Accuracy of Unenhanced Breast MRI Compared to Dynamic Contrast Enhanced MRI in Detection and Characterization of Breast Masses

Arwa Ashraf Ahmed Mansour, Fatma Zaitoun, Maged Abdelglil Hamed, Mohamed Zaitoun
Department of Radiodiagnosis, Faculty of Medicine, Zagazig University, Alsharquia, Egypt
***Corresponding author:** Arwa Ashraf Ahmed, **Mobile:** (+20)01063403763, **Email:** arwaashraf301@gmail.com

ABSTRACT
Background: Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females worldwide. Obtaining an accurate diagnosis is of considerable importance as it informs the choice of treatment and the prognostic outcomes of the disease. Magnetic resonance imaging (MRI) has a higher sensitivity for the diagnosis of breast cancer than mammography and ultrasound.
Objective: We aimed to assess the diagnostic efficacy and efficiency of unenhanced MRI sequences for detection and characterization of breast lesions. Accordingly, we evaluated the breast unenhanced- MRI (UE-MRI) protocol as a reliable alternative for dynamic contrast-enhanced MRI (DCE-MRI).
Patients and Methods: 90 female patients underwent MR examination with a diagnostic protocol including UE-MRI sequences (T1WI, T2WI, short TI inversion recovery (STIR) and diffusion weighted imaging (DWI)) and CE-MRI. UE-MRI results were compared with DCE-MRI and the gold standard results having the latter as the reference standard.
Results: UE-MRI results obtained sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 90%, 80%, 90%, 80%, and 86.7% respectively. On the other hand, those for the DCE-MRI were 95%, 90%, 95%, 90%, and 93.3% respectively. It was revealed that there was no significant difference between the two methods. **Conclusion:** UE-MRI could be considered as a reliable diagnostic tool and an effective substitute for DCE-MRI when contrast administration is not feasible or contraindicated.
Keywords: ADC, Breast lesions, Diffusion weighted imaging, STIR, T2WI, Unenhanced MRI.

INTRODUCTION
Breast cancer is now a significant cause of worldwide morbidity and mortality. Further, the increasing rate of breast cancer continues to be a major area of concern for both clinicians and researchers. Increased awareness in the affected population leads to more frequent physical examinations and diagnostic imaging procedures, which results in earlier diagnosis and hence improved prognosis [(1)]. Breast magnetic resonance imaging (MRI) has gained a major role in the detection and characterization of primary and recurrent breast cancer, and in the evaluation of the response to therapy [(2)].

Dynamic contrast-enhanced MRI (DCE-MRI) had been introduced and has become an important tool in the workup of breast lesions [(3)]. However, two major limitations are represented by its specificity which ranges from 37% to 97% [(4)] and by the injection of contrast material, which increases examination time and costs and may lead to various reactions as well as nephrogenic systemic fibrosis syndrome in patients with impaired renal function [(5)].

These limitations have been overcome by the introduction of diffusion weighted imaging (DWI) in the field of breast imaging. It provides important functional information without the need for contrast material [(6)]. The biologic information provided by DWI and DWIBS images combined with morphological and signal intensity data of STIR (Short TI Inversion Recovery), T1 weighted and T2 weighted TSE can be used to characterize breast lesions without the injection of contrast material [(7,8)].

We aimed to evaluate the diagnostic efficacy and efficiency of unenhanced MRI sequences for detection and characterization of breast lesions.

PATIENTS AND METHODS
A total number of 90 female patients with suspected breast lesions diagnosed by mammography or ultrasonography were scheduled for MRI at Radiodiagnosis Department, Zagazig University Hospitals. They were referred from General Surgery and Oncology Departments.

Inclusion criteria: Patients with suspected breast lesions diagnosed by mammography or ultrasonography of any age group.
Exclusion criteria: Patients with previous breast surgery or who received chemotherapy, any contraindications for MRI (Implanted electric and electronic devices, heart pacemakers, implanted hearing aids), patients with renal impairment (GFR less than 30) unless the examination was followed by renal dialysis.

Ethical considerations:
We explained our study to our patients and a written informed consent was obtained. The study was approved by the Research Ethical Committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.
Patients' preparations:

Received: 10/7/2021
Accepted: 6/9/2021

Full history taking and clinical analysis was done, we asked all patients to get rid of any metallic subjects (except those made of titanium), also they were asked about any contraindication to MRI examination.

