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Malignant Breast Tumors: Role of MRI in Predicting Histopathological Grading

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ABSTRACT

Introduction: Magnetic Resonance Imaging (MRI) is an established supplemental technique to mammography and ultrasonography for evaluation of breast lesions**.** Diffusion-weighted MR imaging (DWI) has recently been integrated into the standard breast MRI in addition to images obtained from dynamic contrast enhanced MRI. DWI is quantified using the Apparent Diffusion Coefficient (ADC) value which is the measurement of the mean diffusivity of water in tissues along three orthogonal directions.

Aim of the Work: The aim of this study was to investigate the relationship between DWI findings (represented by ADC values) and the dynamic contrast enhanced MRI findings (including functional parameters and morphological criteria) with the histopathological grade of malignant breast tumors.

Methodology: 25 Patients (age >30 years) were enrolled in this study. All patients were referred either from the screening clinic or the outpatient clinic of Eldemerdash Hospital with clinically suspicious findings and the abnormality was detected by mammography and/or ultrasound. Included masses are those with BI-RADS 5 category on imaging, with no previous biopsy or treatment. There was no knowledge about the histopathological diagnosis at the time of initial evaluation. Exclusion criteria were breast masses with diagnosed or proved benign features. All patients were scheduled for dynamic MRI with diffusion weighted imaging in addition to the conventional MR imaging.

Results: Histopathological analysis revealed all 25 lesions to be invasive ductal carcinomas not otherwise specified. Grading of included carcinomas was as follows: 3 lesions (12.0%) were grade I, 14 lesions (56.0%) were grade II and 8 lesions (32.0%) were grade III.

Conclusion: That makes DWI the best non-invasive tool available to predict grades of breast carcinoma. However, further larger and more detailed studies are still needed to fully understand the role MR imaging in distinguishing different histological grades of breast cancer.

Keywords: Malignant Breast Tumors, MRI, DWI, ADC, Histopathological

INTRODUCTION

Magnetic Resonance Imaging (MRI) is an established supplemental technique to mammography and ultrasonography for evaluation of breast lesions [(1)]**.**

Dynamic contrast enhanced breast MR imaging is currently accepted as the most sensitive imaging technique for diagnosis of breast cancer. It provides important information not only on the morphology of the lesion but also on the functional aspect reflected by the pattern of uptake of the contrast medium. Integration of both kinetic and morphological features is important for accurate diagnosis [(1)]. However, it provides no direct information about tumor cellularity, which is known to be an important index of tumor grade. Consequently, there has been an increasing interest in the development and the use of diffusion-weighted breast imaging for its potential to improve the diagnosis of breast lesions at the cost of a small increase in the examination time [(2)].

Diffusion-weighted MR imaging (DWI) has recently been integrated into the standard breast MRI in addition to images obtained from dynamic contrast enhanced MRI. It is a non-invasive technique that has a high sensitivity for detection of changes in the local biological environment, without the need for intravenous contrast material injection [(2)].

DWI is quantified using the Apparent Diffusion Coefficient (ADC) value which is the measurement of the mean diffusivity of water in tissues along three orthogonal directions. ADC value can be affected by cellularity of the tissue, fluid viscosity, and membrane permeability. Several potential applications for DWI and ADC value have been suggested and studied; including detection, characterization, and differentiation of breast lesions [(3)].

Aim of the Work:

The aim of this study was to investigate the relationship between DWI findings (represented by ADC values) and the dynamic contrast enhanced MRI findings (including functional parameters and morphological criteria) with the histopathological grade of malignant breast tumors.

PATIENTS AND METHODS

25 patients (age >30 years) were enrolled in this study. All patients were referred either from the screening clinic or the outpatient clinic of

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Eldemerdash Hospital with clinically suspicious findings and the abnormality was detected by mammography and/or ultrasound.

Included masses are those with BI-RADS 5 category on imaging, with no previous biopsy or treatment. There was no knowledge about the histopathological diagnosis at the time of initial evaluation. Exclusion criteria were breast masses with diagnosed or proved benign features.

All patients were scheduled for dynamic MRI with diffusion weighted imaging in addition to the conventional MR imaging.

Histopathologic Diagnosis:

The final tumor diagnosis and grading were established by means of surgery or core needle biopsy. Hematoxylin and Eosin stained sections from all tumors were reviewed by two independent pathologists. Grading was done according to Nottingham grading system into three grades [(4)].

MRI examination:

Conventional MRI, diffusion MR imaging and post Gd- DTPA dynamic MRI were performed. First, detection and characterization of breast lesions was performed, and then the diffusion images with ADC values were reviewed. MR imaging was performed on high field system (1.5 Tesla) magnet units (Philips Acheiva XR) using a 7 channel breast coil with the patient in the prone position.

