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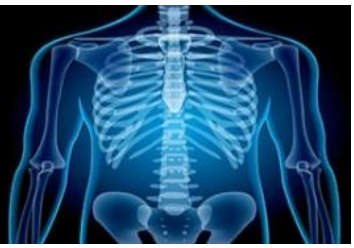

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The cut-off value of ADC to differentiate benign from malignant breast lesions

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Abstract
Background: Diffusion-weighted MRI is a fast, unenhanced modality that shows promise in identifying mammographically occult malignancy and warrants further investigation as an alternative supplemental breast cancer screening tool.
Aim of study: To estimate the diagnostic accuracy of diffusion wighted imaging and apparent diffusion coeffient (ADC) value in the differentiation between benign and malignant breast lesions, and to obtain a cutoff ADC value between benign and malignant breast lesions along with histopathological correlation.
Materials and Methods: A prospective study of 56 patients with present with breast mass who examined at 1.5 tesla MRI & proved by histopathology. ADC value were a quired at b values of 0, 600, 850 s/mm² after identification of ROI (Region of interest) placement. ADC value with histopathology correlation was analyzed.
Results: From total 56 lesions, 24 lesions were histologically malignant and 32 were histologically benign. With an ADC cut-off value of 1.31 × 10−3 mm2/s for malignant lesions, a sensitivity of 100% and specificity of 72.1% was obtained. The false-postive lesions were one intraductal papilloma & 3 abcesses in which a low ADC value was obtained. Purely DCIS (Ductal carcinoma *in situ*) lesions presenting as non-mass-like enhancement had a high ADC value of 1.2-1.3 × 10−3 mm2/s, thereby decreasing specificity.
Conclusion: Diffusion-weighted Imaging is a functionl quantitative assessment by ADC value, may act as an efficient tool in increasing the diagnostic accuracy and specificity of breast MRI in the characterization of different breast lesions.

Keywords: apparent diffusion coefficient; breast mass; diffusion-weighted imaging

Introduction

Breast MRI

Diffusion-weighted (DW) magnetic resonance imaging (MRI) is a rapid, unenhanced imaging technique that measures the motion of water molecules within tissues and provides information regarding the cell density and tissue microstructure [1].
DW MRI has demonstrated the potential to improve the specificity of breast MRI, facilitate the evaluation of tumor response to neoadjuvant chemotherapy and can be employed in unenhanced MRI screening. However, standardization of the acquisition and interpretation of DW MRI is challenging [2]. Diffusion-weighted (DW) imaging is a functional MRI technique that can produce contrast in tissues without using gadolinium contrast medium injections and the process of whole breast imaging can be completed within a few minutes [2].

Breast MRI interpretation

All lesions should be evaluated regarding its shape, margin, pre-contrast T1 and T2 weighted image (T1 and T2 WI) signal intensity, enhancement characters as well as any change from the previous study. In general bright signal on T1 and T2 WI is indicative of benign finding with the exception of colloid carcinoma show high signal intensity on T2 WI, while most invasive carcinomas demonstrate low to intermediate signal intensity on T2WI [3].
According to BI-RADS, the morphologic mass analysis is made with enhancement characteristics of the masses. In case of non-mass enhancement, the distribution and internal enhancement pattern will be evaluated.

Regarding the kinetic analysis the delayed-phase enhancement pattern is usually used to describe the curve shape [4-5].

Diffusion weighted imaging (DWI)

DWI is regarded as a method for characterizing tissue properties by giving information about the free movement of water molecules (Brownian) in various tissue of the body [6, 7], in example of cysts, blood vessels, bladder and tissues with big intercellular spaces, water move freely without any restriction and will show signal loss after the application of diffusion gradient [8]. On the other hand, in case of solid tumors with high cellularity there will be a significant drooping in the extracellular space, free water movement will be restricted, so the signal will be greater after the application of diffusion gradients [9, 10].

The parameter used to change the gradient amplitude and duration is b Value, measured by sec/mm [2, 10].

Analysis of DWI

The ADC is considered as the parameter to quantify the DWI. ADC can be calculated during post-processing by the use of minimum two different b values, the final image with various ADC values measured for each pixel of the image is known as an ADC map [11].

DWI in breast

The high signal intensity seen on DW images represent the restricted diffusion of water molecules in case of malignant tissue with plenty of cellularity.