Imaging and image analysis: (preoperative MRI):

All MR sequences were done using 1.5 Tesla superconducting MR imager (Achieva-class IIa, Philips medical system, equipped with a dedicated breast coil. The patient was laid prone on the examination couch with her arms above her head, the breasts hanging freely in the breast coil and the nipples pointing down. MR examination was performed in the second week of menstrual cycle in premenopausal women.

Each examination protocol was divided into two sections:

Unenhanced magnetic resonance imaging techniques (UE-MRI): Axial T1WI utilizing the following parameters: TR 540 m/s, TE 10 m/s, FOV 250 x 450 mm, matrix 256 x 160, slice thickness 3 mm and interslice gap 1 mm. Axial and sagittal T2WI utilizing the following parameters: TR 4000-4800 m/s, TE 120 m/s, FOV 250 x 450 mm, matrix 256 x 160, slice thickness 3 mm and interslice gap 1 mm. Short TI inversion recovery (STIR) utilizing the following parameters: TR 2000-7500 m/s, TE 55-170 m/s, FOV 250x450 mm, matrix 256 x 160, slice thickness 3 mm and interslice gap 1 mm. Diffusion weighted (DWI) imaging with b values = 600 s/mm^2 and b= 1000 s/mm^2.
Dynamic contrast-enhanced breast MRI (DCE-MRI): The contrast material was administered at a maximum dose of 0.1 mmol per kg of body weight with a flow rate of 2 mL/sec. An image was taken before contrast administration and repeated multiple times after contrast administration.

Image interpretation:

Each exam was divided in two parts first was the UE-MRI sequences and the other was the full exam (unenhanced and DCE sequences), the two parts was evaluated on two separate sessions by two blinded radiologist with experience in breast MRI 10 and 7 years for both respectively**,** they were asked to comments on**;** morphological configuration: as site and number of lesions, shape and margins. Signal intensity of lesion in relation to the surrounding glandular tissues on T1WI, T2WI, STIR and DWI sequences: as iso-, hypo-, or hyperintense.
CE-MRI sequences were interpreted of: Pattern of lesion enhancement and the time signal intensity curve.
Gold standard reference: Final diagnosis was obtained by histopathology or serial negative follow-ups according to MRI provisional diagnosis.

Statistical Analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for the Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Qualitative data were represented as frequencies and relative percentages. Quantitative data were expressed as mean ± SD (Standard deviation). P value < 0.05 was considered significant. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy for UE-MRI and DCE-MRI were calculated. UE-MRI results were compared with those of DCE-MRI which still represent the main sequence for detecting and evaluating breast lesions.

RESULTS

In the current study, we included 90 patients with suspected breast lesions diagnosed by mammography or ultrasonography, their ages ranged from 30 to 68 years with a mean age ± standard deviation (SD) of 48.9 ± 6.6 years. The most frequent age group was from (50 to 60 years) which represented 33.3 % of the total.

Out of the 90 patients included, 48 patients (53.3 %) were presented by painless lump, 24 (26.7%) by skin changes, 18 (20%) by nipple discharge, 12 (13.3%) by pain, while 33.3% of them had no symptoms and came for routine check-up.

Regarding the gold standard diagnosis, 60% of the benign lesions were fibroadenomas, 20% mastitis, 10% abscesses and 10% papillomas, whereas regarding the malignant lesions 70% were proven to be invasive ductal carcinomas and 15% invasive lobular carcinomas, 5% ductal carcinoma in situ, 5% mucinous carcinoma and 5% inflammatory carcinoma.
As regard the anatomical distribution of the studied lesions, the majority of the examined breast lesions were located in the upper outer quadrant (Table 1).

Table (1): Anatomical location of the studied breast lesions

Site of lesion	Benign (n=30)		Malignant (n=60)		Total
	Frequency	%	Frequency	%	
Upper outer quadrant	15	50.0	33	55.0	48 (53.33 %)
Upper inner quadrant	6	20.0	6	10.0	12 (13.33 %)
Lower outer quadrant	3	10.0	3	5.0	6 (6.67 %)
Lower inner quadrant	0	0.0	9	15.0	9 (10.0 %)
Retro-areolar	6	20.0	9	15.0	15 (16.67 %)

The signal intensity of the lesions in relation to surrounding glandular tissues was interpreted on UE-MRI sequences including T1WI, T2WI and STIR sequences. Where at T1WI most of the examined lesions exhibit isointense signal, while on T2WI, most of the benign lesions 60% were hyperintense (Table 2).