MR Protocol Used:

a) Pre-contrast imaging included:

- T1 weighted (T1W) images (turbo spin echo): TR = 540 ms, TE= 10 ms, FOV:300 , matrix : 340 x 271 , slice thickness 3.5 mm and no slice gap.
- T2 weighted (T2W) images (turbo spin echo): TR ≥4861ms, TE=120 msec, matrix 424 x 384 with a FOV:300, slice thickness 3.5mm, no slice gap.
- STIR sequence with TR = 6806 ms, TE =165 ms, TI = 70 ms, matrix: 272x 223 with FOV: 300, slice thickness 3.5 mm and no slice gap.

b) Diffusion study:

Diffusion-weighted MRI was carried out using a single shot spin-echo echo-planar imaging sequence with fat saturated spectral pre-attenuation inversion recovery SPAIR in the transverse plane with tri-directional diffusion gradients by using b values 0, 50& 850 sec/mm^2 to increase sensitivity to cellular packing. The other parameters were as follows: repetition time (TR) = 8923 m sec, echo time (TE) = 81 m sec, number of excitations (NEX) = 2 , matrix 188x 186 with a field of view: 400, slice thickness 3 mm, no gap, scan time 2 minutes . Sense is used to shorten acquisition time and reduce distortion.

c) Dynamic study:

Dynamic study was performed after manual bolus injection of 0.1mmol/kg body weight of Gd-DTPA, flushed with 20ml of sterile 0.9% saline solution from the antecubital vein.

Quantitative analysis was done by placing the region of interest (ROI) at the most enhanced part within the lesion resulting in automatically created time / signal intensity curve.

Imaging Evaluation:

The morphological features, the dynamic MRI parameters and the diffusion weighted imaging findings of each lesion values were recorded. The criteria of malignancy of the lesions in the study included the following:

- Morphological: irregular or spiculated margins, low or intermediate signal on T2 weigthed image, bright signal on STIR image and pathological axillary lymph nodes.
- Dynamic MRI: avid enhancement, with rapid initial rise followed by plateau or washout pattern in the delayed phase on the time/signal intensity curve.
- Diffusion weighted imaging: persistent bright signal at b 850 and low to intermediate signal in the ADC map denoting true restricted diffusion, ADC value of less than 1.25×10^{-3} mm^2/s which is the cutoff value between benign and malignant lesions as described by **Bogner *et al* (2009)**.

ADC Calculation

ADC was generated for each pixel of the diffusion –weighted image in the form of parametric maps on the operating console or on the workstation. The mean ADC of each lesion detected is measured by drawing a region of interest (ROI) over the lesion in the ADC maps. ROI ranged from 60 to 150 mm^2 and was traced within the boundaries of the lesion using an electronic cursor. multiple values were taken and then their mean was considered the ADC value.

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

Statistical Analysis:

Correlation between tumor grading and MRI findings was done. Data was analyzed using SPSS win statistical package version 21 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done

using either student t-test or Mann-Whitney test (non-parametric t-test) as appropriate. A *p*-value of less than 0.05 was considered significant.

Comparison of median between more than 2 groups was done by Kruskall Wallis ANOVA, and then pairwise comparison was done with Bonforoni adjustment.

Spearman's rho correlation was done to test the correlation between Grade & ADC value.

ROC analysis (Receiver Operator Characteristic) was done to select the best cutoff point for ADC value to discriminate high grade from low grade.

RESULTS

Twenty five female patients were included in this study, their age > 30 years. Histopathological analysis revealed all 25 lesions to be invasive ductal carcinomas not otherwise specified. Grading of included carcinomas was as follows: 3 lesions (12.0%) were grade I, 14 lesions (56.0%) were grade II and 8 lesions (32.0%) were grade III (Fig 1).

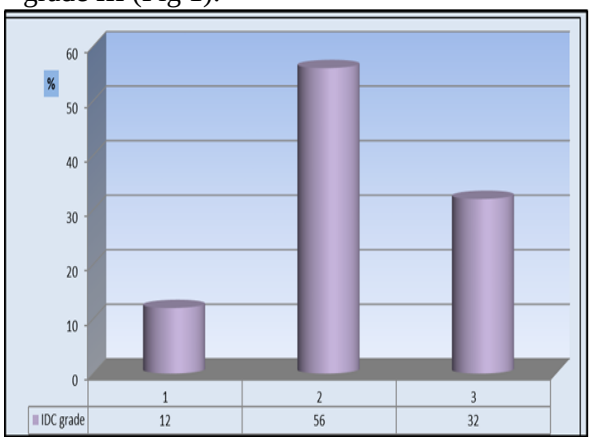

Fig (1): The distribution of different histological grades in the study

Points of analysis included:

- Diffusion-weighted imaging analysis
- Dynamic MRI parameters
- Morphological criteria such as the margins of the lesion, the presence of pathological axillary lymph nodes and the T2 weighted-image signal intensity of the lesion.

