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The Role of Dynamic Contrast Enhanced and Diffusion Weighted MRI in Characterization of Suspicious Breast Masses

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ABSTRACT

Background: Early detection and diagnosis of breast cancer are mandatory for accurate management. Traditionally, mammography and ultrasound are the basic imaging techniques for the detection and localization of breast masses. The low sensitivity and specificity of these imaging tools resulted in a demand for new imaging modalities.

Aim of study: to evaluate the role of either diffusion weighted images-MRI or dynamic contrast enhanced MRI in differentiating malignant from benign breast lesions comparing with histopathology results.

Patients and Methods: from November 2016 to July 2017, a total of 20 patients presented with suspicious breast lesions BIRADS (4&5) were included in the study. All participants underwent breast DWI and DCE-MRI. Results were compared with histopathological results as a standard final diagnostic method. **Results:** the study included 20 female patients with suspicious breast lesions, there was 15 (75%) malignant lesions while benign lesions, while benign lesions were 5 (25%) cases. DCE-MRI was found to have a sensitivity of 86.7% and specificity of 80%. ADC cutoff value was found to have a value of $1.143*10^{-3}$, which was the best to differentiate between benign and malignant breast masses. DWI MRI was found to have sensitivity of 93.3% and a specificity of 80%.

Conclusion: DW-MRI alone gave the same performance as in combination with DCE-MRI. The comparison of DWI and DCE-MRI provides a dramatic superiority in the sensitivity, specificity and accuracy of breast DWI-MRI over other modality.

Keywords: Breast, DWI, DCE, BIRAD

INTRODUCTION

Breast cancer is the second leading cause of death after lung cancer[1]. It is commonest cancer in females[2]. Improving diagnostic methods will subsequently improve outcome in survival rate in patients with breast cancer[3]. New techniques in MR imaging of breast (i.e. DWI and DCE) are under the scope in recent literatures to study their sensitivity and specificity to differentiate between benign and malignant lesions[4]. The reported diagnostic indices for DCE are highly variable[5].

This variability can be allocated to lesion criteria used to differentiate from the start[6,7].

Lesion morphology and enhancement kinetics are commonly used biomarkers in DCE[8]. BIRAD MRI lexicon involves morphological evaluation of breast lesion. This can be achieved by evaluating margin, shape, enhancement pattern, shape and internal enhancement pattern[9]. Kinetic assessment is achieved by detecting initial and post-initial enhancement of breast lesion.

Diffusion-weighted imaging was added in many centers world-wide to increase sensitivity and specificity of conventional MRI[10,11]. Usefulness of breast DWI-MRI was reported by many literatures from 2002. The sensitivity was in range of 80%-96% and its specificity was in range of 46%-91%[12]. However, combination of DWI-MRI and DCE-MRI to differentiate lesion nature is now widely established[5].

PATIENTS AND METHODS

Patients

This was a prospective trial carried out in the period from November 2016 to July 2017 in diagnostic radiology department of Ain-Shams University Hospital. The study consisted of 20 female patients (age range 25-73 years old with mean± SD 9.05± 12.75years). Suspicious lesions were examined by triple maneuvers (history taking, clinical examination, sono-mammography and biopsy).

Ethical Approval

All study procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Inclusion criteria

1- Adult female gender only
2- Newly diagnosed lesions
3- BIRAD 4 & 5

Exclusion criteria

1- Recent breast trauma or surgery in the last 6 months

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2- Contraindication to MRI and / or contrast administration

Data Processing

All patients underwent full history, clinical examination, sono-mammography and pathology results were obtained retrograde. Through imaging process, DWI and DCE-MRI were added to conventional MRI of the breast to whole sample individuals.

Imaging protocols

All patients were examined using a 1.5 T magnetic resonance machine. Examination was done in prone position wearing a dedicated breast coil. MR imaging was done within the 1st days of diagnosis of a mass lesion by ultrasonography. Examination included image acquisition followed by image post-processing.