Table (2): Signal intensity of UE MRI sequences

T1WI	Benign (n=30)		Malignant (n=60)		Total
	Frequency	%	Frequency	%	
Isointense	12	40	45	75.0	57 (63.3%)
Hypointense	18	60.0	1	25.0	33 (36.7%)
Hyperintense	0	0.0	0	0.0	0 (0.0)
T2WI	**Frequency**	**%**	**Frequency**	**%**	
Isointense	6	20.0	12	20.0	18 (20%)
Hypointense	6	20.0	42	70.0	48 (53.3%)
Hyperintense	18	60.0	6	10.0	24 (26.7%)
STIR	**Frequency**	**%**	**Frequency**	**%**	
Isointense	0	0.0	3	5.0	3 (3.3%)
Hypointense	0	0.0	0	0.0	0 (0.0)
Hyperintense	30	100	57	95.0	87 (96.7%)

30% of the benign and 85% of the malignant lesions were hyperintense on DWI with corresponding hypointense signal on ADC map in keeping with restricted diffusion. On the other hand, 70% of the benign and 5% of the malignant lesions displayed low and high signal on DWI and ADC map respectively reflecting facilitated diffusion. 6 cases (6.7%) were controversial due to their intermediate signal on both DWI and ADC map. UE-MRI agreed with gold standard results in 90% true malignant cases and 80% of true benign cases, while there were 20% false negative cases and 10% false positive cases. The value was highly significant (P=<0.001) with very good agreement (K=0.7). DCE-MRI sequences were interpreted by assessment of the pattern of lesion enhancement and the time signal intensity curve (Table 3).

About the pattern of enhancement in our patients, homogenous enhancement was noted in 21 lesions (23.3%): 19 lesions were benign, while the heterogeneous enhancement was noted in 57 lesions (63.3%) 54 lesions were malignant, rim enhancement was noted in 6 lesions (6.7%): all of them were benign and faint enhancement was noted in 6 lesions (6.7%): 3 lesions were benign and 3 were malignant. The time signal intensity curve was rising (type I) among 30% of studied cases, all of them were benign. Type III (washout curve) was found among 50% of the studied cases, all of them were malignant, while type II (plateau curve) was found in 20% of the studied cases (Table 3).

Table (3): Time signal intensity curve analysis

	Benign (n=30)		Malignant (n=60)		Total
	Frequency	%	Frequency	%	
Type I	27	90.0 %	0	0.0 %	27 (30.0 %)
Type II	3	10.0 %	15	25.0 %	18 (20.0 %)
Type III	0	0.0 %	45	75.0 %	45 (50.0 %)

DCE-MRI agreed with gold standard results in 95% true malignant cases and 90% of true benign cases, while there were 10% false negative cases and 5% false positive cases, with excellent agreement between DCE-MRI and gold standard results. The value was highly significant with excellent agreement (K=0.85). The recorded sensitivity of DCE-MRI was 95%, its specificity 90%, accuracy 93.3%, PPV 95% & NPV 90%. While the sensitivity of UE-MRI was 90%, its specificity 80%, accuracy 86.7%, PPV 90% & NPV 80%. UE-MRI agreed with DCE MRI in 95% true malignant cases and 90% of true benign cases, while there were 10% false negative cases (diagnosed as benign lesions but they were proven to be malignant) and 5% false positive cases (diagnosed as malignant masses but they were proven to be benign), with excellent agreement between both (K = **0.85)** (Table 4).

Table (4): Agreement between UE-MRI and DCE-MRI

		DCE-MRI			K test	P value
		Malignant	**Benign**	**Total**		
UE MRI	**Malignant**	TP 57 (95%)	FP 3 (5%)	60	0.85	<0.001 HS
	Benign	FN 3 (10%)	TN 27 (90%)	30		
Total		60	30	90		

HS: High significant, TP: True positives, TN: True negatives, FP: False positives, FN: False negatives

Table 5 shows that after applying multivariate regression analysis for significant predictors of UE MRI used for differentiation between benign and malignant, T2WI, DWI and ADC were still highly significant parameters that can be used in differentiation.

