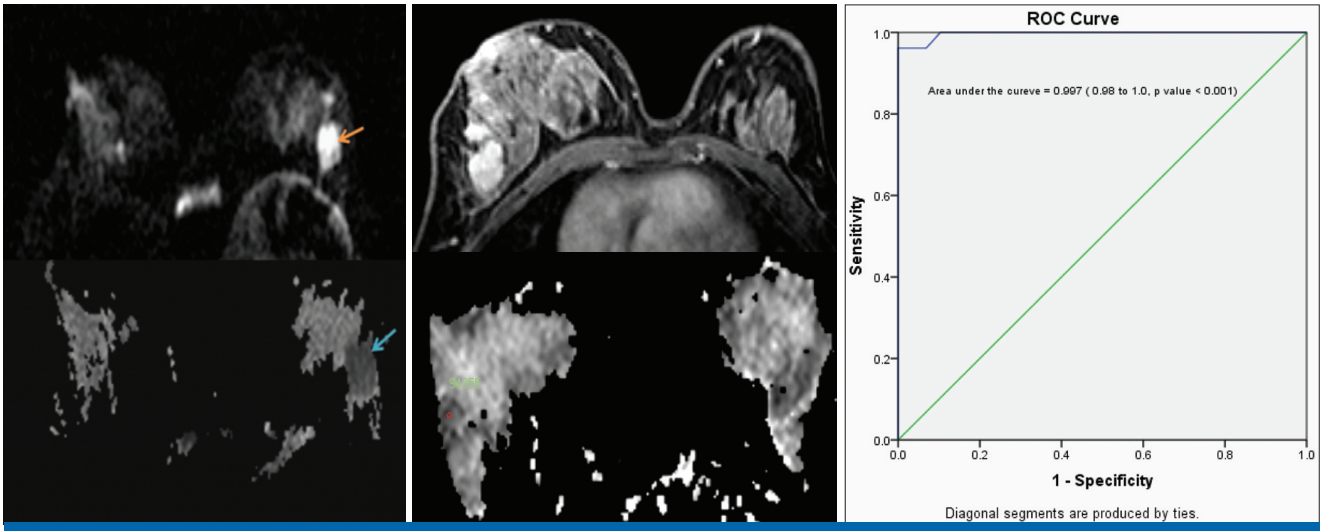
[Table/Fig-3]: Histopathology shows tight cluster of benign ductal epithelial cells suggestive of Fibroadenoma.

Parameter	Frequency	Percentage
Margins in MRI		
Irregular	15	27.3
Smooth	30	54.5
Speculated	10	18.2
Histopathological examination		
Malignant	29	52.7
Benign	26	47.3

[Table/Fig-4]: Descriptive analysis of MRI and HPE findings in Study population (n=55).

Type of lesion	Median (IQR)	Mann-Whitney U test to compare distributions	Independent sample median test (to compare medians)
ADC			
Malignant	0.89 (0.83 to 0.94)	< 0.001	< 0.001
Benign	1.53 (1.50 to 1.62)		

[Table/Fig-5]: Comparison of lesion size and ADC values in benign and malignant lesions.



[Table/Fig-6]: DWI and ADC map shows restricted diffusion within the mass with an ADC value of 0.746 x 10-3 mm2/s, suggestive of malignant lesion. Histopathology revealed invasive ductal carcinoma. **[Table/Fig-7]:** (7a) – Contrast MRI shows a well defined lobulated mass with homogeneous enhancement. (7b) DWI- ADC map of the same patient shows restricted diffusion of the mass with an ADC value of 1.14 x 10^{-3} mm^2/s suggesting a malignant lesion.Core needle biopsy of this lesion revealed invasive ductal carcinoma. **[Table/Fig-8]:** Receiver operating curve analysis to assess the predictive validity of ADC.

observed for an ADC cut off value of 1.31 in study population. When slightly lower cut off value of 1.15 is considered the sensitivity remained at 96.2 but specificity has declined to 99.97%. When slightly higher cut off of 1.42 is considered, the sensitivity has declined to 93% with specificity remaining at 100%.

