DYNAMIC CONTRAST-ENHANCED MR IMAGING IN DIAGNOSIS OF BREAST LESIONS

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ABSTRACT

Objectives: To describe the diagnostic performance of dynamic contrast enhanced MRI in differentiating between benign and malignant breast lesions. **Methods:** the study was conducted on 40 patients with 40 lesions. MR examinations were performed using a closed MRI machine with magnets of intensity field 1.5 Tesla system,equipped with bilateral dedicated breast coils. All lesions were biopsied considering histopathologic findings as the standard of reference. Probability of malignancy was assessed according to BI-RADS for DCE-MRI. Diagnostic accuracy of DCE-MRI was statistically analyzed. **Results:** Regarding to the final outcome of the reviewed 40 MRI studies depending on the histopathological results accepted as standard reference, histopathology revealed malignancy in 67.5 % of lesions (27/40) and DCE-MRI showed sensitivity (96.3%) and specificity (76.9%) **Conclusions:** Dynamic contrast enhanced MRI facilitates differentiating benign and malignant breast lesions.

Key words: Breast lesions.Dynamic MRI

Abbreviations:

DCE-MRI: dynamic contrast enhanced MRI**,** BI-RADS : Breast Imaging-Reporting and Data System ,FNAC: Fine needle aspiration cytology ,IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma , ROI : Region of interest

INTRODUCTION

Breast cancer is the most common cancer among women, and the second leading cause of cancer death in women worldwide. So, early screening, primary staging and monitoring of treatment requires efficiency for accurate management. Many invasive imaging techniques are used nowadays for this purpose as mammography, ultrasonography, magnetic resonance imaging (MRI) and tomosynthesis [(1)].

Magnetic resonance imaging was not used previously as a routine examination in diagnosis of breast cancer; however, it is now used when findings of diagnostic mammographic and/or ultrasound are unclear. It provides morphological data regarding lesions as well as functional criteria as tissue perfusion and enhancement kinetics [(2, 3)]. Also, MRI is non-operator dependent and not significantly impaired by dense tissue, which make it more sensitive and super passing other imaging modalities in detection of breast lesions [(4)].

Nowadays, Dynamic contrast material–enhanced MR imaging (DCE-MRI)is gaining popularity as an important imaging modality for breast cancer diagnosis due to the ability of visualising three-dimensional (3D) high-resolution dynamic (functional) information, not available with mammography or with ultrasound by requiring a time-signal intensity curve obtained by repeated MRI scans after contrast agent injection [(5)].

Evaluation and quantification of lesion vascularity through time course kinetics gives an autonomous diagnostic parameter that can help distinguish benign lesions (e.g., fibroadenoma) from well-circumscribed breast cancer [(6)].

The aim of this study is to demonstrate the diagnostic performance of dynamic contrast enhanced MRI in differentiating benign from malignant breast lesions.

MATERIALS AND METHODS

Patients

Forty female patients (mean age, 50.03 years; age range, 34–69 years) were examined during the period from July 2016 to August 2017. Approval of Research Ethics Committee (REC) and informed consent were obtained from all participants in this study after explanation of the benefits and risks of the procedure as well as accurate informing of the duration of the MRI examination. Privacy and confidentiality of all patients' data were guaranteed. All data provision were monitored and used for scientific purpose only.

Inclusion criteria:

1- Patients having malignant axillary lymph nodes with negative mammographic and clinical findings.
2- Women with previous breast surgery to differentiate post surgical scar from recurrent carcinoma in case of undefined mammographic findings.
3- Patients referred for pre-operative evaluation and staging of cancers diagnosed by percutaneous needle biopsy.
4- Patients referred for assessment of chemotherapy response.
5- Women having breast masses with equivocal sonomammographic findings.
6- No age predilections.

Exclusion criteria:

1- Patients with any contraindications to MRI as presence of cardiac pacemakers or ferromagnetic intracranial aneurysm clips, or claustrophobic patients.
2- History of allergy from intravenous contrast media (Gadolinium).
3- Pregnant patients (Gadolinium cross the placenta blood barrier).

Methods:

<u>All patients were subjected to the followings:-</u>

<u>Data collection</u>

a) Personal history: name, date of birth, age, risk factors, and menstrual cycle.
b) Past history of prior malignancy.
c) Present history, focused upon the recent malignancy, its site, dates of diagnosis, biopsy results and treatment (surgery, radiation, and chemotherapy and current medications), all the previous imaging studies, and any other investigations.
d) The optimum time for MRI examination is during days 5 -15 of the menstrual cycle, for 4-6 weeks after stopping hormone replacement therapy, or 6 months post-surgery and at least 9 months (preferably 12 months) post radiotherapy for detection of suspected recurrence.
e) Recent creatinine level and history of allergies to contrast material.
f) The patients were asked about their ability to lie for the duration of the scan (30–45 min) and history of claustrophobia.