Table (5): Multivariate regression for predictors of UE MRI used for differentiation between benign and malignant masses

	Univariate analysis		Multivariate analysis
T1WI	0.108	NS	
T2WI Isointense	0.68	NS	
T2WI Hypointense	0.02	S	0.008
T2WI Hyperintense	<0.001	HS	0.005
STRI	0.67	NS	
DWI Isointense	0.54	NS	
DWI Hypointense	<0.001	HS	<0.001
DWI Hyperintense	0.005	S	0.002
ADC Isointense	0.54	NS	
ADC Hypointense	0.005	S	0.002
ADC Hyperintense	<0.001	HS	<0.001
ADC value	0.005	S	<0.001

NS: Not significant, S: significant, HS: highly significant

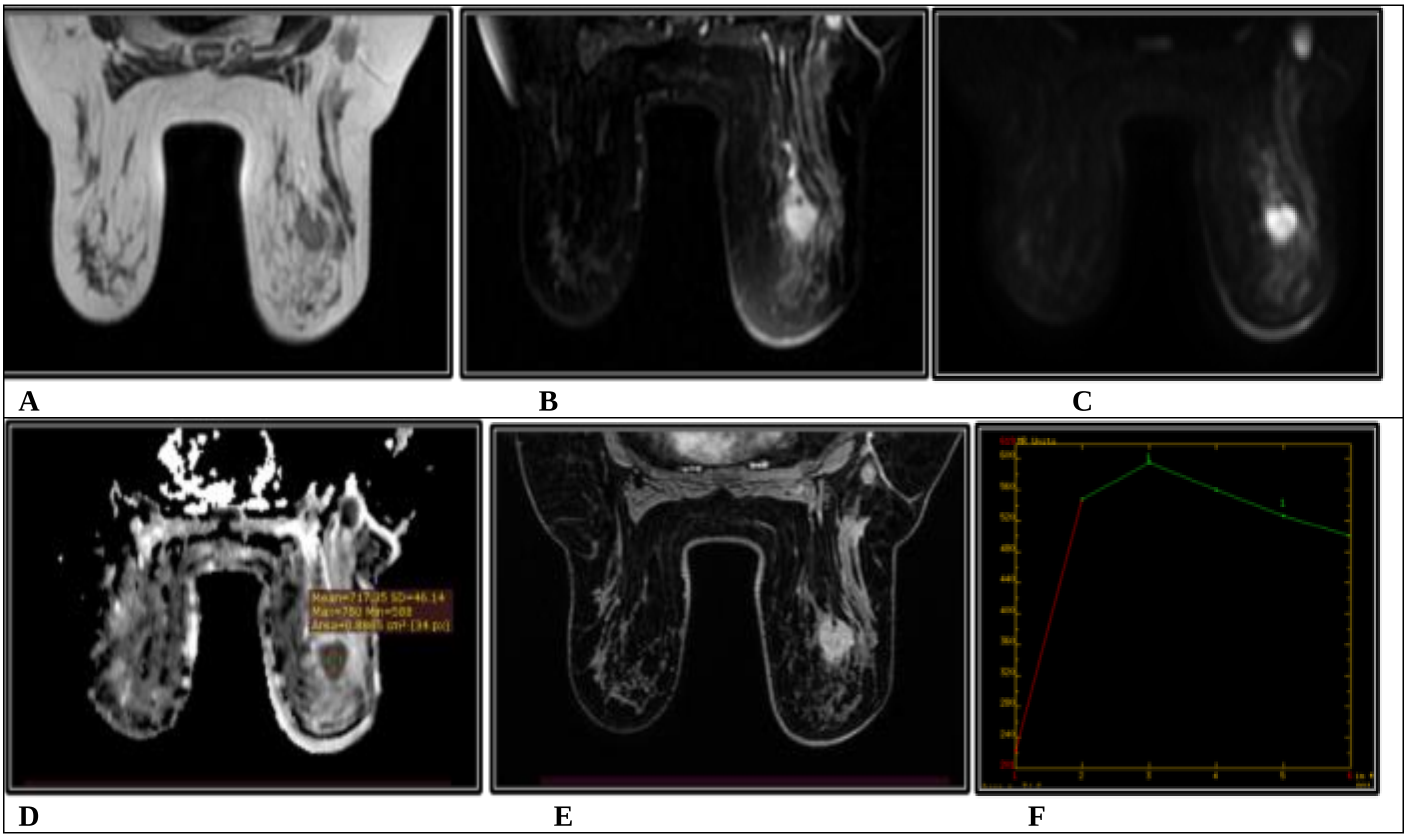

Figure 1: Case 1, Right breast invasive ductal carcinoma in a 45-year-old female patient. (A) Axial T2WI shows an ill-defined mass with spiculated margins at the upper outer quadrant of the right breast (opposite 11 O'clock) displaying isointense signal to the surrounding glandular tissues. (B) Axial STIR shows hyperintense signal to the surrounding glandular tissues. (C) Axial DWI sequence (b= 1000) shows hyperintense signal. (D) Axial ADC map shows hypointense signal denoting restricted diffusion with calculated mean ADC value = 0.72 x 10^{-3} mm^2/s. (E) In post-contrast series, the mass displays heterogenous enhancement. (F) Time-signal intensity curve reveals type III curve (wash-out pattern). The mass was correctly classified as malignant (BIRADS 5) according to combined imaging protocol.