Image Acquisition

The formal MRI protocol poses localizing sagittal view, axial nonfat saturated T1WI obtained by FSE. All sequences' parameters as in table below:

Table 1: Criteria of image sequences in our study

Sequence	Criteria
T1	TR 450 ms TE 14 ms Slice thickness 3 mm Field of view 300–360 mm Matrix was 307 × 512
STIR	TR 7000–9000 ms TE 70 ms TI150 ms Slice thickness 3–4 mm Inter slice gap 1 mm Field of view (FOV) 300–360 Matrix was 307 × 512.
DWI	Sensitizing diffusion gradients in three orthogonal directions with b values of 0, 500, and 1000 s/mm2 were applied. The ADC maps were created automatically and the ADC values were calculated.
DCE-MRI	TR 4–8 ms TE 2 ms Flip angle 20°–25° Slice thickness 2 mm No inter-slice gap Field of view 300–360 mm Matrix was 307 × 512

Diffusion-weighted images were done prior to imaging by dynamic study using a diffusion-weighted echo-planar imaging (EPI) sequence by parallel imaging.

Dynamic contrast enhanced MRI has been made in the fat suppression-axial plane. The sequence used was FLASH 3 D GRE-T1W1. The dynamic contrast enhanced MRI was performed after injection of a bolus of gadopentetatedimeglumine, in a dose of 0.1 mmol/kg using an automated injector at a rate of 3–5 ml/s. Contrast injection was followed by a bolus injection of saline (total of 20 ml at 3–5 ml/s).

Image post-processing

Image post-processing includes Image subtraction which was obtained by subtracting each of pre-contrast images from each post-contrast series images, Creation of time to signal intensity curves for suspicious enhancing lesions and maximum intensity projection (MIP) views obtained through each orthogonal plane, producing sagittal, coronal and axial projections.

MRI interpretation

At first, STIR images were examined to investigate mass lesions. In dynamic contrast enhanced MRI,enhancement pattern (non-mass-or mass like enhancement) was determined and morphologic features were reported. For mass enhancement lesions, all criteria on STIR and T1 weighted images were recorded as well as enhancement pattern of the lesion. For non-mass lesions, the enhancement distribution, symmetrypattern, and internal enhancement were recorded.

Statistical analysis

A receiver operating characteristic (ROC) per modality analysis was performed to compare sensitivity and specificity of both groups. ROC curves were drawn, and the areas under curves were compared using the Z test. Sensitivity, specificity, accuracy, as well as positive and negative predictive values were evaluated.$P< 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 20 (SPSS Inc.) and MedCalc 10.5.4 (Med- Calc Software).

RESULTS

Among the included 20 patients,most of the lesions were located at the left side, which was found in 14 (70%) patients and, while the least frequent location of breast lesions encountered among the studied group was found in right side were the lesion found in 6 (30%) patient. Tables (2&3) show the pathology of breast lesions in the study group.

Table 2: Histopathology distribution of the study group.	
Histopathology	**Total (N=20)**
Benign	5 (25%)
Malignant	15 (75%)

Table 3: Histopathology distribution of the study group.	
Histopathology	**Total (N=20)**
Benign	
Acute mastitis	1 (5%)
Fat necrosis	1 (5%)
Hamartomas	1 (5%)
Intraductal hyperplasia	1 (5%)
Sclerosingadenosis	1 (5%)
Malignant	
DCIS	2 (10%)
IDC	8 (40%)
ILC	3 (15%)
ILC, IDC	1 (5%)
Undifferentiated Carcinoma	1 (5%)

In DWI 5 patient which represent (25%) of study group show facilitated diffusion in DW sequence while 15 patients (75%) show restricted diffusion. ADC value ranged from (0.54-1.605) x10-3 mm2/sec with mean 0.991x 10-3 mm2/sec and SD ±0.314.

Table 4: Comparison between benign and malignant according to ADC value x10-3 mm^2/sec			
Mean ADC value	**Benign**	**Malignant**	**Cut-off**
Mean±SD	1.341±0.400	0.874±0.371	1.143
Range	0.652-1.605	0.540-1.073	

In DWI, there was facilitated diffusion cases in patients with benign lesions in 4 (80.0%) and 1 (6.7%) of malignant pathology while one case (20.0%) of benign lesions and 14 cases (93.3%) show restricted diffusion of malignancy as in Table 6-6

And ADC value of benign lesions rang 0.652-1.605 x 10-3 mm^2/sec with mean 1.341 x 10-3 mm^2/sec and SD ±0.400, for malignant lesions rang 0.540-1.073 x 10-3 mm^2/sec with mean 0.874 x 10-3 mm^2/sec and SD ± 0.371. Table (4) shows statistically significant difference between benign and malignant lesions according to DWI and Mean ADC value.By using Chi-square, there was a difference between mean ADC levels at both sub-groups. This difference was statistically significant showing elevated levels at benign lesions (p=0.02).