DISCUSSION

In our study, DWI was done using a maximum b-value of 1000. Similar protocol was also used in previous studies by Marini et al, Guo et al., Rubesova et al, Yabuuchi et al and Park et al [5,7,9,15,18].

The ADC values of the benign lesions in our study, ranged from 1 x 10^{-3} mm^2/s to 1.9 x 10^{-3} mm^2/s, with a mean value of 1.54 x 10^{-3} mm^2/s. The malignant lesions showed a mean ADC of 0.89 x 10^{-3} mm^2/s, with the values ranging from 0.69 x 10^{-3} mm^2/s to 1.2 x 10^{-3} mm^2/s. Similar results was also reported by Marini et al., Park et al., and Rubesova et al., in their studies [5,9,18] [Table/Fig- 9].

	Mean ADC value	
	Benign lesions	Malignant lesions
Marini et al.,[5]	1.48 x 10^{-3} mm^2/s	0.95 x 10^{-3} mm^2/s
Rubesova et al.,[9]	1.51 x 10^{-3} mm^2/s	0.95 x 10^{-3} mm^2/s
Park et al.,[18]	1.41 x 10^{-3} mm^2/s	0.89 x 10^{-3} mm^2/s
Present study	1.54 x 10^{-3} mm^2/s	0.89 x 10^{-3} mm^2/s

[Table/Fig-9]: Mean ADC values of benign and malignant lesions in different studies.

Using the Mann-Whitney test, difference between the mean ADC value of the benign and malignant lesions was found to be statistically significant and the threshold ADC value with highest possible sensitivity and specificity was determined as 1.31 x 10^{-3} mm^2/s based on ROC analysis. This had a sensitivity of 96.62% and a specificity of 100%.

Threshold values derived by other studies viz. Marini et al., (1.1 x 10^{-3} mm^2/s), Rubesova et al., (1.13 x 10^{-3} mm^2/s) and Yabuuchi et al., (1.1 x 10^{-3} mm^2/s) are also comparable to our threshold ADC value [5,9,16].

It has been reported that the most important factor that affects measured ADC value was the maximum b-value. The ADC values tend to be higher at low b-values used for calculation, because of contribution from perfusion effects at the low b values. The maximum b values of at least 500–800 sec/mm^2 are needed to separate diffusion from perfusion effects. In particular, because invasive ductal carcinoma (IDC) has an increased number and size of capillaries, the ADC value can be strongly affected by perfusion effects, when the maximum b value is small. Therefore, in the more recent studies, ADC values were calculated using relatively large maximum b factor. Another advantage of using a relatively large maximum b factor is the elimination of signals from normal (non cancerous) tissue, where ADC value is higher, and to highlight signal from malignant tumours on DWI resulting in detect ability of malignant lesions [19].

One benign lesion which was incorrectly classified as malignant was an epidermoid cyst which was mimicking a solid lesion on ultrasound. The epidermoid cysts, although being benign are known to show restricted diffusion due to the thick viscous contents of the cyst. This lesion did not show contrast enhancement and contrast enhanced MRI was useful in characterising this lesion as benign.

According to the determined threshold value (1.15 x 10^{-3} mm^2/s) from our study, the sensitivity, specificity and diagnostic accuracy of DWI in characterising breast lesions is 96.6%, 96.2% and 96.6% respectively which was statistically significant on chi square test ($p < 0.001$). Wenkel et al., reported a sensitivity of 98% and specificity of 93% [4], Woodhams et al., reported a sensitivity of 93% and specificity of 88%, which were similar to our results [11]. Tsushima et al., [20], in their meta-analysis of 11 studies derived a pooled sensitivity of 89% and specificity of 77% [Table/Fig-10]. The high sensitivity and specificity of our study could be because of our exclusion of small sized lesions.