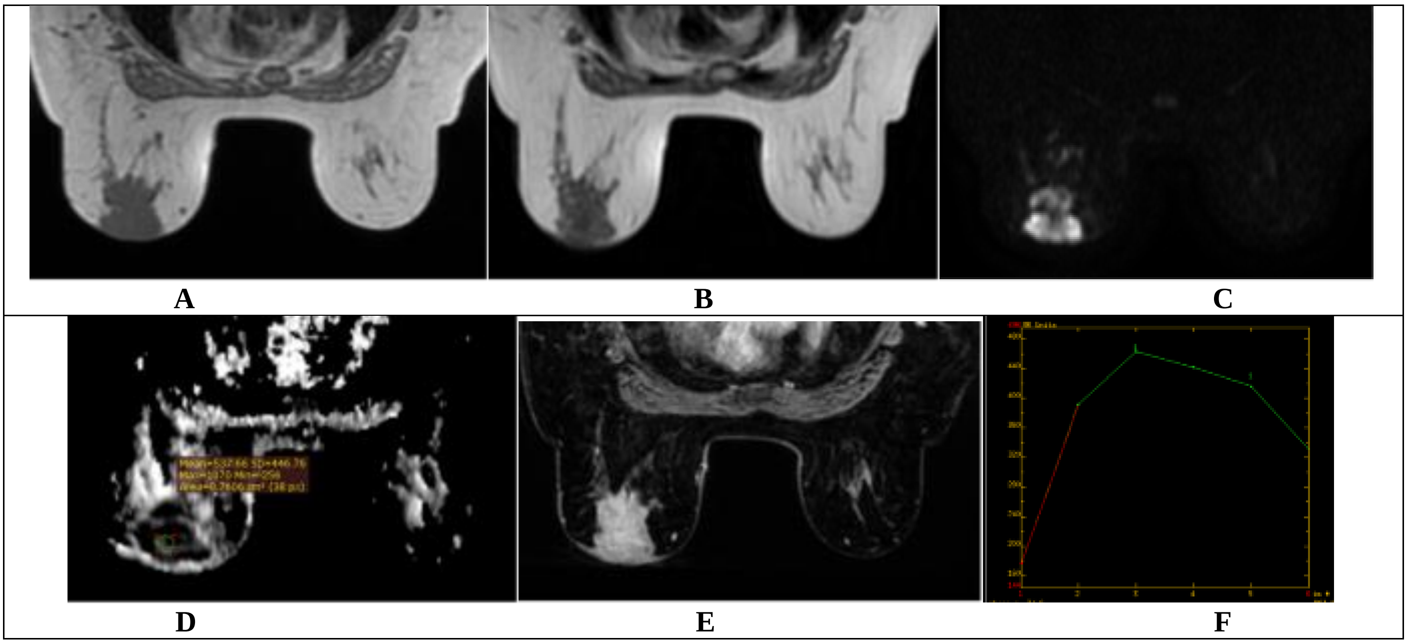

Figure 2: Case 2, Left breast invasive ductal carcinoma in a 55-year-old female patient. (A) Axial T1WI shows an ill-defined mass with spiculated margins at the retro-areolar region of the left breast displaying isointense signal to the surrounding glandular tissues. (B) Axial T2WI shows hypointense signal. (C) Axial DWI sequence (b= 1000) shows hyperintense signal. (D) Axial ADC map shows hypointense signal with calculated mean ADC value = 0.54 x 10^{-3} mm^2/s. (E) Post-contrast series displays heterogenous enhancement. (F) Time-signal intensity curve reveals type III curve (wash-out pattern). The mass was correctly classified as malignant (BIRADS 5) according to combined imaging protocol.

DISCUSSION

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females worldwide [(9)]. Obtaining an accurate diagnosis is of considerable importance as it informs the choice of treatment and the prognostic outcomes of the disease. Magnetic resonance imaging (MRI) has a higher sensitivity for the diagnosis of breast cancer than mammography and ultrasound [(10)].

Our study included 90 female patients; their ages ranged from 24 to 62 years with a mean of 48.9 ± 6.6 years old. In relation to the final gold standard reference, the age of patients with benign lesions was younger than that of those with malignant lesions.

As regards the patient complaint, 53.3% of patients complained of painless lump, 26.7% of skin thickening, 20% show nipple retraction, 13.3% of pain and 33.3% came for routine check-up. A similar finding was reached by **El Fiki *et al.*** [(11)], they found that the most common clinical presentation was the painless lump representing 58.8% of included patients.

In our study, the most common site for both benign and malignant breast lesions was the upper outer quadrant harboring 48 lesions (53.33%). Our results agreed with **El Bakry *et al.*** [(12)], who stated that the most common location of both benign and malignant lesions was the upper outer quadrant.

Our study reported that on T2WI, 20% of the benign lesions were isointense, 20% hypointense and 60% were hyperintense, whereas 20% of malignant lesions were isointense, 70% were hypointense and 10% were hyperintense on T2WI. Our study was broadly in line with **Khalil *et al.*** [(3)], who found that the lesion signal intensity in T2WI was a helpful indicative of its nature, as most of malignant lesions were hypointense in T2WI, opposing most benign lesions which displayed high signal intensity.