PATIENT PREPARATION

The patients were instructed to wear hospital gowns and remove all metallic objects such as hair pins, coins & ear rings, then the procedure was explained to the patient for reassurance. At this point, the patient was ready to have the intravenous line which was inserted at the dorsum of the hand before positioning the patient on the table to ensure lack of movement between scans.

The MRI of breast was performed with the patient lying in a prone position on a platform placed in the MR imager using a dedicated breast coil that allows the breasts to be in a dependent position.

<u>MR image acquisition</u>

- **Pulse sequences and scanning planes:**

MR examinations were performed using a closed GE explorer MRI machine with magnets of intensity field 1.5 Tesla system equipped with bilateral dedicated breast coils (bilateral breast MRI in the same sitting) and advantage workstation release 4.7 software. Transverse, sagittal and coronal plane localization scans were done and the following sequences were taken:

a) Axial T1-weighted fast spin-echo (T1WFSE) with repetition time in millisecond (ms)/ echo time in ms (TR/TE) of 500/12 ms; slice thickness: 4 mm; spacing: 1mm; image matrix: 512×256.
b) Axial T2WI with fat suppression with TR/TE of 5600/59 ms; slice thickness: 4 mm; spacing: 1mm; image matrix:320 x 314.
c) STIR (TR=3000 ms, TE=30 ms, TI=150 ms) in the transverse and sagittal plane; slice thickness:4 mm; spacing: 1mm; image matrix: 320 x 314.
d) Dynamic contrast MRI was performed by two-dimensional fast spoiled gradient-recalled echo with fat suppression in T1WI (TR=4.3 ms, TE=1.3 ms), flip angle 80^o axial scan, FOV 34 x 34 cm, image matrix 448 x 322, slice thickness 1mm, spacing 1mm.The entire breast was imaged before and seven times immediately after manual intravenous injection

of 0.1 mg of Gd-DTPA/Kg of body weight at 1,2,3,4,5,6,7 and 8 minutes.

e) Other features of MR imaging include automated functions like computer aided detection, image registration, multiplanar reformatting, subtractions, angiogenesis maps, curves, maximum intensity projections(MIPS) and volume summaries.

Image interpretation

The description of lesions included: shape (round, oval, irregular), margin (circumscribed, irregular, spiculated), enhancement pattern (homogenous, heterogeneous, rim, dark internal septation), and enhancement kinetics (persistent enhancement [type I], plateau phase [type II], wash-out [type III]). Regions of interest (ROIs) were manually placed on the most enhancing part of lesions, and then intensity courses were plotted against time by the workstation software rendering time-signal strength curve. For non mass enhancement, distribution (focal, linear, segmental, regional, multiple regions, diffuse), internal enhancement (homogenous, heterogeneous, clumped and clustered ring) were assessed.

Histopathology

Histopathological findings were obtained from the 40 studied patients. Nineteen patients underwent fine needle aspiration biopsy which was ultrasound guided in 7 patients and without ultrasound guidance in 12 patients, ultrasound guided true cut biopsy was done in 1 pateint, and excisional biopsy in 22 patients.

Two patients had two kinds of biopsies (fine needle aspiration cytology with ultrasound guidance &excisional biopsy).

STATISTICAL ANALYSIS

The data were collected, tabulated and statistically analyzed. Statistical calculation was performed using computer program Microsoft excel 2007 (Microsoft corporation, NY, USA) and Statistical Package for the Social Science (SPSS) Version 21. Descriptive statistic was performed in a form of number and percentage for the qualitative data. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and diagnostic accuracy were used to test validity of DCE-MRI in evaluation of different breast lesions.

RESULTS

This study included 40 female patients who were either presented clinically with breast complaints, and/or had abnormal mammographic findings, or referred for routine postoperative follow up of removal of malignant mass.

Depending on the biopsy results as standard of reference, 13 patients in this study (32.5%) had benign lesions, and 27 patients (67.5%) had malignant lesions **(table 1).**

Table (1):Distribution of studied cases according to histopathological results (n=40):

	Pathological results	No.	%
Malignant lesions (n= 27)	Ductal carcinoma in situ (DCIS)	1	2.5
	Invasive ductal carcinoma(IDC)	20	50
	Invasive lobular carcinoma(ILC)	5	12.5
	Paget's disease of nipple	1	2.5
Benign lesions (n=13)	Fibroadenoma	3	7.5
	Post-operative scar	6	15
	Fat necrosis	3	7.5
	Fibrocystic changes (FCC)	1	2.5

The MRI findings detected in the studied cases were one or more of the following patterns: enhancing mass, enhancing foci, non enhancing mass, non mass enhancement, cystic lesion, fibrocystic changes and suspicious lymphadenopathy. More than one sign may be present in each patient **(table 2).**