	Cut-off ADC value	Sensitivity	Specificity
Present study	1.31x 10^{-3} mm^2/s	96.2%	100%
Marini et al., (2007) [5]	1.1 x 10^{-3} mm^2/s	81%	79%
Rubesova et al., (2006) [9]	1.13 x 10^{-3} mm^2/s	85%	86%
Yabuuchi et al., (2008) [16]	1.1 x 10^{-3} mm^2/s	83%	81%
Wenkel et al., (2007) [4]	1.26 x 10^{-3} mm^2/s	98%	93%
Meta analysis Tsushima et al., (2009) [20]	1.23 x 10^{-3} mm^2/s	89%	77%

[Table/Fig-10]: Sensitivity, specificity and cut-off ADC values derived in different studies.

Magnetic resonance imaging of the breast is being increasingly used as an important tool for detecting breast cancer and as problem solving tool in characterising indeterminate lesions on mammography or ultrasound. DCE-MRI has high sensitivity for detecting malignant lesion, reportedly as high as 88%–100%, but with a low specificity ranging from 68%–96% [21-23]. Limitation of our study included small sample size and exclusion of subcentimetric lesions.

DWI using cut-off ADC value is a promising MRI technique which could improve the diagnostic accuracy of the breast MRI in lesion characterisation. It could prove to be an useful adjunct to the established DCE-MRI . More validated studies are required to standardise the DWI protocol, optimise the b-values and to determine the optimum cut-off ADC values. To us, a high 'b' value of 1000 is required for optimum results. Use of multiple b values results in prolonged scan time with not much added information.

CONCLUSION

DWI MRI and ADC values are a useful tool which will help in the better characterisation of breast masses with high diagnostic accuracy, in MR imaging. We recommend that DWI should be included in the routine breast MRI protocol.