Diffusion-Weighted Imaging:

All 25 lesions (100%) showed persistent bright signal on DWI (b 850) with low to intermediate signal on ADC map denoting restricted diffusion.

ADC values ranged from 0.2 to 1.28 × 10^{-3} mm^2/s (mean=0.81± 0.22 × 10^{-3} mm^2/s) (Table 1).

- The mean ADC value of grade I was 1.04 ± 0.11 × 10^{-3} mm^2/s.
- The mean ADC value of grade II was 0.83 ± 0.21 × 10^{-3} mm^2/s.
- The mean ADC value of grade III was 0.70 ± 0.21 × 10^{-3} mm^2/s.

Table (1): ADC values of different histological grades

	Mean	Std. Deviation	Min	Max
Grade 1	1.04	0.11	0.914	1.12
Grade 2	0.83	0.21	0.461	1.28
Grade 3	0.70	0.21	0.2	0.934
Total	0.81	0.22	0.2	1.28

Tumors with higher grade showed lower ADC value compared with those of lower grade, with a statistically significant difference (*p*= 0.002). There was also significant difference between the mean ADC value of tumors of grade I and III (*p*= 0.012); and between grade II and III (p =0.005). However, there was less significant difference between grade I and II (*p*= 0.051).

Moreover, statistical analysis of the data revealed that using the ADC value of 0.852 × 10^{-3} mm^2/s as a cutoff value between high grade tumors (grade III) and low grade tumors (grades I and II), has a sensitivity and specificity of 87.5% and 92% respectively with an accuracy percentage of 88%. One (4%) false positive result and two (8%) false negative results were noted out of the total number of lesions in the study.

Dynamic MRI Results

Both qualitative (morphological) and quantitative assessment were performed.

Sixteen lesions (64.0%) showed type 2 (plateau) curve, while 9 lesions (36.0%) showed type 3 (washout) curve (Fig2 and table 2).

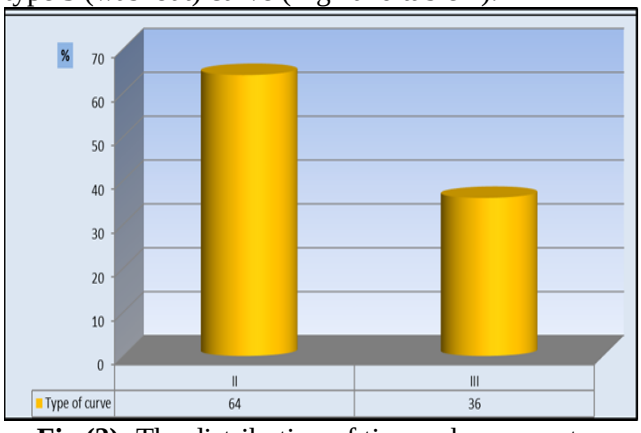

Fig (2): The distribution of time enhancement curves in the study

High grade tumors (grade III) were significantly associated with washout curve compared to those with lower grades (grades I and II) (p =0.04).

Table (2): The dynamic curves of different histological grades.

			Grade			Total
			1	2	3	
Dynamic curve	plateau	№ of cases	3	10	3	16
		% within Grade	100.0%	71.4%	37.5%	64.0%
	washout	№ of cases	0	4	5	9
		% within Grade	0.0%	28.6%	62.5%	36.0%
Total		№ of cases	3	14	8	25
		% within Grade	100.0%	100.0%	100.0%	100.0%

However, there was no statistically significant relation between the grade of the tumor and the pattern of enhancement (Table 3).

Table (3): Patterns of enhancement of the lesions in the study.

			Total
Enhancement pattern	Hetrogenous	Count	14
		%	56.0%
	Homogenous	Count	6
		%	24.0%
	Rim	Count	5
		%	20.0%
Total		Count	25
		%	100.0%

Other Morphological Criteria

Morphological criteria including the margins of the lesion, the presence of pathological axillary lymph nodes, and the signal of the lesion on T2WI were evaluated.

The following tables (table 4-6) show the distribution of each of the morphological criteria within the different histological grades in the study.