Table (2):Patterns of MRI findings in the studied cases (n=40)

MRI findings	No.	%
Enhancing foci	5	12.5
Enhancing mass	29	72.5
Non mass enhancement	2	5
Cystic lesion	1	2.5
Fibrocystic changes	1	2.5
Suspicious lymphadenopathy	12	30
Discoid enhancement of nipple	1	2.5

According to BI-RADS classification, the patients were categorized in a descending manner as BI-RADS 4 (12 patients representing 30%) followed by BI-RADS 5 (10 patients representing 25%), then BI-RADS 2 (11 patients representing 27.5%) and lastly BI-RADS 6 (3 patients representing 7.5%). None of the studied patients were classified as BI-RADS 1 **(table 3).**

Table (3):Distribution of studied cases according to MRI BI-RADS evaluation (n=40):

BI-RADS	No.	%
1	0	0.0
2	11	27.5
3	4	10
4	12	30
5	10	25
6	3	7.5
Total	40	100

Kinetic curves of the enhanced lesions were described as washout curve in 25 lesions (62.5%) denoting its malignant nature, plateau curve in 4 lesions (10%) denoting its suspicious nature, and rising curve in 11 lesions (27.5%) denoting its benign nature **(table 4)** .

Table (4):Types of dynamic curves in studied cases, in dynamic breast MRI(n=40)

Interpretation	Post initial part of the curve	No.	%
Benign lesion	Rising	**11**	**27.5**
Suspicious lesion	Plateau	**4**	**10**
Malignant lesions	Washout	**25**	**62.5**

Dynamic Contrast-enhanced MRI sequences showed that type III curve was the most common type in the pathological proved malignant cases and has been found in 23 out of 27 total malignant cases (85.2%),while being found in only 15.3% of pathologically proven benign lesions **(table 5)** .

The most common type of curve expressed by the pathologically proved benign cases in our study was type I curve and was seen in 10 out of 13 cases (77%),while being found in only 3.7% of pathologically proven malignant lesions, while type II dynamic curve was 11.1 % for the biopsy proven malignant lesions **(table 5) .**

Table (5): Correlation between pathology results and MRI curve types (n=40):

	Pathological results					
	Benign (n=13)		Malignant (n=27)		Total (n=40)	
MRI curve types	No.	%	No.	%	No.	%
Type I	10	77	1	3.7	11	27.5
Type II	1	7.6	3	11.1	4	10
Type III	2	15.3	23	85.2	25	62.5

In our study dynamic ***Contrast-enhanced*** MRI overestimated 3 lesions with BIRADS III, IV and V and they were pathologically proved to be benign post operative changes (operative scars and seroma) & underestimated 1 case with BIRADS II and it was pathologically proved to be malignant. (Table 6)

Table (6): Correlation between MRI BI-RADS evaluation and pathology results (n=40):

	Pathological results					
	Benign (n=13)		Malignant (n=27)		Total (n=40)	
MRI BI-RADS type	No.	%	No.	%	No.	%
Type II	10	77	1	3.7	11	27.5
Type III	1	7.6	3	11.1	4	10
Type IV	1	7.6	11	40.7	12	30
Type V	1	7.6	9	33.3	10	25
Type VI	0	0	3	11.1	3	7.5

Regarding the final outcome of the studied cases depending on correlation between MRI findings and histopathological results, DCE-MRI defined 26 true positive cases, 10 true negative cases , 3 false positive cases with MRI findings of malignancy and histopathologically proved benign lesions and 1 false negative case who was missed by DCE-MRI **(table 7).**