REFERENCES

[1] Kuhl CK. Current status of breast MR imaging. Part 2. Clinical applications. *Radiology*. 2007;244(3):672-91.
[2] Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. *Annals of internal medicine*. 2008;148(9):671-79.
[3] Kuhl CK, Jost P, Morakkabati N, Zivanovic O, Schild HH, Gieseke J. Contrast-enhanced MR imaging of the breast at 3.0 and 1.5 T in the same patients: initial experience. *Radiology.* 2006;239(3):666-76.
[4] Wenkel E, Geppert C, Schulz-Wendtland R, Uder M, Kiefer B, Bautz W, et al. Diffusion weighted imaging in breast MRI: comparison of two different pulse sequences. *Academic Radiology*. 2007;14(9):1077-83.
[5] Marini C, Iacconi C, Giannelli M, Cilotti A, Moretti M, Bartolozzi C. Quantitative diffusion-weighted MR imaging in the differential diagnosis of breast lesion. *European Radiology.* 2007;17(10):2646-55.
[6] Hatakenaka M, Soeda H, Yabuuchi H, Matsuo Y, Kamitani T, Oda Y, et al. Apparent diffusion coefficients of breast tumors: clinical application. *Magn Reson Med Sci*. 2008;7(1):23-29.
[7] Guo Y, Cai YQ, Cai ZL, Gao YG, An NY, Ma L, et al. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. *J Magn Reson Imaging.* 2002;16(2):172-78.
[8] Kuroki Y, Nasu K, Kuroki S, Murakami K, Hayashi T, Sekiguchi R, et al. Diffusion-weighted imaging of breast cancer with the sensitivity encoding technique: analysis of the apparent diffusion coefficient value. *Magn Reson Med Sci*. 2004;3(2):79-85.
[9] Rubesova E, Grell AS, De Maertelaer V, Metens T, Chao SL, Lemort M. Quantitative diffusion imaging in breast cancer: a clinical prospective study. *J Magn Reson Imaging.* 2006;24(2):319-24.
[10] Sinha S, Lucas-Quesada FA, Sinha U, de Bruhl N, Bassett LW. In vivo diffusion-weighted MRI of the breast: potential for lesion characterization. *J Magn Reson Imaging.* 2002;15(6):693-704.
[11] Woodhams R, Matsunaga K, Iwabuchi K, Kan S, Hata H, Kuranami M, et al. Diffusion-weighted imaging of malignant breast tumors: the usefulness of apparent diffusion coefficient (ADC) value and ADC map for the detection of malignant breast tumors and evaluation of cancer extension. *J Comput Assist Tomogr*. 2005;29(5):644-49.
[12] Yankeelov TE, Lepage M, Chakravarthy A, Broome EE, Niermann KJ, Kelley MC, et al. Integration of quantitative DCE-MRI and ADC mapping to monitor treatment response in human breast cancer: initial results. *Magn Reson Imaging*. 2007;25(1):01-13.
[13] Kuroki-Suzuki S, Kuroki Y, Nasu K, Nawano S, Moriyama N, Okazaki M. Detecting breast cancer with non-contrast MR imaging: combining diffusion-weighted and STIR imaging. *Magn Reson Med Sci*. 2007;6(1):21-27.
[14] Palle L, Reddy B. Role of diffusion MRI in characterizing benign and malignant breast lesions. *Indian J Radiol Imaging*. 2009;19(4):287-90.
[15] Riedl CC, Ponhold L, Flory D, Weber M, Kroiss R, Wagner T, et al. Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at high risk for breast cancer. *Clin Cancer Res*. 2007;13(20):6144-52.
[16] Yabuuchi H, Matsuo Y, Okafuji T, Kamitani T, Soeda H, Setoguchi T, et al. Enhanced mass on contrast-enhanced breast MR imaging: Lesion characterization using combination of dynamic contrast-enhanced and diffusion-weighted MR images. *J Magn Reson Imaging*. 2008;28(5):1157-65.
[17] Kim SH, Cha ES, Kim HS, Kang BJ, Choi JJ, Jung JH, et al. Diffusion-weighted imaging of breast cancer: correlation of the apparent diffusion coefficient value with prognostic factors. *J Magn Reson Imaging*. 2009;30(3):615-20.
[18] Park JM, Park JH. Human in-vivo 31P MR spectroscopy of benign and malignant breast tumors. *Korean J Radiol*. 2001;2(2):80-86.
[19] Pereira FP, Martins G, Figueiredo E, Domingues MN, Domingues RC, da Fonseca LM, et al. Assessment of breast lesions with diffusion-weighted MRI: comparing the use of different b values. *AJR Am Jo Roentgenol*. 2009;193(4):1030-35.
[20] Tsushima Y, Takahashi-Taketomi A, Endo K. Magnetic resonance (MR) differential diagnosis of breast tumors using apparent diffusion coefficient (ADC) on 1.5-T. *J Magn Reson Imaging.* 2009;30(2):249-55.
[21] Warren RM, Pointon L, Thompson D, Hoff R, Gilbert FJ, Padhani A, et al. Reading protocol for dynamic contrast-enhanced MR images of the breast: sensitivity and specificity analysis. *Radiology*. 2005;236(3):779-88.
[22] Huang W, Fisher PR, Dulaimy K, Tudorica LA, O'Hea B, Button TM. Detection of breast malignancy: diagnostic MR protocol for improved specificity. *Radiology*. 2004;232(2):585-91.
[23] Kinkel K, Helbich TH, Esserman LJ, Barclay J, Schwerin EH, Sickles EA, et al. Dynamic high-spatial-resolution MR imaging of suspicious breast lesions: diagnostic criteria and interobserver variability. *AJR Am J Roentgen*. 2000;175(1):35-43.

AUTHOR(S):

1. Dr. Rajalakshmi Preethi G
2. Dr. Mariappan Murugan
3. Dr. Mahesh K Mitttal
4. Dr. Brij Bhushan Thukral

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Radiodiagnosis, Velammal Medical College Hospital & Research Institute, Madurai, Tamil Nadu, India.
2. Assistant Professor, Department of Radiodiagnosis, Velammal Medical College Hospital & Research Institute, Madurai, Tamil Nadu, India.
3. Professor, Department of Radiodiagnosis, VMMC & Safdarjung Hospital, New Delhi, India.
4. Professor, Department of Radiodiagnosis, VMMC & Safdarjung Hospital, New Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Rajalakshmi Preethi G,
Department of Radiodiagnosis,
Velammal Medical College Hospital & Research Institute,
Madurai, Tamil Nadu-625009, India.
E-mail: preethi.doc@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Publishing: **Oct 01, 2016**