But some of the benign breast tumors (e.g, intra-ductal papilloma) may also show abundance of cellularity and demonstrate a low ADC value. In contrast, malignant tumors exhibit scanty cellularity (e.g duct carcinoma *in situ*) might show low signal intensity on DWI [12, 13].

Most of the studies have shown an obvious distinction in ADC value among the malignant and benign lesions. Every one determines the cutting-off point for the ADC value to obtain a high accuracy for the diagnosis of different breast lesions [14].

When measuring the ADC number, the suspected lesion should be shown on the ADC map and diffusion-weighted images and the region of interest must be placed carefully over the solid part of the tumor and to assure the cystic or necrotic parts as well as the normal breast parenchyma are not included in this region [6]

Abscess and Hemorrhage may demonstrate low value of ADC, comparable to malignant diseases. So it should be conducted with other MRI sequences such as T2 and T1 weighted image to avoid misdiagnosis [21].

Nonmass lesions such as DCIS and fibrocystic changes can show in between normal fibro-glandular tissue or fatty tissue, which might impact the measurement of ADC. Therefore, non-mass forming DCIS can be overlooking on DWI [14].

Intraductal papilloma may be mis interrupted as a suspicious lesion. So amass with low ADC but shows bright at T2 sequence along the direction of the breast duct and close to the nipple [15].

Cyst, fibroadenoma, and fibrocystic disease depict high signal intensity on T2-weighted MR images; so the signal intensity of benign tumors are changeable on diffusion-weighted images and may be affected by b value much frequently than the SI of malignant tumors because of T2 shine through effects [16]. Those benign lesions perhaps show high signal intensity on DWI acquired at lower b values; on DW images acqired at higher b values, these tumors become isointense and could not be specified [17, 18].

Breast Cancer: In general has high internal cellularity. At DW MRI, breast cancers typically exhibit reduced diffusivity and appear hyperintense to surrounding tissues in DWI and low signal intensity at ADC map [20].

The Aim of Study

1. To estimate the diagnostic accuracy of DW-MRI and ADC value in the differentiation between benign and malignant breast lesions.
2. To obtain a cutoff ADC value between benign and malignant breast lesions.

Patients and method

Study sample

A cross sectional analytic study was performed at the al-Yarmouk teaching hospital in Baghdad /Iraq within the period from July 2018 to July 2019. A total of 56 female patients with 56 lesions evaluated by physician, ± US and/or mammography.

Inclusion criteria

Patients with breast lesions referred by the physician after doing conventional imaging (Ultrasound and/or mammography) according to the criteria in the breast clinic of the Yarmouk teaching hospital

Exclusion criteria

1. Patients with contraindication to MRI examination or its contrast media.
2. Patient refused MRI examination.
3. Patient refused biopsy or surgery.

Data collection

Relevant clinical history (age, presenting complain, menstrual history, previous breast surgery and family history of breast cancer, then organize an appointment at MRI unit, according to the menstrual cycle. The diffusion wighted images and ADC map was compare with the histopathological results. 22 core biopsy (inscional biopsy) and other 34 lesions were excisional biopsy done to them.

MRI protocol

All patients had written consent before MRI examination.

The patients are suƄjected to MRI examination in prone position on 1.5 tesla MR system (with acheiva Philips medical system, Netherlands) Ƅilateral eight-channel Ƅreast coils.

Diffusion weighted image: was done at spin-echo sequence using Ƅreast surface coil at the following b values(0, 600,850 sec/mm2), slice thickness= 3mm, field of view=175x346 mm, intersection gap= 1mm, matrix size= 80x158, echo time= 83ms, repetition time= 12577.7 ms, total acquisition time=5min.ADC map was derived automatically in the MR system.

The measurement of ADC was obtained from the ADC maps.

T2&T1-weighted images and subtracted dynamic MR images are considered as a reference for localizing the lesion. The ROIs were drawn manually within the soft tissue

component of the lesion & avoiding the necrotic and hemorrhagic areas. To make the possibility of error less, a minimum two to three measurements were done for all lesions and the mean ADC values at two different b-value of these regions were calculated.

P – Value less than 0.05 was considered a statistically significant

Results

Fifty –six patients who recruited in the study. All of them had breast lesions and investigated by MRI. The age was ranging from 25 to 75 years with a mean of 54.1 years and standard deviation (SD) of ± 12.69 years.

The distribution of study patients according to histopathological results, of all 56 breast lesion, 29 patients (51.8%) were complaining from benign lesion, while the remaining 27 patients (48.2%) complained from malignant lesion.