On STIR images, 96.7% of the examined breast lesions were hyperintense. A similar finding reached by **Telegrafo *et al.*** [(4)], who found that all breast lesions, including all malignant ones, were hyperintense on STIR images. Therefore, STIR sequences could be useful to detect breast lesions in all cases while their characterization could be performed by integrating TSE-T2 and DWIBS results.

On CE-MRI, 90% of the malignant masses showed heterogenous enhancement, 5% homogenous and 5% faint enhancement. However, 60% of the benign masses showed homogenous enhancement, 10% heterogenous, 10% faint and 20% rim enhancement. Our results were broadly in line with **Tezcan *et al.*** [(13)], who found that the heterogenous enhancement was noted in 88.6% and 37.8% of the malignant and benign masses respectively, while homogenous enhancement was noted in 10% and 59.5% of the malignant and benign masses respectively.

The most widely used form of DCE-MRI analysis is the assessment of the type of time–signal intensity curve (i.e., kinetic curve) by categorizing the washout pattern of a gadolinium contrast agent [(14)]**.** By DCE-MRI time–signal intensity curve, type I (persistent curve) was noted in 27 lesions: all were benign, type II (plateau curve) was noted in 18 lesions: 15 lesions were malignant and 3 lesions were benign, while type III (washout curve) was found in 45 lesions: all were malignant. A similar finding was reached by **Elwakeel *et al.* [1],** who found that 16 lesions showed persistent curve and by follow-up the 16 lesions were benign, 6 lesions showed plateau curve, and all the 6 lesions were malignant, and 8 lesions showed rapid washout curve, and all were proven by histopathology as malignant. Our results disagree with **El Bakry *et al.* [12]**, who reported that type I curve was noted in 39 lesions: 34 lesions were benign and 5 lesions were malignant; type II curve was noted in 12 lesions: 3 lesions were benign and 9 lesions were malignant; and type III curve was noted in 23 lesions: 1 lesion was benign and 22 lesions were malignant.