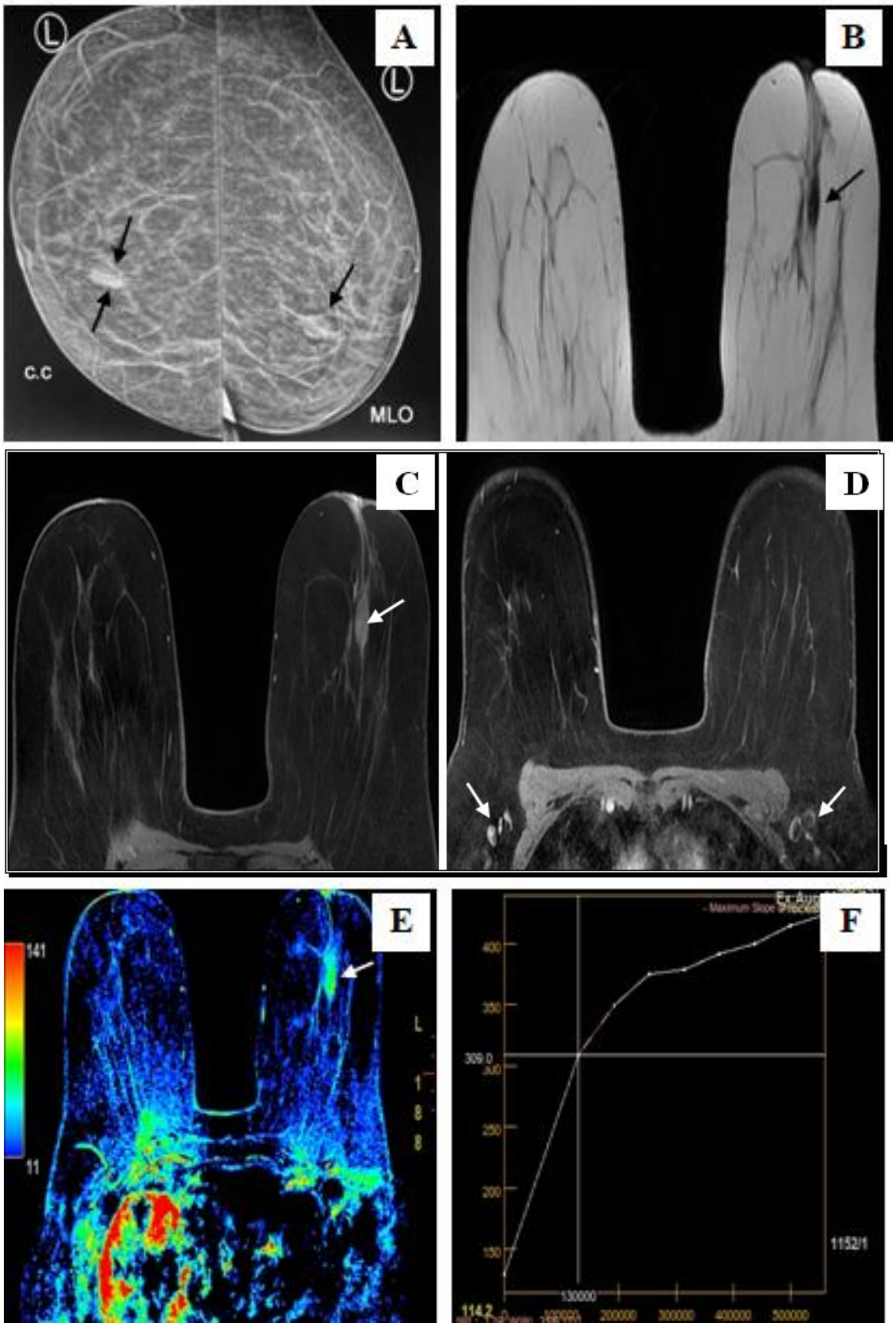
The study-based statistical analysis revealed sensitivity of 96.3%, specificity of 76.9%, positive predictive value (PPV) of 89.7%, negative predictive value of 90.9% and accuracy of 90% for dynamic contrast-enhanced MRI diagnosis. **(table 7)**.

Table(7): Final results of DCE-MRI in the studied cases (n=40):

Results	DCE-MRI
True-positive (n)	**26**
True-negative (n)	**10**
False-positive (n)	**3**
False-negative (n)	**1**
Sensitivity	**96.3%**
Specificity	**76.9%**
Positive predictive value	**89.7%**
Negative predictive value	**90.9%**
Accuracy	**90.0%**