The histopathological results of malignant lesions were 88.9% invasive ductal carcinoma, one lesion (3.7%) was each of ductal carcinoma *in situ*, atypical ductal hyperplasia, and malignant phylloid tumor. Regarding the 29 benign lesions, 41.4% of lesions were fibroadenoma, 10.4% were abscess, 24.3% were fibrocystic changes, 6.9% were fat necrosis, while one lesion (3.4%) was each of intra ductal papilloma, hematoma, lipoma, duct ectasia, and galactocele.

In this study, there was a distict variation in (P= 0.019) in means of ADC values regarding the types of benign lesions. Also there was difference in means of ADC values between the types of malignant lesions, but this difference was not statistically significant (P= 0.249). the difference in means of ADC value according to histological results of breast lesions is shown in table 1.

DWI Findings: Regarding DWI findings, most of the benign cases (82.8%) showed no restriction, while all of the patients with malignant lesions showed restriction with DWI imaging.

Comparison in ADC Value Between Benign and Malignant Lesions: The comparison in the means of ADC value between both types of breast lesions. We found that ADC value in benign cases was higher than in malignant cases (0.815 versus 1.287x(10^{-3}) with a statistically significant difference (P= 0.001) comparison in the means of ADC value by DWI findings. we found that, ADC value of the patients with non-restricted lesions was higher than that in patients who showed restriction DWI findings (784 versus 1427) with a statistically significant difference (P= 0.001).

The sensitivity (SN), specificity (SP), Positive predictive value (PPV), negative predictive value (NPV), and accuracy of DWI findings.

The DWI study was of 100% SN, 82.8% SP, 84.4% PPV, 100% NPV, and 85.3% accuracy.

Receiver operating characteristic (ROC) curve analysis was constructed for ADC value to differentiate benign from malignant lesions, the cut point of ADC value was $1.31x10^{-3}$ mm^2/s, so lesions considered malignant when ADC values are below $1.31x10^{-3}$ mm^2/s, as a large significant area under the curve (AUC= 82.6%) indicating significant association between lower value of ADC and higher risk of malignancy. ADC value was 100% sensitive, 72.1% specific, and 85.7% accurate as a marker for diagnosis of malignant lesions.

Discussion

Diffusion weighted image is a functional non-invasive MRI sequence. It represent the Brownian movement of water molecules in the body tissues and it is able to obtain the physiological feature of the different body tissues by the quantitative analysis of water molecules (ADC) [17].

Malignant tumors tend to demonstrate lower ADC value than the benign tumors, this is due to the malignant tumors show restriction at diffusion wighted image & this is related to increased in cellular density, larger nuclei and less extracellular space in the malignant tumors [18].

In previous studies demonstrated that the mean ADC value for malignant tumor are lower than those of benign tumor with a variable results of sensitivity and specificity and the DW imaging had hopeful role in the differentiation between benign and malignant breast lesions [13, 14].

Our study show the mean value of ADC in malignant lesions was (0.815 ± 0.258 x 10^{-3} mm^2/sec), while in benign lesion the value was (1.287 ± 0.404 $x10^{-3}$ mm^2/sec) demonstrating significant distinct (P value 0.001). In this study the breast lesions differentiated with high sensitivity (100%) and high specificity (82.8%) as benign or malignant with the aid of ADC readings and a cutoff value of ($1.31x10^{-3}mm^2$/sec).

Our result were relatively in agreement with Ibrahim *et al*. [21] who found that the median value of ADC for malignant lesions was 0.93×10^{-3} mm^2/s and the median value of ADC for benign lesions was 1.51×10^{-3} mm^2/s.

In this study there were 3 abscess lesions, two of them displayed restricted diffusion, the mean of ADC value was 0.85×10^{-3} mm^2/s & one case of intraductal papilloma with low ADC value, benign papillary lesions frequently showed restriction at diffusion images which may confuse in the diagnosis of the papillary lesions both at DCE-MRI and DWI, also we note there is some lesion with partial restriction such as fat necrosis which also showed low ADC value (due to high viscosity), lead to false-positive DWI results.

The sensitivity and specificity reported in our study in comparison with other studies are relatively similar ADC thresholds in the table [2].

These differences can be attributed to the variation in the examination protocols of MRI machines. ADC measurement and different field strength in addition to the size of the study sample.