Our study revealed that the calculated UE-MRI sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were 90%, 80%, 90%, 80%, and 86.7% respectively. On the other hand, those for the DCE-MRI were 95%, 90%, 95%, 90%, and 93.3% respectively. It was revealed that there was no significant difference between the two methods and hence UE-MRI could be considered as a reliable diagnostic tool and a valid alternative to CE-MRI for evaluating breast lesions.

Our results have been found consistent with **Telegrafo *et al.* [4]**, who reported that UE-MRI sequences obtained sensitivity, specificity, diagnostic accuracy, PPV and NPV values of 94%, 79%, 86%, 79% and 94%, respectively, while CE-MRI sequences obtained sensitivity, specificity, diagnostic accuracy, PPV and NPV values of 98%, 83%, 90%, 84% and 98%, respectively with no statistically significant difference between UE-MRI and CE-MRI.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Elwakeel A, Omar S, Bayoumy A (2018):** Role of magnetic resonance imaging in differentiation of benign and malignant breast lesions. Menoufia Medical Journal, 31(2): 502-6.
2. **Leithner D, Wengert G, Helbich T *et al.* (2018):** Clinical role of breast MRI now and going forward. Clinical Radiology, 73(8): 700-714.
3. **Khalil R, Osman N, Chalabi N *et al.* (2020):** Unenhanced breast MRI: could it replace dynamic breast MRI in detecting and characterizing breast lesions? Egyptian Journal of Radiology and Nuclear Medicine, 51(1): 1-8..
4. **Telegrafo M, Rella L, Ianora A *et al.* (2015):** Unenhanced breast MRI (STIR, T2-weighted TSE, DWIBS): An accurate and alternative strategy for detecting and differentiating breast lesions. Magnetic Resonance Imaging, 33(8): 951-955.
5. **Czeyda-Pommersheim F, Martin D, Costello J *et al.* (2017):** Contrast agents for MR imaging. Magnetic Resonance Imaging Clinics, 25(4): 705-711.
6. **Tsien C, Cao Y, Chenevert T (2014):** Clinical applications for diffusion magnetic resonance imaging in radiotherapy. Seminars in Radiation Oncology, 24 (3): 218-226.
7. **Bickelhaupt S, Tesdorff J, Laun F *et al.* (2017):** Independent value of image fusion in unenhanced breast MRI using diffusion-weighted and morphological T2-weighted images for lesion characterization in patients with recently detected BI-RADS 4/5 x-ray mammography findings. European Radiology, 27(2): 562-569.
8. **Trimboli R, Verardi N, Cartia F *et al.* (2014):** Breast cancer detection using double reading of unenhanced MRI including T1-weighted, T2-weighted STIR, and diffusion-weighted imaging: a proof of concept study. American Journal of Roentgenology, 203(3): 674-681.
9. **Torre L, Bray F, Siegel R *et al.* (2015):** Global cancer statistics, 2012. Cancer Journal for Clinicians, 65(2): 87-108.
10. **Liu L, Yin B, Shek K *et al.* (2018):** Role of quantitative analysis of T2 relaxation time in differentiating benign from malignant breast lesions. Journal of International Medical Research, 46(5): 1928-1935.
11. **El Fiki I, Abdel-Rahman H, Morsy M (2015):** Assessment of breast mass: Utility of diffusion-weighted MR and MR spectroscopy imaging. The Egyptian Journal of Radiology and Nuclear Medicine, 46(4): 1327-1335.
12. **El Bakry M, Sultan A, El-Tokhy N *et al.* (2015):** Role of diffusion weighted imaging and dynamic contrast enhanced magnetic resonance imaging in breast tumors. The Egyptian Journal of Radiology and Nuclear Medicine, 46(3): 791-804.
13. **Tezcan S, Ozturk F, Uslu N *et al.* (2021):** The role of combined diffusion-weighted imaging and dynamic contrast-enhanced MRI for differentiating malignant from benign breast lesions presenting washout curve. Canadian Association of Radiologists Journal, 72(3): 460-469.
14. **El Khouli R, Macura K, Jacobs M *et al.* (2009):** Dynamic contrast-enhanced MRI of the breast: quantitative method for kinetic curve type assessment. American Journal of Roentgenology, 193(4): 295-300.