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# Role of Diffusion Weighted Imaging with Corresponding Apparent Diffusion Coefficient Values in Differentiating Benign and Malignant Breast Lesions

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**ABSTRACT**

***Introduction:*** The objective of this study is to assess the role of diffusion weighted (DW) magnetic resonance imaging (MRI) along with its corresponding apparent diffusion coefficient (ADC) values in differentiating malignant from benign breast lesions.

***Material and Methods:*** Patients with breast lesions and those who met inclusion and exclusion criteria were included in this study. MR Mammography (MRM) was performed on 1.5 Tesla MR Scanner (Siemens® Magnetom Avanto®). DWI was performed at b-values of 50, 400 and 800 s/mm$^2$ followed by ADC sequence.

***Results:*** 50 patients with a total of 81 breast lesions and whose diagnosis was histopathologically confirmed following MRM were included in the study. We observed that benign lesions showed no restricted diffusion with an ADC value of >1.3 x $10^{-3}$ mm$^2$/s. Most of the malignant lesions showed restricted diffusion with ADC value of < 1.3 $10^{-3}$ mm$^2$/s. A non-malignant condition, Benign Phyllodes tumor (n=1) showed no restricted diffusion but had a low ADC of 1.1 x $10^{-3}$ giving false positive result. Mucinous carcinomas (n=5) showed no restricted diffusion and had a mean ADC value of >1.3 x $10^{-3}$. We observed sensitivity of DWI along with ADC value to be 86.8% and specificity as 97.6%.

***Conclusion:*** DW-MRI can be employed as a fast unenhanced screening modality for breast cancer with high sensitivity. Considering ADC values along with DW-MRI increased its detection rates and hence both can be incorporated as supplementary techniques in multiparametric MRM.

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## Introduction

Breast cancer is the commonest cancer in female population in developed and developing countries as well [1]. It is a multifactorial ailment and several factors contribute to its incidence. Based on the genetic factors, type of population and demography; frequency, death rate and survival rates of breast cancer differ globally among various parts of the world [2].

Prevalence of breast cancer is 2.3 million in 2020 globally as per the World Health Organization (WHO), and mortality was about 6,85,000 patients. The main cause of increased death rate in breast cancer is due to extensive metastasis. Nearly 7.8 million cases having breast cancer have been newly diagnosed in a span of 5-years from 2016 upto 2020. However, mortality rate has been steeply decreased over the past few years due to the early detection by mammography, sonomammography and MRI; thereby helping in its early intervention [3]. Considering increase in incidence rate of breast cancer, it is vital in diagnosing breast cancer at the earliest, which helps in reducing morbidity and mortality rates. Imaging modalities in diagnosing breast lesions are X-ray mammography, tomosynthesis, sonomammography, elastography and MRM.

Due to increase in awareness among the people, there is rise in periodic physical examinations and screening imaging diagnostic procedures. This has led to early diagnosis of the disease and faster treatment; resulting in improved prognosis amongst the women with breast lesions. X-ray mammography is been used as the common screening modality [4]; however, it has low sensitivity compared to other modalities even when performed with digital breast tomosynthesis, especially in young patients with dense breasts. Many imaging techniques are proposed as potential supplemental screening tools to mammography as the health care system moves towards personalized patient-centred care. Sonomammography has adequate sensitivity and specificity in identifying and assessing breast mass, but its sensitivity is however less as compared to MRI. Lesions not found or which are small or inconclusive on mammography and ultrasonography can be detected on MRM. It is also

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more veracious than other imaging modalities in detecting tumor extension. MRM has been regarded as the most sensitive screening technique with sensitivity of 94 – 100 % and is recommended for population under high risk and in patients with dense breasts [5].

As recommended by the American College of Radiology, conventional breast MR imaging incorporates multiple pulse sequences, including a T2-weighted (T2W) and dynamic contrast enhanced MRI (DCE-MRI) sequences which consists of T1-weighted sequences (T1W) before and after contrast injection and is included as one of the protocol of standard-of-care MRI [6]. Short duration scan like DW-MRI is accessible on most commercial MR scanners which will not require any contrast administration. Utility of advanced MRI technology like DWI was analysed in many studies and was indicated to be included in routine breast MRI protocol [7]. It has been observed in the latest studies that DWI provides additional information of lesion assessment which overcomes the limitations of MRM [8, 9].

The rate of Breast MRI as an imaging modality has increased in the recent times because of its more accurate diagnosis both for primary and recurrent breast cancers, increased sensitivity and specificity as compared to other screening or diagnostic modalities, particularly in cases where mammography and sonomammography findings are inconclusive or yield discrepancies. MRM also has a greater significance in improved local staging of breast cancer by revealing multifocal tumor growth in patients. This accurate staging using MRM has led in selecting the correct treatment and operative method. Excellent sensitivity of MRM has proved advantageous in the preoperative assessment particularly [9,10].

DWI is a fast and easily available unenhanced MRI technique which provides information of degree of diffusion of water molecules; thereby gives an idea about perfusion, vascularity and microscopic cellular environment. This supplementary information about breast lesions and its relative ease in implementation have made DWI an imaging tool of interest for enhancing breast carcinoma diagnosis and characterization [10,11]. In combination with improved treatments, screening MRM is one of the reasons for substantial decline in mortality because of carcinoma breast in the last decade. Many publications have described about an increase in specificity for diagnosing breast lesions with the use of DWI; and its usefulness in the detection, assessment and monitoring of treatment response [7,10,12]. ADC is a quantitative expression of diffusion [7]; expressed by marking the degree of signal loss on its map which occurs upon applying diffusion gradient [13,14].

DW images are acquired with two or more different b-values, ADC value of the target site is calculated and analysed [14,15,16]. Breast lesions appear hyperintense on DWI with lower ADC values relative to normal breast parenchyma because of increased cellularity of the lesions as in comparison to the adjacent parenchyma. Breast lesions are more easily visible on DWI, because such images will have confounding T2-shine through effects [12]. Hence, most clinical applications depend on quantitative ADC measures for characterising the lesion [13,14,15].

The intention of the study is to evaluate the significance of DWI in differentiating benign and malignant breast lesions. To derive cut-off ADC value in differentiating malignant from benign lesions. And to assess the diagnostic performance and combined role of DWI with its corresponding ADC values; deriving sensitivity and specificity and its role in using it as a screening modality.

## Materials and Methods

Study was validated by the Ethical committee of our institutional review board. After obtaining informed consent, patients who met the inclusion and exclusion criteria were included in this study. Patients with breast lumps or the ones with inconclusive mammography and sonomammography findings were considered. Cases who underwent chemotherapy or radiotherapy for carcinoma breast; or in whom biopsy or fine needle aspiration cytology of breast lesion was performed over the past 3 weeks were not included as they could alter the findings.

### *Image acquision and analysis*

MRM of bilateral breasts was performed on 18 channel, 1.5 Tesla MR Scanner (Siemens® Magnetom Avanto®, NUMARIS/4 software, Version-syngo MR D13, from Erlangen, Germany) using dedicated double breast coil with patient in prone position. Variable sized cushions were used to hold the breasts firmly, thereby reducing motion artefacts. MRI protocol was standardized in all patients. DWI sequence at b-values of 50, 400 & 800 s/mm$^2$ & its corresponding ADC sequences were performed.

### *Diffusion weighted MRI and Apparent diffusion coefficient*

Water mobility within single voxel is proportional to intensity on DWI sequence. ADC is rate of diffusion which is described as the mean area that is occupied by single water molecule per unit time (in mm$^2$/s). Calculation of ADC map is done using image acquisitions at ≥2 different b values.

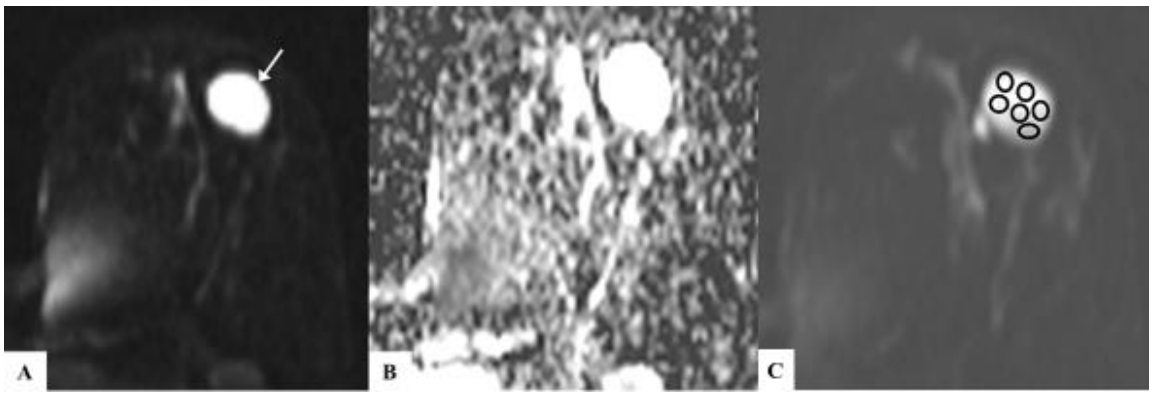


Figure1. Benign breast lesion –A) DWI image showing a well-defined ovoid hyperintense lesion in left breast parenchyma (white arrow). B) ADC sequence showing no restricted diffusion of the lesion. C) Calculation of mean ADC value- Multiple ovoid ROI each measuring ~ 25 $mm^2$ are placed throughout the lesion on DWI sequence; ADC value of each ROI is calculated and mean ADC value of all the ovoid ROI is considered as final value. The lesion was diagnosed as fibroadenomas. (*ADC – Apparent diffusion coefficient, DWI – Diffusion weighted image, ROI – region of interest*).

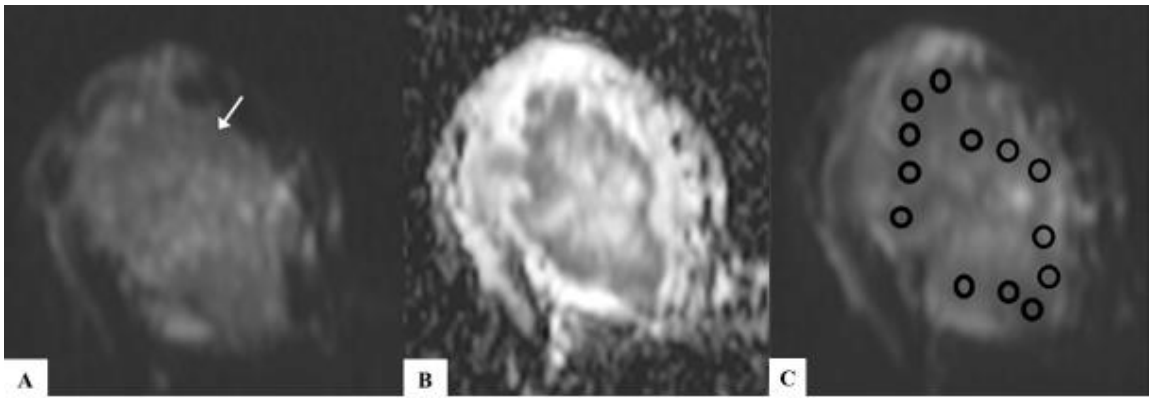


Figure 2. Malignant breast lesion-A) DWI image showing a lesion with irregular margins in right breast (white arrow). B) ADC sequence shows patchy areas of restricted diffusion, predominantly in the periphery of lesion. C) Calculation of mean ADC value- Multiple ovoid ROI each measuring ~ 25 $mm^2$ are placed over the areas of restricted diffusion and ADC value of each ROI is calculated. Mean ADC value of all the ROI is considered as final value. The lesion is diagnosed as infiltrating ductal carcinoma. (*ADC – Apparent diffusion coefficient, DWI – Diffusion weighted image, ROI- Region of interest*).

It quantitatively reflects the composite of tissue factors affecting net mobility of water in every single voxel (it includes microcirculation, organization, cellular density and membrane integrity) [5,10].

DWI axial sequence (Slices- 32, thickness- 4 mm, TR-7200ms, TE- 85ms) was performed at b-values of 50, 400 & 800 s/$mm^2$. 800 s/$mm^2$ sequence, following which a corresponding ADC sequence was generated by the system. Sometimes, small lesions can be missed on T1 non Fat Saturated & T2W sequences but can be picked upon DWI as hyperintense lesions.

Unlike the common method of deriving ADC values by placing a single large region of interest (ROI) over the lesion; in this study we have used a unique method for ADC value calculation by manually placing multiple ROI within the target lesion as explained below. As per Hirano M, et al [13], a feasible size of each ROI measuring ~25 $mm^2$ was chosen to be placed over the lesions. ROI smaller than 25 $mm^2$ were difficult to be placed. And if ROI size of > 25-30 $mm^2$ was considered, multiple ROI could not be placed on smaller breast lesions. Breast lesion will usually have different densities at different points within the lesion; hence considering mean ADC value by placing multiple ROI gives more accurate average ADC value of the lesion than considering ADC value by placing a single ROI.

Benign lesions appear hyperintense on DWI (Figure 1A) and they show no restricted diffusion on ADC; that is they appear hyperintense on ADC (Figure 1B). For calculating ADC values from the benign breast lesions, multiple ovoid or round ROI each measuring ~ 25 $mm^2$ are placed throughout the lesion (Figure 1C). Value of each ROI is calculated and mean of all the ROI is taken as final value. Even a minor displacement of the selected ROI within the lesion affects the calculated ADC value on the map and may result in incorrect ADC values. No ROI were placed if the area of interest was less than 25 $mm^2$ in order to avoid false positive/ negative results due to inclusion of adjacent normal parenchyma.

Malignant breast lesions appear hyperintense on DWI (Figure 2A) and they are seen to restrict on ADC sequence; that is they appear hypointense (Figure 2B). Multiple ROI each measuring ~ 25 $mm^2$ were placed over the areas of restricted diffusion and its mean ROI was calculated (Figure 2C). ROI were not placed over

the regions with no restricted diffusion, as they can alter the final mean ADC value and the findings can be misled; thereby increasing the false negative rates.

## Results

### *Age and gender distribution*

In this study, 50 female patients having breast lesions were evaluated. These 50 patients who were included had 81 lesions in total, where few of them had more than one lesion in same breast and few others had lesions in both breasts. Youngest patient included in the study was 16 years and oldest patient being 85 years. Most of the patients were of perimenopause age group with a range of 40-49 years of age (Table 1).

Table 1. Age group distribution

| age of patients (years) | no. of patients | no. of lesions |
|---|---|---|
| <20 | 2 | 8 |
| 20-29 | 3 | 3 |
| 30-39 | 7 | 8 |
| 40-49 | 16 | 31 |
| 50-59 | 15 | 20 |
| 60-69 | 4 | 6 |
| > 70 | 3 | 5 |

Mean age of the population was 47.7 years, Median was 48 years (Interquartile range-15) with a standard deviation of ± 13.1 years. 30 patients had lesions in right breast, 17 patients had lesions only in left breast and 3 of them had lesions on both sides. As we observed 35% of the breast lesions were observed in upper outer quadrant of the breast, followed by 23% of them were seen in upper inner quadrant (Table 2).

Table 2. Localisation of breast lesion

| quadrant of breast involved | number of lesions | | Percentage (%) |
|---|---|---|---|
| | right breast | left breast | |
| Upper outer | 18 | 8 | 32 |
| Upper inner | 11 | 11 | 27.1 |
| Lower outer | 8 | 8 | 19.7 |
| Lower inner | 8 | 4 | 14.8 |
| Retroareolar/ Central | 4 | 1 | 6.1 |
| | 49 | 32 | |
| | Total - 81 lesions | | |

### *DWI and ADC sequences*

All the lesions whose diagnosis was confirmed by histopathology were included in the study. Totally 81 lesions were assessed and their findings were later compared with the histopathological diagnosis (Table 3), of which 48 lesions showed no restricted diffusion on DWI (Table 4) and these lesions also showed high ADC values > 1.3 x $10^{-3}$ (Table 5) which is suggestive of benign etiology; except for one non-restricting lesion which had a low mean ADC value of 1.1 x $10^{-3}$ (Figure 3A-C) and was diagnosed to be benign Phyllodes tumor on histopathology. 42 lesions of 48 were diagnosed to be fibroadenomas (n-38) and simple cyst (n-4) on histopathology, having findings consistent with DWI and its ADC value (Table 6). Remaining 5 non-restricting lesions which also had high ADC values were misdiagnosed to be benign, but were confirmed to be mucinous carcinoma (Figure 4A-C) on histopathology which is a malignant condition (Table 6). Mucinous carcinomas had a very high ADC values which was slightly more than other benign lesions like fibroadenomas. Remaining 33 lesions showed restricted diffusion; most of the lesions showed complete restricted diffusion while few others showed patchy areas of restricted diffusion (Figure 2A & 2B). They had low ADC values < 1.3 ×$10^{-3}$ $mm^2/s$ and all of these were considered to be of malignant etiology on MRI. Infiltrating ductal carcinoma was the most common malignant type on histopathology (Table 3).

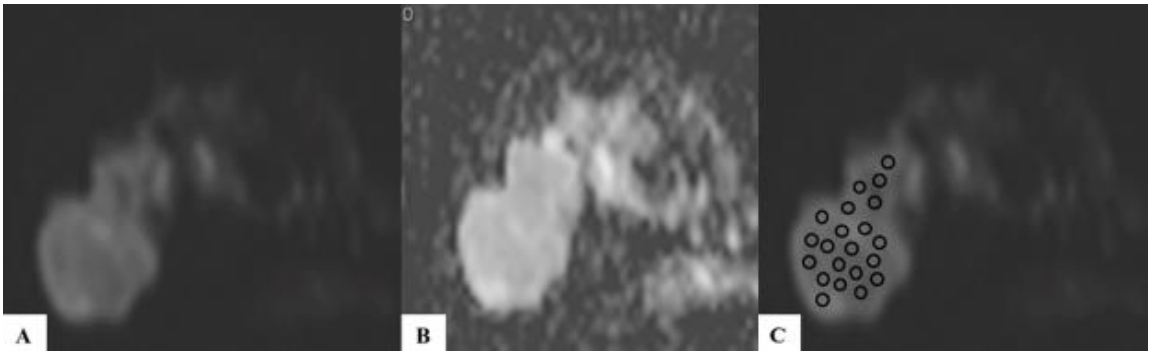


Figure 3. A) DWI sequence showing a well-circumscribed lesion which is hyperintense. B) ADC sequence is showing no restricted diffusion. C) Multiple ovoid ROI each of ~ 25 $mm^2$ were placed throughout the lesion and its mean ADC value was 1.1 × $10^{-3}$. The lesion was diagnosed to be benign Phyllodes tumor on histopathology. (*ADC – Apparent diffusion coefficient, DWI – Diffusion weighted image, ROI- Region of interest*).

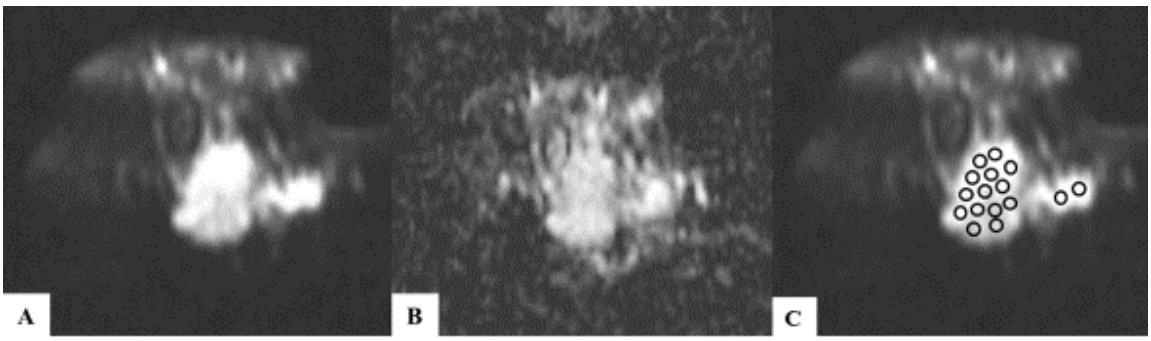


Figure 4. A) DWI sequence showing an irregular lesion which is hyperintense. B) ADC sequence is showing no restricted diffusion. C) Multiple ovoid ROI each of ~ 25 $mm^2$ were placed throughout the lesion and its mean ADC value was $1.8 \times 10^{-3}$. The lesion was diagnosed to be mucinous carcinoma on histopathology. (*ADC – Apparent diffusion coefficient, DWI – Diffusion weighted image, ROI- Region of interest*).

Table 3. Histopathological diagnosis of breast lesions

| | Histopathological diagnosis | Number of lesions |
|---|---|---|
| Malignant | Infiltrative ductal carcinoma | 20 |
| | Ductal carcinoma insitu | 7 |
| | Squamous cell carcinoma | 2 |
| | Pure Mucinous carcinoma | 5 |
| | Intracystic papillary carcinoma | 1 |
| | Lobular carcinoma insitu | 1 |
| | Medullary carcinoma | 1 |
| | Secretory carcinoma | 1 |
| | Total | 38 |
| Benign | Fibroadenoma | 38 |
| | Benign Phyllodes tumor | 1 |
| | Simple cyst of breast | 4 |
| | Total | 43 |

Table 4. Restricted diffusion of the lesions On DWI

| Restricted diffusion in the lesion | Number of lesions |
|---|---|
| Absent | 48 |
| Present | 33 |

** DWI- Diffusion weighted image*

Table 5. Mean ADC values of the breast lesions

| Mean ADC value of the lesion | Number of lesions |
|---|---|
| $>1.3 \times 10^{-3} mm^2/s$ | 47 |
| $<1.3 \times 10^{-3} mm^2/s$ | 34 |

** ADC- Apparent diffusion coefficient*

Table 6. Benign and malignant lesions on DWI & ADC in comparison with histopathology

| Neoplasticity | DWI with ADC values | Histopathology |
|---|---|---|
| Benign | 47 (38 fibroadenomas +4 simple breast cysts+ 5 mucinous carcinoma lesions) | 43 |
| Malignant | 34 (33 malignant lesions + 1 benign Phyllodes tumor) | 38 |

** DWI- Diffusion weighted image, ADC- Apparent diffusion coefficient*

Table 7. Observed DWI and ADC value results

| DWI | | | ADC Values | | |
|---|---|---|---|---|---|
| | Malignant | Benign | | Malignant | Benign |
| Restricted diffusion present | 33 (TP) | 0 (FP) | < 1.3 $\times10^{-3}$ $mm^2/s$ | 33 (TP) | 1 (FP) |
| No restricted diffusion | 5 (FN) | 43 (TN) | > 1.3 $\times10^{-3}$ $mm^2/s$ | 5 (FN) | 42 (TN) |

** DWI- Diffusion weighted image, ADC- Apparent diffusion coefficient, TP- True positive, FP- False positive, FN- False negative, TN- True negative*

In this study we observed that sensitivity of DWI along with its ADC value together to be 86.8%. With DWI alone, specificity is 100% and positive predictive value is 100%. Considering both DWI and ADC values together, specificity is 97.6% with a positive predictive value of 97% (Table 7).