The invasive ductal carcinoma (IDC) characterized by densely packed cells with minimum fibrous stroma, while the ductal carcinoma *in situ* demonstrate lower cellular density as well as profuse fibrous stroma and the neoplastic cells does not infiltrate beyond the basement membrane [20, 25]. Previous studies demonstrated that the mean ADC value for DCIS are higher than that of IDC [20], in our study the mean value of ADC in DCIS was 1.002 ± 0 $x10^{-3}$ mm^2/s while the mean value of ADC for IDC was $0.790\pm0.254x10^3$ mm^2/s with a nonsignificant difference (P value =0.017) which is inconsistent with these studies.

We found that the mean ADC value for malignant mass enhancing lesions ($0.815\pm0.25x10^{-3}$ mm^2/s) was lower than the mean ADC value of NME malignant lesions ($1.15\pm0.13x10^{-3}$ mm^2/s) but also no significant difference from benign NME P-value 0.024) but no significant difference had been demonstrated (p value 0.052) and the mean ADC for benign lesion with mass enhancement was ($1.28\pm0.404x10^{-3}$ mm^2/s).

this agree with Kul S. *et al* [23]. Stated that the diagnostic accuracy of DWI is lower for NME than mass lesion but the difference was not significant (1.287 ±0.404 x 10^{-3} mm^2/sec), This agree with Imamura *et al*. [18] demonstrated there was no statistically difference between the mean ADC value of benign and malignant in NME lesions, these differences can be attributed to the fact that the NME lesions tend to replace rather than displace the normal breast parenchyma and can be interspersed with fat or normal glandular tissue. Therefore, ADC measurements at these masses may demonstrate higher partial volume averaging with normal tissue than those with mass forming lesions.**(19)**

Our results demonstrated that the mean ADC value of the breast lesions correlate inversely with tumor cellularity even in the evaluation of the false positive results as one of the 4 false positive lesions was benign highly fibrous fibroadenomas tumor with stromal hypercellularity that resulted in low ADC value (0.543x10^{-3} mm^2/sec) and the other lesion was intra-ductal papilloma demonstrated low ADC value (0.406x10^{-3} mm^2/sec) also abscess that may be attributed to high thick contain.

These results agree with Woodhams. R *et al.* [12] they showed that the value of ADC correlate inversely with tumor cellularity and disagree with Yoshikawa I. *et al*. [13] who stated that there was no significant correlation in between.

These informations provided by the Diffusion weighted imaging depend on the intrinsic properties of the tissue affected by the microscopic mobility of water molecules (Brownian motion), therefore the tissue properties demonstrated by the diffusion weighted imaging are distinct from those of dynamic contrast enhanced MRI in which the enhancement kinetics relies on the difference in various tissue vascularity [19].

Conclusions

The diffusion weighted imaging and ADC value had high sensitivity and specificity in the characterization of breast lesions with a cut –off value of (1.31x10^{-3} mm^2/s).

Recommendations

Incorporating DWI as standard sequence to the breast MRI examination protocol.