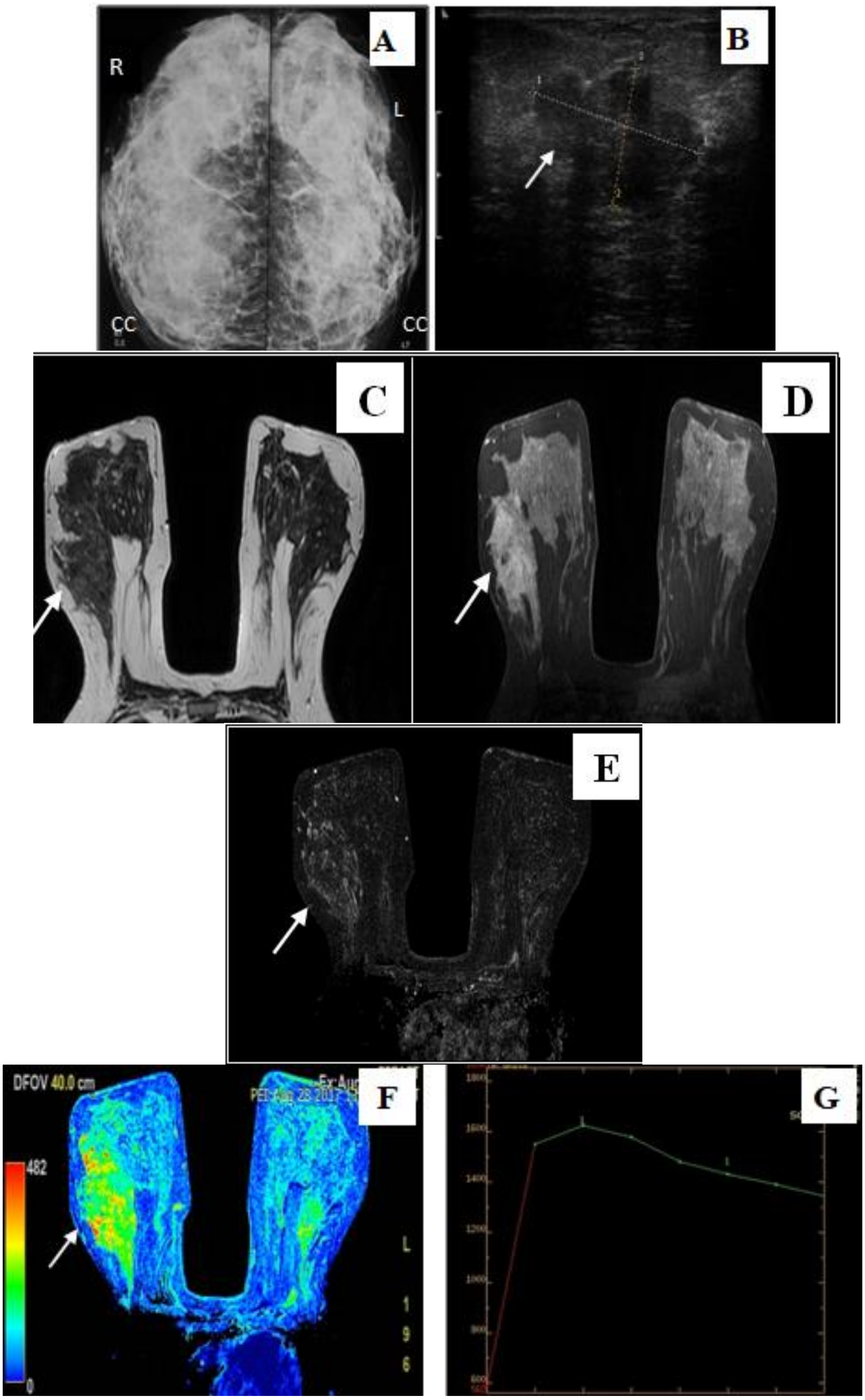
Cases:-

Case 1: Female patient aged 57 years, complaining of left axillary mass.