And regarding site; 4 (80.0%) of benign lesion were in the left side and 1 (20.0%) in the right side and 10 (66.7%) of the malignant lesions were in the left and 5 (33.3%) in the right side.

Comparison between benign and malignant lesions according to type of dynamic curve in DCE-MRI show that type (I) seen in 3 (60.0%) benign lesions and not seen in malignant lesions, type (II) seen in 1 (20.0%) of benign lesions and 6 (40.0%) of malignant lesions while type (III) seen in 1 (20.0%) of benign lesions and 9 (60.0%) of malignant lesions so there are statistically significant difference between benign and malignant lesions according to type of curve as in table (5).

Table 5: Comparison between benign and malignant lesions according to type of dynamic curve in DCE-MRI			
Types of Curve	**Histopathology**		**p-value**
	Benign	**Malignant**	
I	3 (60.0%)	0 (0.0%)	0.005
II	1 (20.0%)	6 (40.0%)	
III	1 (20.0%)	9 (60.0%)	

ADC value sensitivity 93.3% specificity 80% positive predictive value 92%, negative predictive value 79% with diagnostic accuracy 81.3%. Diagnostic Indices were plotted in table 5.

Table 6: Diagnostic Indices of ADC, curve and both modalities			
	DWI	DCE-MRI	Both
Sensitivity	93.3%	86.7%	93.3%
Specificity	80%	80.0%	80%
PPV	92%	92.9%	93.18%
NPV	79%	66.7%	80.60%
Accuracy	81.3%	85%	87.03%

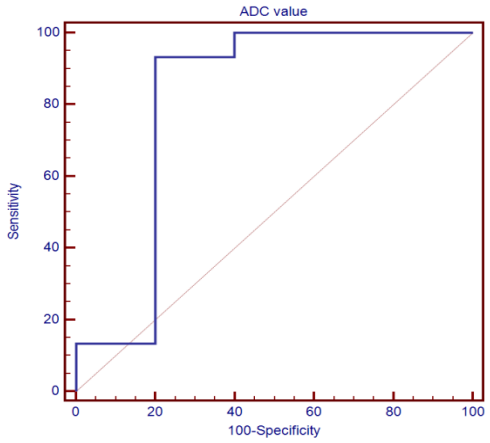

Figure 1: ROC curve sensitivity and specificity, diagnostic Performance of ADC value in Discrimination of benign and malignant.

Receiver operating characteristics (ROC) curve was used to define the best cut off value of combination ADC value and curve with sensitivity of 93.3% specificity of 80% positive predictive value of 93.18%, negative predictive value of 80.6% with diagnostic accuracy of 87.03%.

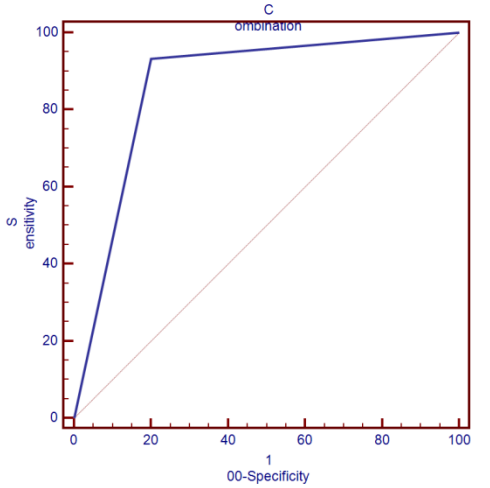

Figure 2: ROC curve, sensitivity and specificity, diagnostic Performance of combination ADC value and Curve in Discrimination of benign and malignant.

DISCUSSION

Dynamic contrast enhancement and diffusion weighted imaging are more accurate in detection, discrimination and follow up of breast lesions especially neoplastic subgroup[13]. Although, they provide data as regard lesion extent prior to surgical intervention and implemented widely in radiology centres. However, both modalities are expensive and not available for all university centers in addition to the scale of contraindications of MR imaging (e.g. contrast agents-related complications)[14].