Table (4): The margins of the lesions in the study

			Total
Margin. Morphology	irregular	Count	11
		%	44.0%
	lobulated	Count	1
		%	4.0%
	speculated	Count	13
		%	52.0%
Total		Count	25
		%	100.0%

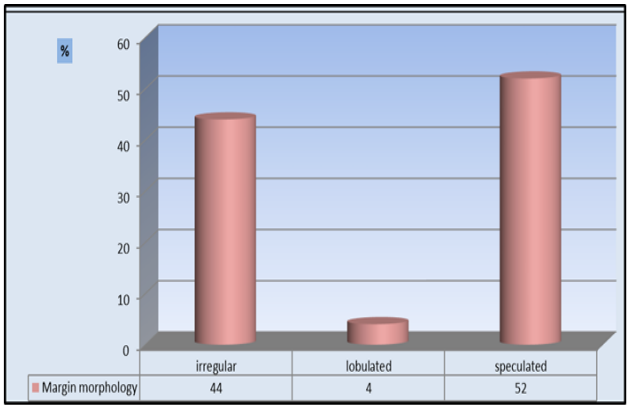

Fig (3): Distribution of margins of the lesions in the study

Table (5): The pathological lymph nodes in the study

			Total
Pathological LN	No	Count	6
		%	24.0%
	Present	Count	19
		%	76.0%
Total		Count	25
		%	100.0%

Table (6): The signal of the lesions in T2WI

			Total
T2WI SI	high	Count	3
		%	12.0%
	Intermediate	Count	8
		%	32.0%
	Low	Count	14
		%	56.0%
Total		Count	25
		%	100.0%

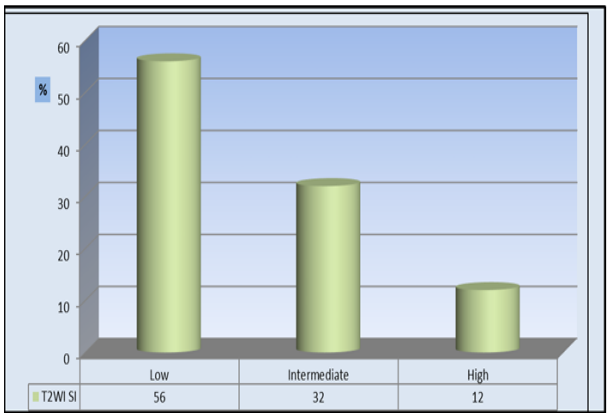

Fig (4): Distribution of T2WI SI in the study

The relation between each of the morphological characteristics and the histological grade of the tumor did not show any statistical significance.

LLUSTRATIVE CASES

CASE 1

History:Sixty year old female presented with left breast lump.