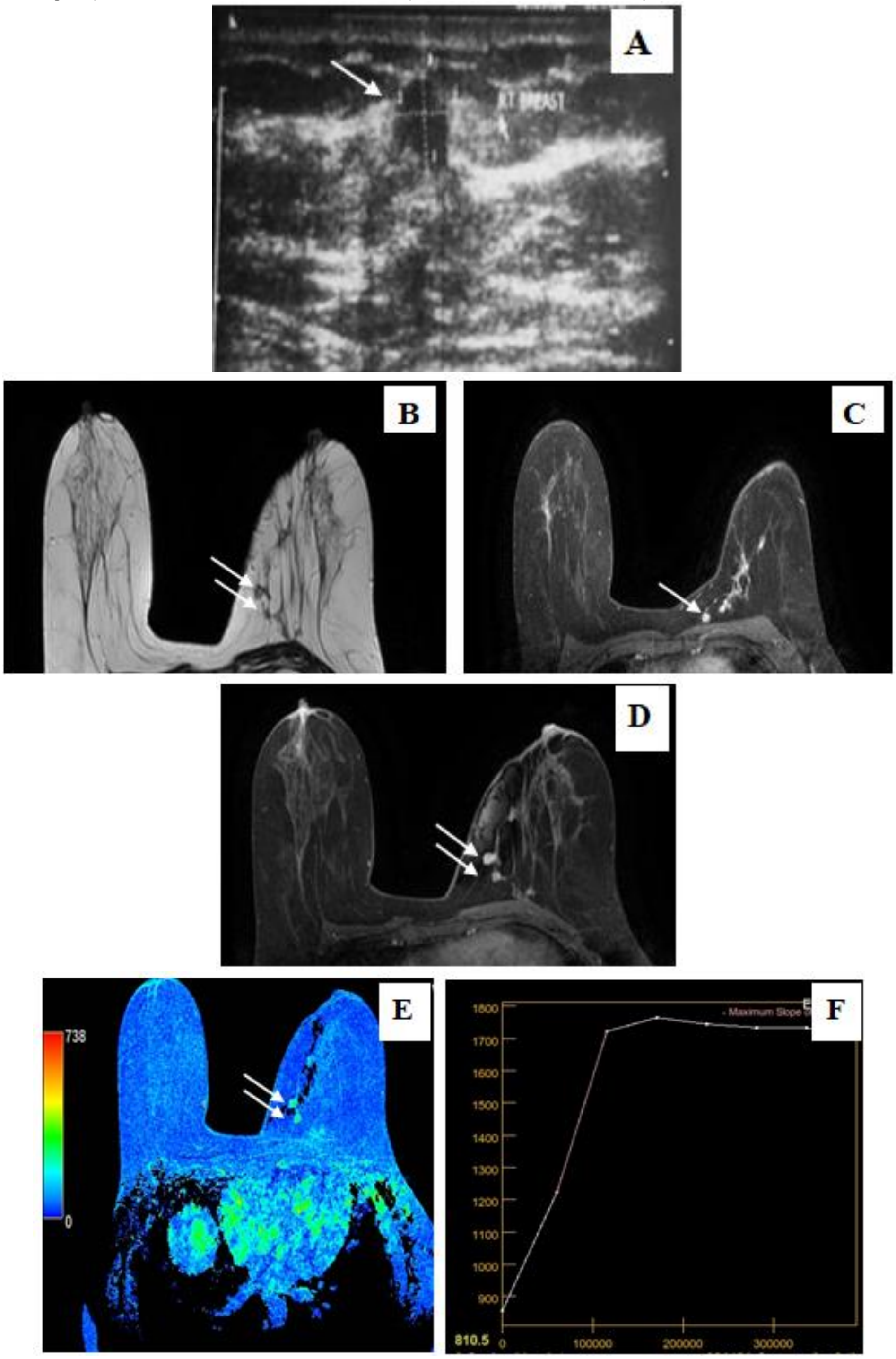
(A)Left breast mammography CC & MLO views showed a well defined left retroareolar oval shaped dense lesion with smooth margin. **(B) Non enhanced MRI axial T1WI image** showed well-defined left retroareolar oval shaped hypointense mass. **(C & D) Gadolinium enhanced MRI axial T1WI images** revealed homogenous intense enhancement of the left breast lesion with no parenchymal distortion in **(C)** and bilateral enlarged reactive axillary lymph nodes with oval in shape with preserved hilum (benign criteria) in **(D)**. **(E) Color mapping** revealed moderate vascularity of the lesion. **(F) Enhancement kinetic curve** revealed type I curve manifested as gradual progressive enhancement pattern. **Final diagnosis:** Overall MRI features were consistent with the benign nature of the mass and was ranked BIRADS II by MRI. The mass was surgically excised, histopathological diagnosis was fat necrosis.

Case 2: Female patient aged 56 years, presented with right breast lump.