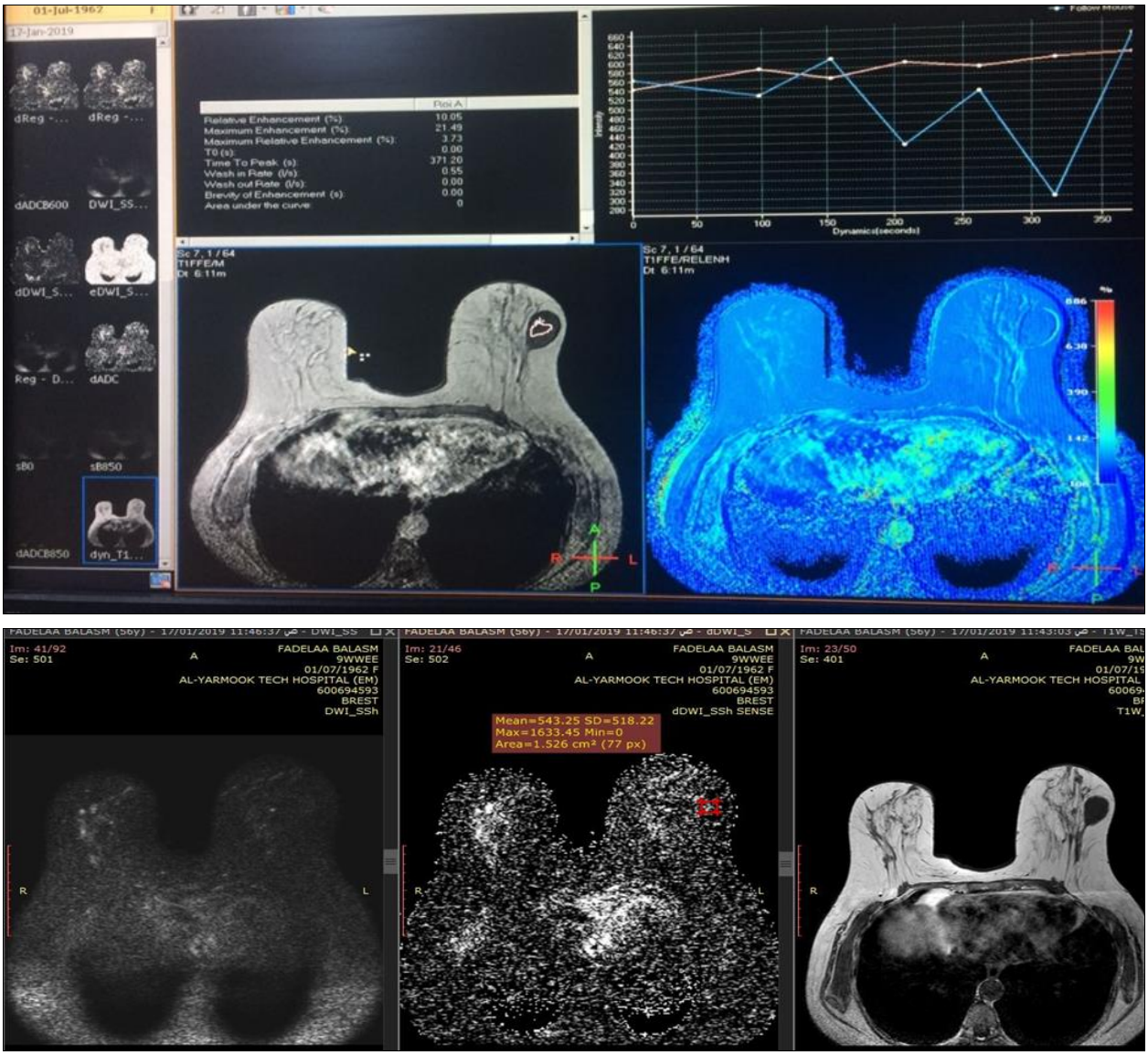

Fig 1: 56 years old female patient presented with palpable lump in the Rt. breast, lobulated margin, a- T1,T1 post contrast, DWI and ADC map. MRI shows well circumscribed non-enhancing oval mass, the mass shows low signa intensity on T2 &T1WI and not restricted on DWI and ADC value is 0.543x$10^{-3}$$mm^2$/s. B- dynamic subtraction contrast enhanced Image not enhanced &time intensity curve with type I curve, histopathology showed highly fibrous fibroadenoma.