MR Mammography Study

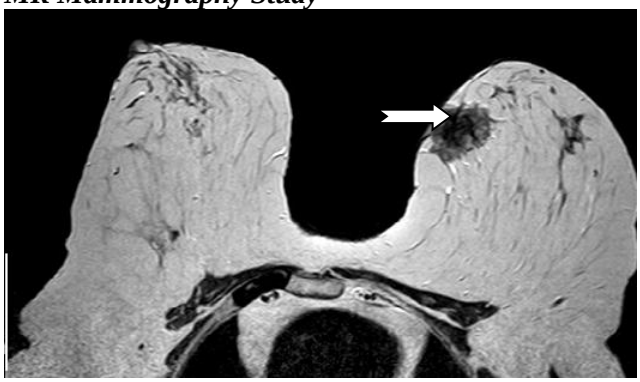

Fig (5): T2WI

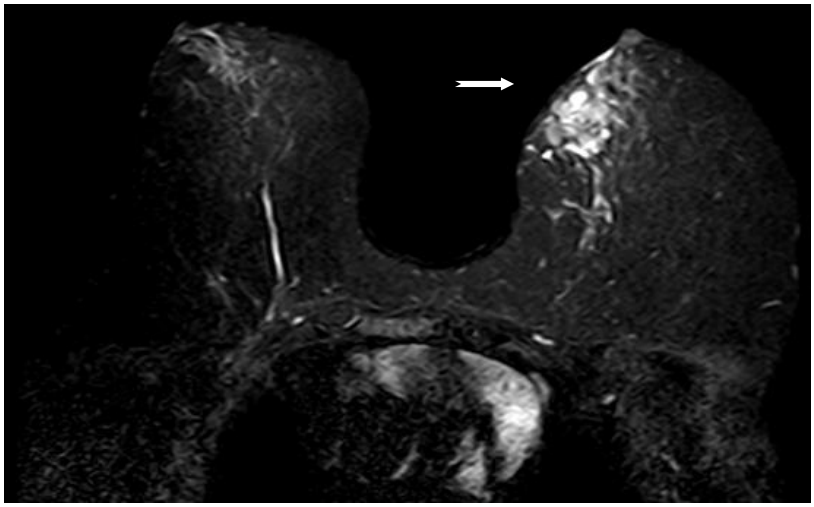

Fig (6): STIR sequence

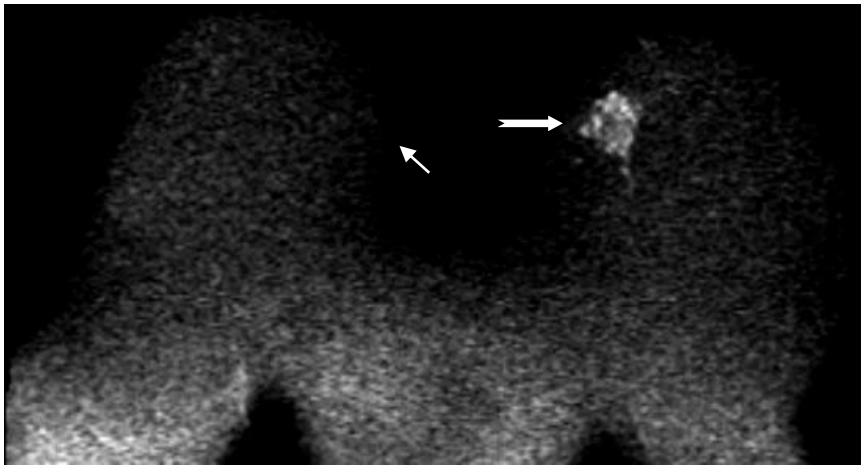

Fig (7): DWI at b 850

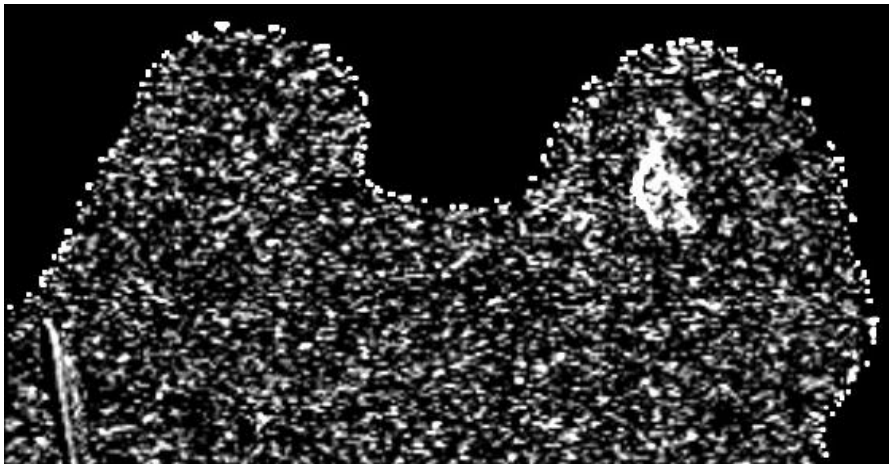

Fig (8): ADC map

Qualitative criteria

- Left breast oval shaped mass (arrow) of spiculated outline .
- *T2WI sequence:* Low signal intensity (SI) (Fig 5)
- *STIR WI sequence:* Bright SI (Fig 6)
- *DWI at b 850:* persistent bright SI (Fig 7)
- Intermediate -low SI in the ADC map (Fig 8) (restricted diffusion).

Quantitative criteria

- ***Kinetics :*** medium initial rise with persistant platue enhancement (type II curve) .
- *ADC value:*0.76×10^{-3} mm^2 /s .

Radiology : Categorized as **BIRADS VI .**

Pathology: Invasive Duct Carcinoma, *grade 2.*

CASE 2

History

Fifty-seven year old female presented with left breast lump .

MR Mammography Study:

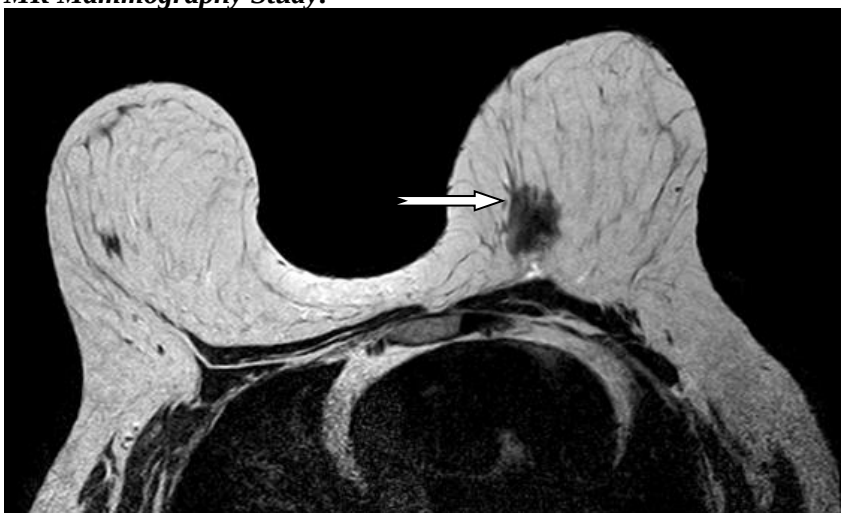

Fig (9):T2WI

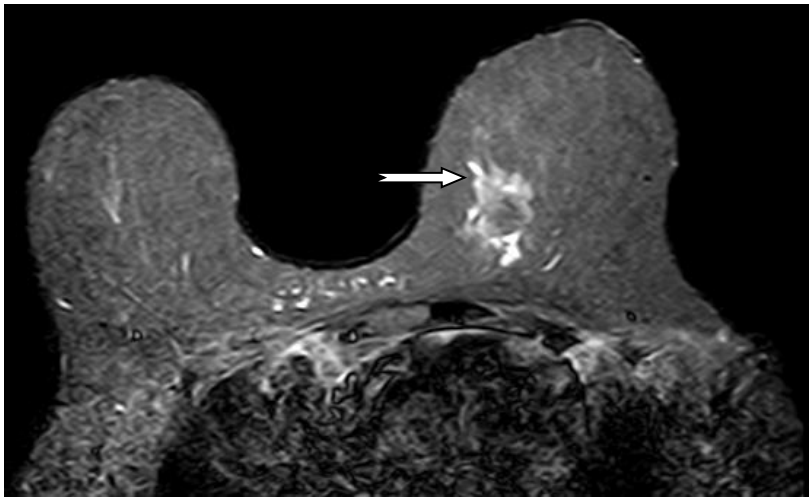

Fig (10): STIR sequence

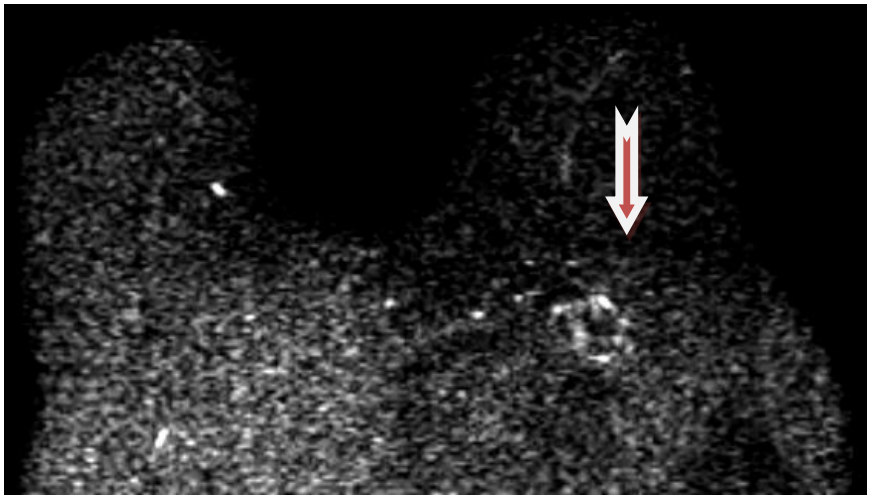

Fig (11):DWI at b 850

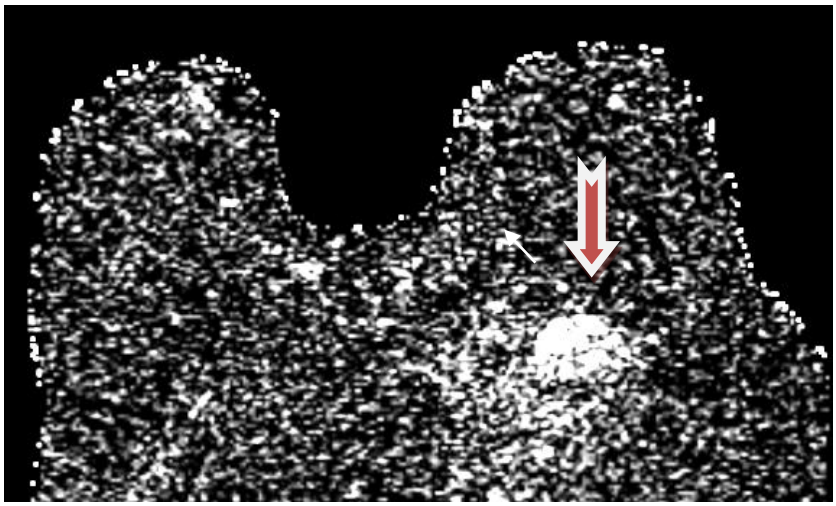

Fig (12): ADC map

Qualitative criteria

- Left lateral upper quadrant breast mass (arrow) of irregular outline& speculated margin .
- *T2WI sequence:* Low signal intensity (SI) (Fig 9).
- *STIR WI sequence:* Intermediate SI (Fig 10).
- *DWI at b 850:* persistent bright SI (Fig 11).
- intermediate-low SI in the ADC map (Fig 12) (restricted diffusion).

Quantitative criteria

- *Kinetics:* Initial peak of contrast uptake.
  Delayed phase rapid washout (type III) kinetic curve.
- *ADC value:(0.753)× 10^{-3} mm^2/s .*

Radiology :

Categorized as : **BIRADS V**

***Pathology*:**

Invasive Duct Carcinoma, *grade 2.*

DISCUSSION

Breast cancer can have a variable biological behavior. Predicting the histopathological grade (and so the aggressiveness) of breast cancer using MRI can be challenging. However, it is important because it can improve the selection of proper treatment and defines the patient's outcome. The histological grade is considered an important prognostic factor for breast cancer along with axillary lymph nodes [(5)].

Dynamic contrast enhanced magnetic resonance imaging has been a useful technique for the detection and diagnosis of breast cancer. It gives information on the morphology of the lesion and also on its kinetics. This means that it provides data on some functional aspects of the tumor such as vascularity and pattern of contrast uptake[(1)].

Diffusion weighted imaging uses the principle of random "Brownian" motion of molecules to assess the extent of water diffusion in tissues. Water diffusion is greatly influenced by factors such as cellularity, fluid viscosity and membrane permeability. High cell proliferation seen in invasive duct carcinoma, which features densely packed tumor cells, creates more barriers to the extracellular motion of water molecules, resulting in restricted diffusion and lower ADC values. This makes ADC value a useful parameter for assessing the cellularity of the tumor, which in turn directly affects the histopathological grading [(3)].

