Value of Dynamic Contrast Enhanced Magnetic Resonant Imaging in Detection of Local Recurrence Breast Cancer

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ABSTRACT:

BACKGROUND:
Breast cancer has become a major threat to female health in Iraq, with a cancer-related mortality rate of (23%). Despite advances in early diagnosis, treatment, and biomarker identification of breast cancer, it carries a high risk of recurrence, about 20-30% and substantially worse overall survival.

AIM:
To evaluate the role of dynamic contrast enhanced magnetic resonance imaging in differentiation between benign postoperative changes and recurrent malignant tumors in postoperative patient with breast cancer.

PATIENTS AND METHODS:
Cross-sectional prospective study was performed at MRI unit of Al-Imamein Al-Kadhimein Medical city in Baghdad/ Iraq within the period from January 2019 to January 2020. The study included 29 female patients with 42 detected lesions suspected as local recurrent.All women were recruited for dynamic contrast enhanced (DCE-MRI).

RESULTS:
The mean age of 29 patients were 50.58±10.01 years (range 21-66 years). of the 42 detected lesions 22 proved histopathologically as local recurrence (17 were invasive ductal carcinoma, 2 were ductal carcinoma insitu and 3 were invasive lobular carcinoma), the remaining 20 were benign postoperative lesions (8 were fibrosis, 5 were granulation tissue, 5 were fat necrosis, 2 were seroma and 1 was diffuse skin thickening and edema). DCE-MRI study show to have a sensitivity of 95.5%, a specificity of 90%, Positive Predictive Value of 91.3% Negative Predictive Value of 94.7% and an accuracy of 92.86% in differentiation between benign postoperative changes and recurrent malignant tumors.

CONCLUSION:
DCE-MRI is a valuable tool in evaluation of postoperative breast as it has high sensitivity and specificity in differentiation between benign postoperative changes and recurrent malignant tumor.

KEYWORDS: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MR), breast cancer, local recurrence.

INTRODUCTION:

Breast cancer is the most common female neoplasm (31% of Primary tumors in females), and the second-leading cause of death after cardiovascular disease [1]. Breast cancer has become a major threat to female health in Iraq, with a cancer-related mortality rate of (23%). It has been the highest-ranked malignancy among the Iraqi population in general since 1986 [2]. The development of high-quality mammography and ultrasound (US) imaging of the breast during the 20th century, have enabled breast cancer to be diagnosed with accuracy and often before clinical signs are apparent. Contrast-enhanced magnetic resonance imaging (MRI) of the breast was first performed in the late 1980s in women with biopsy of proven carcinomas. As compared to US and mammography, it has high sensitivity by using contrast material[3]. Despite advances in early diagnosis, treatment and biomarker identification of breast cancer, it carries a high risk of recurrence, about 20-30% of breast cancer patients experience recurrence and substantially worse overall survival so the earlier the diagnosis of recurrence, the better the outcome[4]. The aims of any follow-up are to detect early local recurrence or contralateral breast cancer and to diagnose and treat cancer and/or therapy-related diseases such as metastases and osteoporosis [5]. Although the most frequently used technique for breast imaging are mammography and ultrasound, contrast enhanced MRI is becoming increasingly significant, mainly because of its

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high sensitivity for detecting invasive breast cancer, that approach 100% in many studies[6]. Breast MRI has considered as a significant adjunct modality in the evaluation of mammographically occult breast lesions, tumor recurrence detection, and screening of women with high-risk cancer and those with breast implants. It is also applied in pre-operative tumor staging and in the evaluation of post-therapy residual disease [7].

AIM OF THE STUDY:
The aim of the study is to evaluate the role of dynamic contrast enhanced magnetic resonance imaging in differentiation between benign postoperative changes and recurrent malignant tumors in patient with breast cancer.

PATIENTS AND METHODS:
Study design: Cross-sectional prospective study was performed at MRI unit of Al-Imamein Al-Kadhimein Medical city in Baghdad/ Iraq within the period from January 2019 to January 2020. The study included 29 female patients with 42 detected lesions suspected as local recurrence; all patients underwent prior surgery for malignant breast cancer and are suspected to have local recurrence (20 patients had modified radical mastectomy, 8 patients had breast conserving surgery (lumpectomy versus quadrantectomy), and 1 patient had lumpectomy plus reconstructive surgery using breast implants). The age range was 21-66 years with a mean of 50.58±10.01 years. The indication of breast MRI was diffuse breast enlargement in 4 patients, palpable lump in 6 patients, and routine postoperative follow-up in 19 patients.

Inclusion criteria: All cases of postoperative breast cancer suspected for either local regional recurrence or post-operative complications by the clinical examination in conjunction with mammography and US.

Exclusion criteria: Patients with recent surgery (of 1 year duration) or recent history of radiotherapy (during the last 6 months following radiotherapy), patients with general contraindication to MRI examination, or its contrast media and patients could not lie in prone position.

Data collection: All the patients included in this study were subjected to full history. Current and prior breast imaging findings (ultrasound and/or mammography) were recorded. Then they referred to the MRI unit. Confirmation of 42 lesions was achieved later on by histopathological diagnosis (excisional biopsy in 17 lesions, fine needle aspiration cytology in 22 lesions), the remaining 3 lesions (7.1%) were

suggestive as benign post-operative changes by short interval follow-up every three months in whom regression and/or stability of the condition was seen. Ethical approval was taken from scientific committee of diagnostic radiology in the Iraqi board of medical specialization. An oral informed consent was taken from all patients included in the study.

MRI protocol: MRI examination was done in prone position on 1.5 tesla MR system (Magnetom Aera; A Tim and Dot system; Siemens Healthineers, Erlangen, Germany) with bilateral sixteen-channel breast coils. **The following sequences were done:** Axial T1WI, