DIAGNOSTIC ACCURACY OF DIFFUSION WEIGHTED MAGNETIC RESONANCE IMAGING IN MALIGNANT BREAST LESIONS, KEEPING HISTOPATHOLOGY AS GOLD STANDARD

Tehmina Sadiq, Hidayat Ullah, Mashkoor Ahmed*

Armed Forces Institute of Radiology & Imaging (AFIRI)/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Combined Military Hospital Peshawar/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To determine the diagnostic accuracy of Diffusion Weighted Magnetic Resonance Imaging/Apparent and Diffusion Coefficient (DWI/ADC sequences) in malignant breast lesions taking histopathology as gold standard.

Study Design: Cross-sectional validation study.

Place and Duration of Study: Combined Military Hospitals Quetta & Peshawar, from Sep 2013 to Mar 2015 and Armed Forces Institute of Radiology and Imaging Rawalpindi, from Apr 2015 to Dec 2015.

Material and Methods: After informed consent, patients scheduled for biopsy of a suspicious breast lesion on sonomammography and/or mammography (BIRADS IV & V), fulfilling the inclusion criteria were evaluated with breast MRI including Diffusion Weighted Imaging (DWI) sequence using *b*-values of 0 & 750 mm^2/sec. Apparent Diffusion Coefficient (ADC) values for the breast lesions were also calculated. MRI findings were correlated with histopathological results.

Results: A total of 299 cases were included in the study. Mean age of the study population was 45.73 years (SD ± 15.02) with a range of 18 to 89 years. On histopathology 77.9% (n=233) lesions turned to be malignant and 22.1% (n=66) were benign. On DWI 73% (n=219) lesions showed restricted diffusion and were labeled malignant while 27% (n=80) lesions showed facilitated diffusion and were considered benign. The mean apparent diffusion coefficient value of the malignant breast lesions was significantly lower than that of the benign breast lesions (p-value<0.001). The calculated sensitivity, specificity, positive predictive value and negative predictive values of DWI/ADC mapping in differentiating between malignant and benign lesions were 92.2%, 93.9%, 98.1% and 77.5% respectively. The diagnostic accuracy was found to be 92.6%.

Conclusion: DWI is a non-invasive diagnostic modality for diagnosing malignant breast lesions. It can be used to reduce the number of unnecessary biopsies and it may help in reaching a definite diagnosis in cases where a suspicious breast lesion cannot be biopsied because of its small size or unsuitable location.

Keywords: ADC, Breast, Cancer, DWI, MRI.

INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy among US women and is second only to lung cancer as a cause of death because of cancer[1]. In Pakistan it accounts for 41% of cancers in females[2]. This emphasizes the need for earlier detection of breast cancer through improved and more sensitive screening procedures. The most common benign tumour is the fibroadenoma. Malignant tumours have been broadly divided into noninvasive and invasive carcinomas. Invasive carcinomas are more common of which infiltrating ductal carcinoma occurs most frequently, accounting for 70% to 80% of invasive lesions. Mammography, sonomammography, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine all have a potential role in the identification and diagnosis of malignant lesions of breast. Over the past two decades, MRI has become a useful imaging modality for the detection and diagnosis of breast cancer. It has the advantage of being a non invasive imaging modality which gives precise anatomical detail

Correspondence: Dr Hidayat Ullah, Classified Radiologist AFIRI Rawalpindi Pakistan *(Email: hidayat781@gmail.com)*
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better than any other imaging modality. However, MRI has limited specificity with an overlap in the appearance of benign and malignant lesions. In the last decade, new MRI techniques and interpretation strategies have been developed to increase the specificity of breast MRI[3]. Diffusion-weighted imaging (DWI) is one such technique which measures the random motion of free water protons to characterize tissues by a mechanism different than table-I and table-II relaxation. For the quantification of this motion, apparent diffusion coefficient (ADC) values are used. Kul et al, Partridge et al and Palle et al have shown that ADC values of malignant breast lesions usually have lower restricted water diffusion and increased cellularity than those of benign lesions with normal cellularity and no restriction of water movement[4-6]. However no such study has been published in Pakistan so far and the local data is lacking. Our study, thus aims to show the difference in DWI/ADC values between benign and malignant lesions of breast in local setting which will add to the national database about diagnostic features of malignant breast lesions.

MATERIAL AND METHODS

This cross sectional validation study was conducted in Radiology departments of Combind Military Hospitals Quetta and Peshawar from Sep 2013 to Mar 2015 and Armed Forces Institute of Radiology and Imaging (AFIRI) Rawalpindi, from Apr 2015 to Dec 2015. A minimum sample size of 292 cases was calculated by using WHO calculator with 95% confidence interval, using expected frequency of 41% for breast carcinoma, expected sensitivity of 92.3% and specificity of 96.2% for DWI in the diagnosis of malignant breast lesions[2,7].

Table-I: Histological subtypes of malignant and benign breast tumor (n=299).

Histological Classification		Number of Patients	
Type	**Subtype**	**Frequency**	**Percentage**
Malignant		233	77.9%
	Invasive ductal carcinoma	193	82.8%
	Ductal carcinoma in situ	21	9%
	Invasive lobular carcinoma	19	8.2%
Benign		66	22.1%
	Fibroadenoma	50	75.8%
	Fibrocystic change	16	24.2%

Table- II: Mean ADC values in Malignant and Benign Breast Tumor (n=299).

Histopathology	ADC value (Mean ± SD) x 10−3mm²/s	95% Confidence Interval (CI)		t-value	*p*-value
		Lower bound	Upper bound		
Malignant (n=233)	0.869 ± 0.263	0.84	0.9	-21.625	<0.001
Benign (n=66)	1.687 ± 0.284	1.62	1.76		

The *t*-value is 21.6247. The *p*-value is <0.001. The result is significant at *p*<0.05.

A total of 299 cases were included in the study by non-probability, purposive sampling after the study was approved by institute's ethical committee for research. All procedures adopted were kept in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Women patients of all ages scheduled for biopsy of a suspicious breast lesion on sonomammography and conventional mammography (BIRADS IV & V) were included in the study. Features on sonomammography requiring biopsy were taller than broader, spiculated margins, posterior acoustic shadowing and microcalcifications. On mammography findings of the suspicious lesions included increased density, spiculated margins, microcalcifications, surrounding architectural distortion and overlying skin thickening and retraction. Those patients having previous or current chemotherapy, radiation therapy; having a history of Fine Needle Aspiration Cytology (FNAC)/biopsy of breast in the last 3 months; having any MRI incompatible metallic devices in their body and those having claustrophobia were excluded from study. After getting informed consent, MRI breast was performed at 1.5 Tesla MRI machine using a standard breast coil with the help of a female doctor for positioning of the patient. The protocol used for breast MRI included (a: Axial table-I, table-II Spine Echo sequences b: Axial Short Tau Inversion recover (STIR) sequence for fat suppression and c: Axial DWI echo planar sequence using a combination of *b*-values of 0 and 750 mm^2/sec). ADC values were automatically calculated by placing the region of interest (ROI) well in the confines of the lesion. A cut off ADC value of 1.26 x 10-3 mm^2/s was used for differentiation of benign and malignant lesions of breast. Two radiologists having at least 2 years experience in MRI interpreted the images and a consensus was reached. After MRI examination the patients were referred for biopsy and histopathology to confirm the exact nature of the lesion. In case of multiple lesions it was ensured that the lesion biopsied is that same evaluated on MRI.

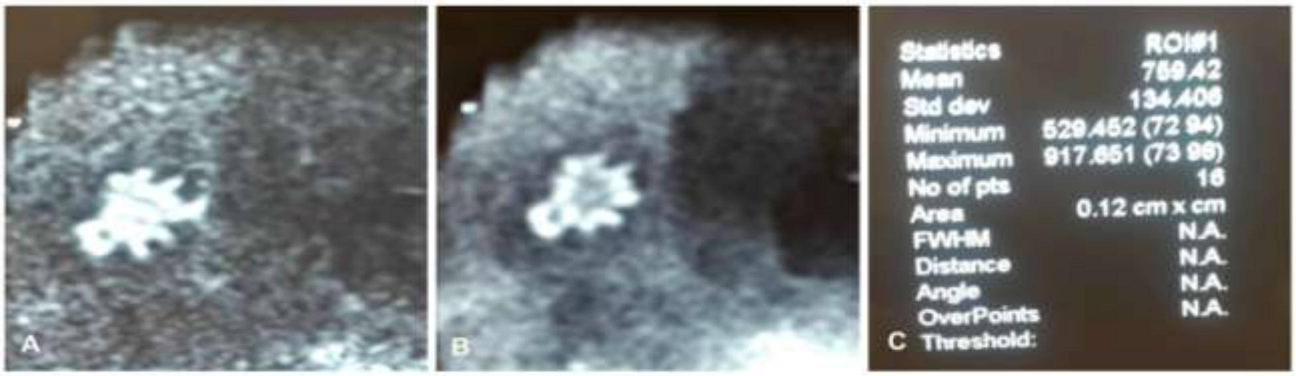

Figure-1: DWI / ADC mapping images with ADC values.
(A): Diffusion weighted (DWI) image showing a hyperintense lesion with spiculated margins in the right breast. (B): Apparent diffusion coefficient (ADC) mapping shows a hypointense centre of the lesion signifying restricted diffusion. The surrounding hyperintensity signifies oedema. (C): Low ADC value of 0.759 x ± 0.134 ×10−3mm²/s was suggestive of malignant breast lesion.

The collected data was analyzed through SPSS version 16. Breast lesions were divided into malignant and benign on the basis of cut off ADC value. Frequency and percentage of both types were calculated along with mean and standard deviation of ADC values for malignant and benign lesions. Student's t-test was applied to compare the means of ADC values for malignant and benign lesions. A 2 x 2 contingency table was generated to calculate the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of DWI/ADC mapping for differentiating malignant and

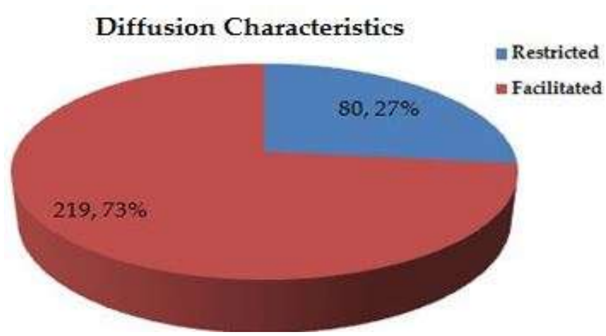

Figure-2: Diffusion characteristics of the breast tumor (n=299). Restricted diffusion signified increased cellularity favouring malignancy while facilitated diffusion indicated a benign aetiology of the lesion.

benign breast lesions by taking histopathology as gold standard.

RESULTS

A total of 299 cases were included in the study. Mean age of the study population was 45.73 years (SD ± 15.02) with a range of 18 to 89 years. On histopathology 77.9% (n=233) lesions turned to be malignant. Out of these malignant lesions 82.8% (n=193) were invasive ductal carcinoma, 9% (n=21) were ductal carcinoma in situ and 8.2% (n=19) were invasive lobular carcinoma. Benign lesions made 22.1% (n=66) of the total cases out of which 75.8% (n=50) were fibroadenomas and 24.2% (n=16) were fibrocystic changes (table-I).

On DWI 73% (n=219) lesions showed restricted diffusion (fig-1) while 27% (n=80) lesions showed facilitated diffusion (fig-2). Comparison of the histopathological results and DWI/ADC mapping is shown in fig-3.

The ADC value of 1.26 × 10^{-3} mm^2/s was used as a cut-off value for the differentiation of benign from malignant breast lesions. Student's *t*-test was used to compare the means of ADC values of malignant and that of benign lesions. The mean ADC value of the malignant breast lesions (0.869 ± 0.263 × $10^{-3}mm^2/s$) was significantly lower than the mean ADC of the benign breast lesions (1.687 ± 0.284 × $10^{-3}mm^2/s$) with a *p*-value of <0.001 (table-II). Facilitated diffusion suggested a benign aetiology while restricted diffusion was suggestive of malignancy. Keeping histopathology as gold standard, parameters of diagnostic accuracy were calculated (fig-4) with true positives 215, false positives 4, true negatives 62 and false negatives

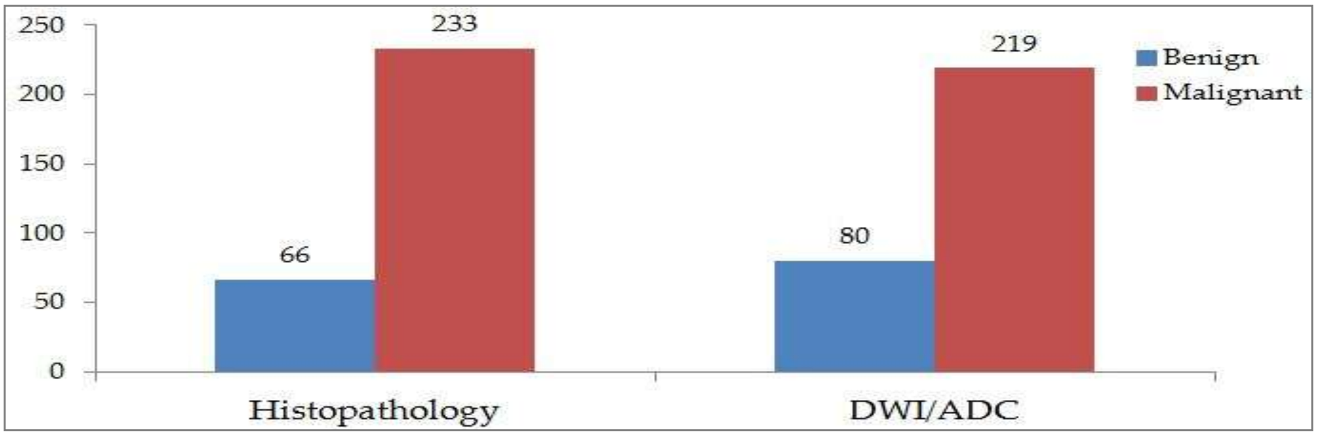

Figure-3: Frequency of malignant tumor on Histopathology vs DWI/ADC (n=299).

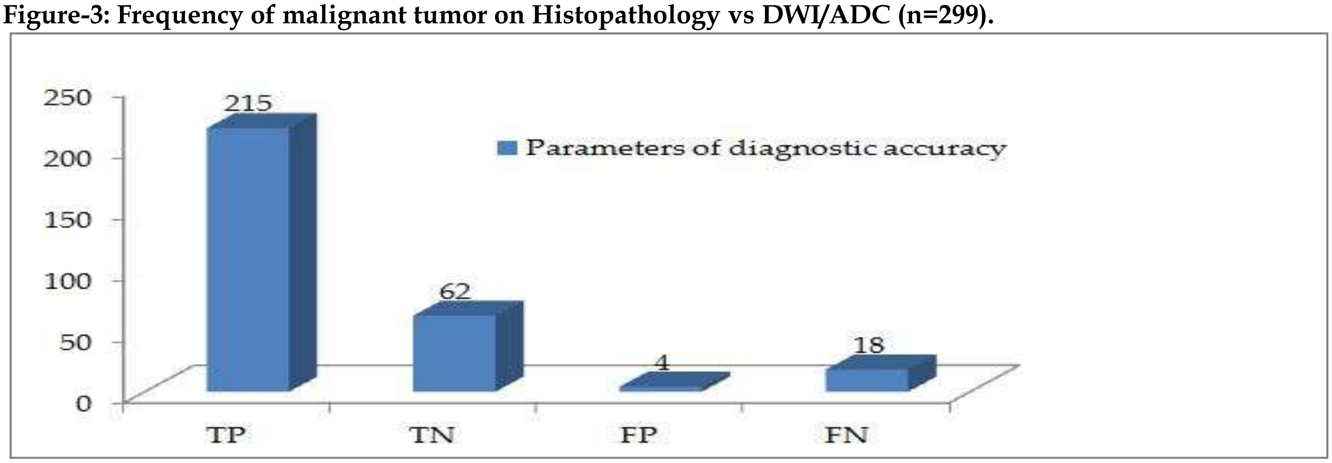

Figure-4: Parameters of diagnostic accuracy (n=299). The sensitivity of DWI/ADC for diagnosing malignant breast lesions is 92.2%. Specificity, Positive Predictive Value and Negative Predictive Value are 93.9%, 98.1% and 77.5%. The diagnostic accuracy of DWI/ADC mapping is 92.6%.

18. Calculated sensitivity, specificity, positive predictive value and negative predictive value of DWI/ADC mapping in differentiating between malignant and benign lesions were 92.2%, 93.9%, 98.1% and 77.5% respectively. The diagnostic accuracy was found to be 92.6%.

Receiver operating characteristic (ROC) curve (fig-5) shows the area under curve (AUC) to be 0.976 with standard error of 0.010 under the nonparametric assumption.

DISCUSSION

Breast cancer is the most frequent cancer of women worldwide. In Pakistan it accounts for 41% of female cancers[2]. Conventional mammography has been the primary screening and diagnostic tool for breast cancer for more than 20 years. However, mammography is not without imperfection, and other modalities have gained ground as an adjuvant to mammographic breast screening. Of these, USG and MRI have proved to have potential role in the identification, diagnosis, treatment and/or follow-up of breast cancer[1].

DWI studies of the breast carried out internationally by Kul et al, Partridge et al and Palle et al have shown significantly lower apparent diffusion coefficient (ADC) measures for breast carcinomas than for benign breast lesions or normal tissue[4-6]. The ADC value calculated by a combination of *b*-values of 0 and 750 sec/mm^2 has shown a slightly better sensitivity and specificity than other *b*-value combinations. High *b*-values (0 and 1000s/mm^2) can cause susceptibility artifacts and should be avoided[7].

Diffusion weighted images often have a low resolution, low Signal to Noise Ratio (SNR), low Contrast to Noise Ratio (CNR) along with various artifacts[8]. In our study anatomical delineation was improved using the fat-suppressed technique. Single shot navigated echo planar technique was used for DWI which reduced image acquisition time and artifacts. Good image quality for diffusion weighted images was obtained by using a *b*-value combination of 0 and 750s/mm^2.

Our study showed that DWI/ADC mapping has high diagnostic accuracy of 93.31% for differentiating between malignant and benign lesions. The ADC value of malignant lesions is significantly lower (*p*-value<001) than that of benign lesions leading to restricted diffusion appearing hyperintense on diffusion weighted MR images. These findings are in accordance with previous studies[4-6,8]. Thus breast MRI with DWI/ADC mapping is a good diagnostic tool for the evaluation of breast lesions and can differentiate between malignant and benign breast lesions.

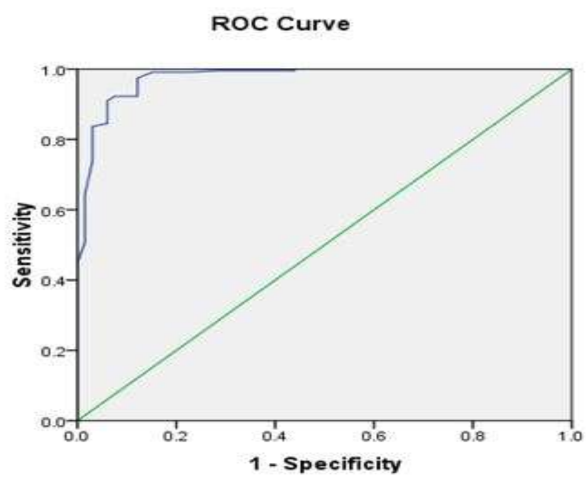

Figure-5: Receiver operating characteristic (ROC) Curve. Area under curve (AUC) is 0.976 with standard error of 0.010 under the nonparametric assumption. Asymptotic 95% Confidence Interval is 0.956 to 0.996.

Our study showed that DWI/ADC mapping MRI not only has a high sensitivity of 92.27% but also has high specificity (96.96%) with only 2 false positive cases reported. This makes DWI/ADC mapping MRI a reliable investigating tool available to clinicians in planning management of the case.

Limitations of the study include inability to completely remove motion and breathing related artifacts. Moreover ROIs to measure ADC are set by the radiologist or radiographer, which is subjective. Little is known about the reproducibility of measurements. In order to reduce the measurement biases and avoid contamination of the data by adjacent structures, we have used a fixed small size of ROI. Another limitation of the study is that the patients included were all having suspicious breast lesions on sonomammography/ mammography (BIRADS IV & V) resulting in unusually high parameters of diagnostic accuracy. Further studies with clinical inclusion criteria are required for more unbiased results.

CONCLUSION

DWI is a non-invasive diagnostic modality for diagnosing malignant breast lesions. It can be used to reduce the number of unnecessary biopsies and it may help in reaching a definite diagnosis in cases where a suspicious breast lesion cannot be biopsied because of its small size or unsuitable location.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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