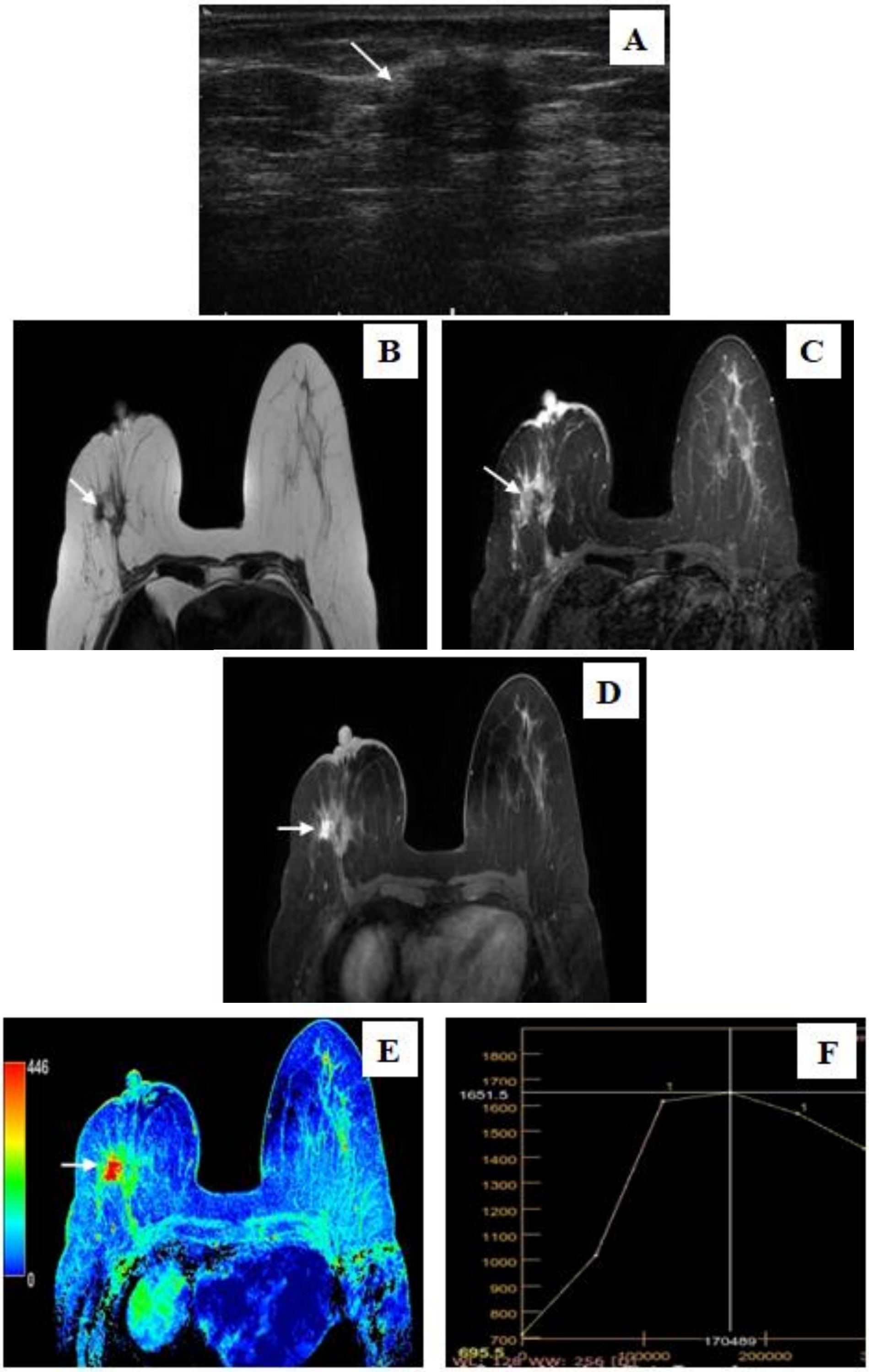
(A) Bilateral breasts mammography CC views showed dense both breasts (ACR d)**. (B) B-mode ultrasonography image** revealed an irregular hypoechoic soft tissue mass with speculated outline and posterior acoustic shadowing seen at 11 O'clock of the right breast. **(C) Non enhanced MRI axial T1WI image** revealed asymmetry of both breasts with an ill defined infiltrative hypointense mass seen at right upper outer quadrant. **(D) Gadolinium enhanced MRI axial T1WI image** revealed regional heterogeneous enhancement of the lesion. **(E) Axial subtraction post contrast view** showed better localization of the hyper intense mass at the right upper outer quadrant. **(F) Color mapping** revealed moderate heterogeneous vascularity of the lesion. **(G) Enhancement kinetic curve** revealed type III curve washout enhancement pattern. **Final Diagnosis:** Overall MRI findings were consistent with the malignant nature of the mass and was ranked BIRADS V by MRI. Patient underwent modified radical mastectomy histopathological diagnosis was invasive ductal carcinoma.

Case 3: Female patient aged 34 years, had left breast cancer 1 year ago, treated with conservative surgery, received chemotherapy and radiotherapy.



(A) B-mode Ultrasonography showed a small ovoid shaped hypoechoic lesion with irregular outline and posterior acoustic shadowing seen at the upper inner quadrant of the left breast, largest at 9 o'clock. **(B) Non enhanced MRI axial T1WI image** revealed deformed contour of the left breast as well as the irradiation changes and multiple small rounded hypo intense masses at the inner quadrant of left breast. **(C& D) Gadolinium enhanced MR axial T1WI images** showed moderate homogenous enhancement of the masses. **(E) Color mapping** revealed moderate vascularity of the masses. **(F) Enhancement kinetic curve** revealed type II plateau curve. **Final diagnosis:** Overall MRI features were consistent with the malignant nature of the mass and was ranked BIRADS V by MRI. The mass was surgically excised, histopathological diagnosis was invasive ductal carcinoma.

Case 4: Female patient, aged 56 years, had right breast cancer 3 years ago, treated with conservative surgery, received chemotherapy and radiotherapy.



(A)B-mode ultrasonography showed an ill defined irregular hypoechoic soft tissue mass with spiculated outline and posterior acoustic shadowing seen at 11 O'Clock of right breast. **(B) Non enhanced MRI axial T1WI image** showed decreased size of the right breast in relation to the left side with deformed contour (post-operative sequel) and a suspicious ill-defined irregular hypo intense mass at the right upper outer quadrant. **(C) Non enhanced MRI axial STIR image** revealed slight hyperintensity of the lesion with irregular and distorted parenchyma. **(D) Gadolinium enhanced MRI axial T1WI image** revealed homogenous intense enhancement of the lesion with parenchymal distortion and thickened irregular enhanced overlying skin. **(E) Color mapping** revealed intense vascularity of the lesion. **(F) Enhancement kinetic curve** revealed type III curve washout enhancement pattern. **Final Diagnosis:** The overall MRI features were consistent with upper outer quadrent soft tissue lesion of malignant nature, and was ranked BIRADS V by MRI. Histopathological examination revealed fat necrosis (post treatment sequale).

DISCUSSION

In the last few decades, many researchers studied the role of breast MRI in diagnosis of breast cancer and proved its efficiency in detection and characterization of different breast lesions depending on its higher sensitivity of contrast material enhancement[7].

However, the analysis of the MRI findings regarding to morphology, enhancement kinetics and T2 characterization of breast lesions only without any functional information is not conclusive due to the overlap between benign and malignant lesions' criteria[8].

As regard to biopsy results of the studied 40 patients, benign lesions accounted for 32.5% as found in 13 cases; 23 % were fibroadenomas, 46 % were post-operative scar, 23% were fat necrosis and 8 % were fibrocystic changes.This result does not agree with **Warren and Coulthard, 2003** [9] who reported that fibroadenoma is the most common benign breast mass comprising about 60% of benign masses in their study and we attributed that to the limited number of cases in our study.

Also, malignant lesions were found in 27 cases representing 67.5% of the studied lesions; 74% of them were invasive ductal carcinoma, 18.5 % were invasive lobular carcinoma, ductal carcinoma insitu and Paget's disease of nipple were 3.75 % for each. This cope with **Yang et al,2016** [3] who reported that of the 46 lesions analyzed in his study, 31 (67%) were malignant, including 25 patients (80.6%) with invasive ductal carcinoma (IDC).

To reduce the risk of increased false positive cases, we realized that premenopausal women underwent the MRI examination ideally on day 5-15 of the menstrual cycle and this was based on the fact that, the premenopausal breast is hormonally responsive [10].

For generation of time intensity curves, ROIs were set based on visual inspection. Time intensity curve was obtained from a small ROI inside the mass and away from areas of central hemorrhagic necrosis or fibrosis [11].

Type III curve was the most common type in the pathologically proved malignant cases and has been found in 23 cases out of the total 27 malignant cases(85.2%). This matches with the study done by **Jack,2011**[12] who found that type III(washout) curve was 86.49%(32/37). Type I curve was seen in 3.7 % of malignant lesions compared to 10.81% in Jack's study. Otherwise, the most common type of curve expressed by the pathologically proved benign lesions in our study was type I curve (77%), which also agreed with Jack's results in which type I for benign lesions was 65%.

The three fibroadenomas cases in the current study were correctly classified by DCE-MRI. Usually, it is not difficult to diagnose fibroadenomas with convential imaging techniques. But with the presence of high risk groups or when the first diagnosis is in an elderly woman or when it is single and palpable, it is not accepted to deal with such fibroadenoma-like masses as benign and DCE-MRI is mandatory for confirming diagnosis.[13].

Like other imaging modalities, false positive findings may results from MRI. In the present study, 2 false positive studies were recorded; one of them was proved pathologically to be fat necrosis (post treatment squeal) despite being diagnosed by MRI as BIRADS V (highly suggestive of malignancy) as the lesion had irregular outline, spiculated margin and washout curve in kinetic assessment **(case 4)**, the other case was diagnosed by MRI as BIRAD IV(probably malignant) and its biopsy yielded post-operative scar.

In this study, there was one case with histopathological diagnosis of intraductal carcinoma of lactiferous ducts, DCE-MRI underestimate intraductal carcinoma .

Consistent with previous results, DCE-MRI achieved 96.3% sensitivity, 76.9% specificity and 90.0% accuracy in this study; **Kul, et al, 2011**[13] reported 97.9% sensitivity, 75.7% specificity with DCE-MRI.

Also, **Yildiz, et al, 2017** [14] reported 83.3% sensitivity,69.5% specificity and 72.4% accuracy of DCE-MRI & **Ma, et al, 2017** [15] reported the sensitivity, specificity and accuracy of DCE-MRI as 90.1%, 70.2% and 82.8% respectively.

The correlation between the findings of dynamic-contrast MRI and histopathological results of different breast lesions improved its diagnostic accuracy. This fact gains a wide agreement with a large number of studies[16,17].

Limitations: In addition to the small sample size already mentioned, we should consider the variable filling factor caused by the impossibility of reducing the voxel of interest below 1 ml, thus almost always including surrounding fat or healthy gland parenchyma. More advanced hardware (e.g., field strength higher than 1.5 T, multichannel coils) and dedicated post processing software could provide MR spectra of better quality than those we obtained.

CONCLUSION

Dynamic contrast-enhanced MR imaging is the method of choice for improving evaluation of breast lesions and reducing needless biopsy procedures that yield benign pathologic findings.

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