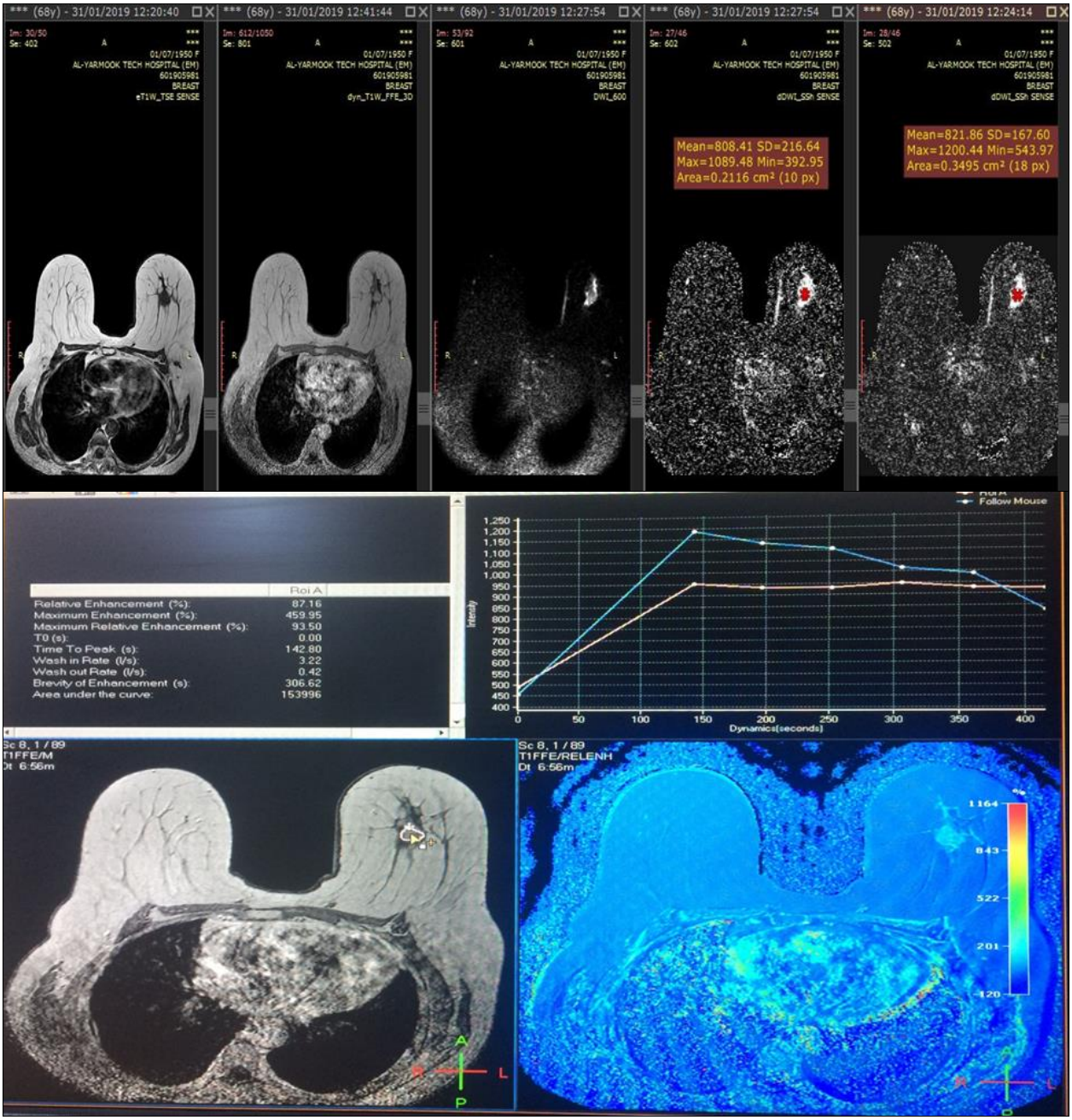

Fig 2: 68 years old female presented as palpable left sided breast mass DWI and ADC map show restricted on DWI, ADC value= $0.808x10^{-3}$ mm^2 /sec on b value 600 & 0.821×10^{-3} on b value 850, hypointense in T1 and in post contrast study reveals homogenous enhancing mass with irregular speculated outline and shape, with washout curve at delay phase, histopathology reveal invasive breast cancer grade 2.

Table 1: Distribution of study patients by histopathological results and ADC values

H Histopathological Results		N No. (n=56) P Percentage	ADC value 10^{-3} 2/ mm^2/sec
T Type of Lesion n= 27			
Malignant lesion	I Invasive Ductal Carcinoma	2 4(88.9)	0 0.795±0.254
	Ductal Carcinoma *In situ*	1 (3.7)	1 1.002 ± 0
	Malignant Phylloid	1 (3.7)	0 0.890±0
	A Atypical Ductal Hyperplasia	1 (3.7)	1 1.234±0
n= 29			
B Benign lesion	F Fibroadenoma	1 2(41.4)	1 1.384±0.325
	F Fibrocystic Changes	7 (24.3)	1 1.475±0.52
	Abscess	3 (10.4)	0 0 .720±0.512
	F Fat Necrosis	2 (6.9)	0 0.949±0.572
	I Intra Ductal Papilloma	1 (3.4)	0 0.406±0
	Hematoma	1 (3.4)	1 1.543±0
	Duct ectasia	1 (3.4)	1 1.543±0
	L Lipoma	1 (3.4)	1 1.566±0
	Galactocele	1 (3.4)	1 1.289±0

Table 2: ADC values, sensitivity and specificity of breast DW-MRI in compare current study with other studies

B Breast DW-MRI S Studies	A ADC threshold (x 10 $^{-3}$ mm^2 / s)	S Sensitivity (%)	S Specificity (%)
T Tan *et al*. [22]	1.21	87	91
S Sharma *et al*. [23]	1.23	92	91.1
Min *et al*. [24]	1.23	82	90
Al-Saadi *et al*. [25]	1.175	95.2	93.8
Yabuuchi. *et al*. [26]	1.3	87	86
Our study 1.31 100 82.8			

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