In the current work, we studied 25 malignant breast lesions. Only invasive ductal carcinoma was considered to avoid bias from the histopathological variability. For every lesion, diffusion-weighted imaging analysis, dynamic MRI parameters and morphological criteria were studied.

In the diffusion weighted imaging; we reported ADC values of the studied tumors and studied their relation with the histological grading. While in the dynamic post contrast sequence, we analyzed the enhancement behavior of the included breast carcinomas that focused on the enhancement peak, amplitude and dynamic curve pattern.

We found that the results obtained from the analysis of ADC values were the most significant.

In agreement with previous studies of [(6,7,8,9,10)] the mean ADC value of the malignant lesions ranged from 0.89×10^{-3} mm^2/s to 1.22×10^{-3} mm^2/s which is comparable to our study ADC value of $0.81 \pm 0.22\times10^{-3}$ mm^2/s.

Also, all the ADC values in our study did not exceed the cut off value between benign and malignant breast lesions set by previous studies such as [(6,11)] which ranged from 1.25×10^{-3} mm^2/s to 1.6×10^{-3} mm^2/s.

After studying the ADC values, we found that there was inverse correlation between the ADC value and the histological grade of the tumor. Tumors with higher grade showed lower ADC value compared with those of lower grade (p= 0.002).

This is consistent with previous studies of [(9,12,13)] which reached the same conclusion. This is also consistent with [(10,14)] who reported a significant correlation between ADC value and tumor cellularity.

Only [(8)] found that the mean ADC of breast cancer did not significantly correlate with cellularity of the tumor.

In our study, the mean ADC value of grade I tumors was $1.04 \pm 0.11\times10^{-3}$ mm^2/s, of grade II was $0.83 \pm 0.21\times10^{-3}$ mm^2/s and of grade III was $0.70 \pm 0.21\times10^{-3}$ mm^2/s.