Recently, advances in breast imaging were scoping on enhancement of specificity and accuracy of breast MRI techniques to detect breast cancers during surveys [15].

Our study sample was 20 patients with different pathologies of breast presented to our radiology department. The mean age at our study was 49 years. The mean age of both benign and malignant lesions was 55.4 and 46 respectively.

Similarly, El-Khouli et al[16] had mean of age 50 years. Shafqat***et al.***study showed a mean of age 44.4 years[6].

In our study, there was only one case presented with multiple foci, the histopathology was IDC. The differential diagnosis of multiple foci in single breast is not wide[17]. Invasive ductal carcinoma is known to present as multifocal (or multicentric) tumor in the breast[18].

In our study, invasive ductal carcinoma was present in 8/20 (45%) patients followed by invasive lobular carcinoma in 3/20 (20%) patients. InShafqat study, there were 38 (64.5%) malignancies, 26 (40%) were invasive ductal carcinoma, 7 (10.39%) invasive lobular carcinomas, 3 (4.68%) mucinous carcinoma and 2 (3.125%) were ductal carcinoma in situ. Benign lesions were 26 (35.6%) were 18 (32.14%)

fibroadenomas, 3 (4.68%) papillomas, and 5 (7.185%) were atypical ductal and 2 (3.125%) lobular hyperplasia. In El Khouli et al. (2009), seventy-eight lesions (77.2%) were malignant: 38 infiltrating ductal carcinoma, 21 mixed in situ and infiltrating ductal carcinoma, seven pure DCIS, seven infiltrating lobular carcinoma, and five miscellaneous. Twenty-two patients (22%) had benign lesions: 12 fibroadenomas; two papillomas; three fibrocystic changes; one atypical ductal hyperplasia (ADH); and five benign breast tissue, fibrosis and adenosis.Cai et al. (2014)[5] study consisted of 149 (36.68%) patients diagnosed with malignancy mainly of IDC (51.3%) while benign lesions were 85 (36.62%) mainly fibroadenoma and fibrocystic changes.

In our study, all lesions were hyointense in T1 and hyperintense or isointense on T2. These sequences are not conclusive in non-contrast fashion to elucidate the pathological nature of the lesion itself [18]. In our study, it has been found that restricted diffusion was found in all malignant lesions while facilitated diffusion was found in 4/5 patients as in table below. It was statistically proven (0.001).

Similarly, **Teama and co-workers** [19] found that of 10 patients with malignant lesion of their study, 6 patients showed restricted diffusion and out of 21 patients with benign breast lesions 19 patients showed non-restricted diffusion. The explanation of this phenomenon is from understanding the mode of action of DWI. The principle of the DWI is related to the Brownian movement of the water particles, which is restricted due to structure of the environment depending on the cellularity degree of the lesions [20].

The motion of water molecules is more restricted in tissues with a high cellular density (e.g., tumor tissue) or with lipophilic cell membranes acting as barriers in both the extracellular and intracellular spaces. In contrast, the motion of water molecules is less restricted in areas of low cellularity or where cell membranes have been destroyed [20].

A less cellular environment provides a larger extracellular space for the diffusion of water molecules[21], which may also freely transgress defective cell membranes to move from the extracellular into the intracellular compartment[15]. Therefore, the degree of water diffusion in tissue is inversely correlated with tissue cellularity and the integrity of cell membranes[14,22]. Diffusion-weighted imaging is used to visualize the degree of water molecule diffusion at in vivo MR imaging. Signal intensity at diffusion-weighted imaging is inversely proportional to the degree of water molecule diffusion, which will be influenced by the histologic structure; in other words, the signal intensity will imply the histologic structure [23].

In our study, the mean ADC value was higher in benign lesions than malignant lesions (1.3 vs. 0.9). It has been found that mean ADC values were statistically different between malignant and benign lesions (p=0.025).

Similarly, benign and malignant lesions had different ADC levels inCai et al.[5].

In **Teama*et al.***study has been found that the mean ADC value was significantly lower (0.5–0.9 · 10×3 mm^2/s) for malignant lesion in comparison with that of benign lesions (1.7–2.7 · 10×3 mm^2/s)[19].

InBostanBozkurt et al. (2016)[23] study, it has been found that the mean ADC values of malignant lesions were significantly different from that of benign lesions (1.04±0.29x10-3 mm^2 /s, Vs. 1.61±0.50x10-3 mm^2 /s) respectively, with high statistical significant difference (p=0.03).

The decreased levels of ADC values of malignant tumors reflect the biological characteristics of tumor[14], such as cellularity and water content. Malignant tumors consisted of intensely packed and randomly organized tumor cells interfere the effective movement and restrict diffusion of water particles [13].

Conversely, higher ADC values are usually associated with well-differentiated tumors or benign conditions[24]. In keeping with our findings, in previous studies, lower ADC values were reported to be associated with malignant breast tumors rather than benign conditions[13]. **Costantini *et al.*** [24]reported an inverse correlation between the tumor grade and ADC values**.**

The best cutoff value was defined as the value corresponding to the highest average of sensitivity and specificity. The cut-off value of ADC in our study was 1.143x10-3 mm2/s detected by the peak of the receiver operating characteristic curve yielded 93.3% sensitivity and 80% specificity for the discrimination of malignant lesions from benign.

InNajahstudy[25], the cut off value was 1.2 ×10-3mm2/s. InMatarstudy[15], the cut-off value was the same as both studies were held in the same department.

Similarly, inSi et al. study[13], the threshold of ADC was set at 1.19×10-3mm2 /s, the sensitivity and specificity were 72.4% and 85.7%, respectively.

Unlike our study, in **BostanBozkurt*et al.***[23], the cut-off value of 1.30x10-3 mm2 /s detected by the

peak of the receiver operating characteristic curve yielded 89.1% sensitivity and 100% specificity for the discrimination of malignant lesions from benign.

The discrepancy of ADC among studies is probably due to bias and different systems used [26].

In our study, ADC value sensitivity 93.3% specificity 80% positive predictive value 92%, negative predictive value 79% with diagnostic accuracy 81.3%. Indeed, DWI had sensitivity 86.7% specificity 80% positive predictive value 92.9%, negative predictive value 66.7% with diagnostic accuracy 85% for discrimination of benign and malignant.

InSi et al., DCI had 93.1% sensitivity and 75.0% specificity. While ADC had had a 72.4% sensitivity and 85.7%, specificity[13].

InBostanBozkurt et al. (2016)[23], ADC detected with receiver operating characteristic analysis yielded 89.1% sensitivity and 100% specificity for the differentiation between benign and malignant breast lesions.

InFusco et al. study, DCE-MRI has shown high sensitivity and specificity for breast cancer detection (89%, 100%) respectively[22].

InTeama et al. study, they found that DCE-MRI had sensitivity(92.3%), specificity (81%) and accuracy (85.3%)[19].

InMatar study, the sensitivity of using DWI was 85% specificity of 93.33%, positive predictive value of 94.4%, negative predictive value of 82.4% with diagnostic accuracy of 90.3%[15].

Cai et al. [5]showed 94% sensitivity and 77.8%specificity during breast imaging with DCE-MRI. **Domingues *et al.***studied the DWI as compared to conventional MRI and found high sensitivity and specificity (both, 92.3%) in the differentiation between benign and malignant lesions[27].

In our study, combined two modalities render indices like sensitivity of 93.3% specificity of 80%, positive predictive value of 93.18%, negative predictive value of 80.6% with diagnostic accuracy of 87.03%.

Similarly, the sensitivity and specificity of DCE-MRI combined with ADC was 92.9% and 79.3%, respectively [13].

In contrast, Teama and Coworkers reported a raised specificity from 81% to 90.5% and a slightly improved PPV from 75% to 77.8% without any improvement in sensitivity (53.8%). NPV was 76% and accuracy was 76.5% when combine both modalities[19].

In Hassan et al. study, applying an ADC threshold of 1.3×10*3 mm2/s sensitivity increased (on conventional DCE-MRI basis) from 86.95% up to 93.47% and the specificity from 91.22% to 96.49% in detection of malignancy with PPV of 95.55% in comparison to 86.95% for enhancement kinetics alone, which would have avoided biopsy for 10.5% (6/57) of benign lesions without missing any cancers[14].

CONCLUSION

DW-MRI alone gave the same performance as in combination with DCE-MRI. The comparison of DWI and DCE-MRI provides a dramatic superiority in the sensitivity, specificity and accuracy of breast DWI-MRI over the other modality.

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