## Discussion

The incidence of breast cancer has been on the rise which can be attributed risks associated with a Western way of lifestyle, which includes caloric surplus diet with excess of fat and lack of physical activity. Women with family history of carcinoma breast among first degree relatives are more prone to breast cancer. Because of increase in the incidence breast cancer, it has become a major concern for both health practitioners and researchers world wide[1,5].

The rate of breast cancer among women increases as the age advances. Few of the risk factors for malignancy is mainly because of unopposed estrogen load like early menarche, nulliparity, infertility, lack of breastfeeding, late menopause, etc. Few other causes are due to genetic mutations (*BRCA1* or *BRCA2* mutation), Li Fraumeni syndrome, Peutz Jegher syndrome, Cowden syndrome, ataxia telangiectasia, MEN 1 10, etc [18].

Marginal characteristics of benign breast lesions (lobular or smooth) usually are in contrast to that of malignant lesions (irregular or spiculated) [4,8]. The resolution of MRM images may not always be adequate in distinguishing these marginal characteristics. Due to similar enhancement patterns in both benign and malignant lesions (as a result of increased vascularity), there can be difficulty in differentiating the two, further leading to improper classification. Combining morphological characteristics on different sequences and pharmacokinetic methods on contrast studies has led to an increasing specificity, but with compromises pertaining to temporal and spatial resolution. DWI and its corresponding ADC sequences have further added a greater value in increasing specificity in diagnosing benign and malignant breast lesions [8,9,13]. It can also be used as screening sequence; or as an addition confirmatory modality to X-ray mammography or sonomammography by increasing the accuracy for diagnosing breast cancer. It can also be used in evaluating efficacy of neoadjuvant therapy in breast cancer treatment [12].

In our present study it is found that DWI and its ADC values are useful in differentiating benign from those of malignant breast lesions. All benign lesions showed no restricted diffusion (Figure 1A & 1B), that is they had no loss of signal on ADC sequence. All malignant lesions showed restricted diffusion (Figure 2A & 2B), where they appeared hyperintense on DWI sequence with restriction of signal or hypointensity on corresponding ADC sequence except for mucinous carcinoma which showed features that of benign lesions (Figure 4A-C). That is, all the mucinous carcinomas appeared to be benign by showing no restricted diffusion. Hence of all the malignant lesions, mucinous carcinomas showed false negative results as benign. These lesions decreased the specificity of DWI sequence when assessed independently from other sequences. According to the diagnostic criteria, DWI and its corresponding ADC is effective in distinguishing fibroadenomas and invasive carcinomas.

DW-MRI of the breast is feasible both before and after contrast media (CM) administration using spectral fat saturation. There is little decrease in the ADC values of the breast lesions following contrast administration and the decrease is more in malignant lesions than as compared to benign lesions.

In our study while assessing ADC values we observed that mucinous carcinomas behaved differently from rest other lesions of malignant etiology. Both pure and mixed type mucinous carcinomas showed a high ADC value (> 1.3 $\times10^{-3}$ $mm^2/s$), especially pure type which noticeably on MRI were not different from other benign lesions. On the other side, of all benign lesions, benign Phyllodes tumors showed altered ADC values with a low ADC value of 1.1 $\times10^{-3}$ $mm^2/s$ which is less than the cut-off value for benign lesions, leading to an overlap of ADC value with that of other malignant lesions.

## Conclusion

DW-MRI and its ADC values play a vital role in diagnosing and differentiating benign and malignant breast masses. It is a safe and easy method. In this study, we assessed restricted diffusion of breast lesions on DWI and explained a unique method of calculating ADC values. Malignant breast lesions showed restricted diffusion and benign lesions showed no restricted diffusion. An ADC value of 1.3 $\times10^{-3}$ $mm^2/s$ was considered as cut-off for differentiating the lesions, where the ones with value < 1.3 $\times10^{-3}$ $mm^2/s$ were considered as malignant. This method having high sensitivity and specificity can be used as a non-invasive imaging diagnostic modality and screening technique in assessing breast lesions. It also gives added information

to rest of the findings on dynamic contrast MRM and hence can be implemented as supplemental sequences to multiparametric MRM protocol.

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