This is comparable to the results obtained by [(13)] who reported that the mean ADC values of grade I, II and III were $0.96 \pm 0.12 \times10^{-3}$ mm^2/s, $0.87 \pm 0.07\times10^{-3}$ mm^2/s and $0.75 \pm 0.12\times10^{-3}$ mm^2/s, respectively.

However, it differs from the results obtained by [(19)] who reported that the mean ADC values for grade I, II, and III tumors were 1.25×10^{-3} mm^2/s, 1.02×10^{-3} mm^2/s, and 0.92×10^{-3} mm^2/s, respectively. This variation may be attributed to the discrepancy in the sample size and the MRI technique specially the use of different b values.

There was significant difference between the mean ADC value of tumors of grade I and III (p= 0.012); and between grade II and III (p=0.005). However, there was less significant difference between grade I and II (p= 0.051). Similar results were obtained by [(13)].

Moreover, analysis of our data revealed that using the ADC value of 0.852×10^{-3} mm^2/s as

a cutoff value between high grade tumors (grade III) and low grade tumors (grades I and II), has a sensitivity and specificity of 87.5% and 92% respectively.

Regarding the dynamic MRI results, 16 lesions (64.0%) showed type 2 (plateau) curve, while 9 lesions (36.0%) showed type 3 (washout) curve. We found that high grade tumors (grade III) were more associated with washout curve compared to those with lower grades (grades I and II).

However, we did not find any significant correlation between the grade of the tumor and the pattern of enhancement (homogeneous, heterogeneous, rim).

There appears to be a controversy between different studies regarding these results. Some studies support our results.

Szabo *et al.* [15] reported that washout phenomenon was associated with higher grade tumors.

Jansen *et al.* [16] reported that there was no significant difference in the enhancement kinetic properties across different grades.

On the other hand, other studies contradict ours.

Lee *et al.* [17], **Jinguji *et al.*** [18] and **Lee *et al.*** [19] found that rim enhancement was associated with higher histological grade.

Regarding the analysis of morphological criteria: margins, the presence of pathological axillary lymph nodes and the T2 weighted-image signal of the lesion, our study did not conclude any significant correlation between each one of these factors and the histological grade of the tumor. Furthermore, no correlation was found between tumor margins, the presence of lymph nodes and ADC value.

This is comparable to **Szabo *et al.*** [15] who reported that no correlation was found between margins of the tumor and the prognostic factors (including the grade).

Also, **Chan *et al.*** [20] reported that no significant difference was found in the morphology (including the margins) between high grade (grade III) and non-high grade (grade I and II).

This is also consistent with **Kim *et al.*** [21] and **Choi *et al.*** [22] . Both studies found no correlation between the presence of lymph nodes and the ADC value.

However, this is different from the results of **Abdel Razek *et al.*** [12], who reported that lower ADC values were associated with the presence of axillary lymph nodes.

In conclusion, although both DWI and dynamic MRI provide detailed information about invasive breast carcinomas, the results obtained from dynamic MRI regarding morphological and kinetic properties of the tumors were subject of controversy.

On the contrary, those obtained from DWI and ADC mapping seem more reliable and more consistent across different studies. Up till now, ADC value appears to be the best indicator of tumor cellularity and grade. This can be very useful to non-invasively identify highly aggressive breast carcinomas.

However, further researches on a larger scale are still needed to acquire more accurate and more detailed information about the value of MR imaging in distinguishing different histological grades of breast cancer.

SUMMARY AND CONCLUSION

Breast cancer can have a variable biological behavior and aggressiveness. The histopathological grade expresses the degree of malignancy of the tumor. Studying the relationship between the grade and MRI findings of breast cancer is essential as the histological grade affects prognosis and outcome.

Dynamic contrast-enhanced MR imaging is a sensitive imaging technique for detection and diagnosis of breast cancer. Although it provides morphological and functional information about the tumor, its role in assessing prognostic factors (including grade) of breast cancer is still controversial.

Diffusion weighted imaging is a fast non-invasive technique that can be easily integrated into the standard breast MRI protocol. It provides information not otherwise available about tissue cellularity, which is a main factor that determines the histological grade.

Our study, as well as others, revealed the usefulness and the reliability of DWI and ADC mapping in differentiating high grade from low grade tumors. There was an inverse correlation between the ADC value and the grade.

It also revealed that high grade tumors (grade III) were more associated with washout curve compared to those with lower grades (grades I and II). However, there was no significant correlation between the grade of the tumor and the pattern of enhancement or any of the morphological criteria of the tumor.

That makes DWI the best non-invasive tool available to predict grades of breast carcinoma. However, further larger and more

detailed studies are still needed to fully understand the role MR imaging in distinguishing different histological grades of breast cancer.

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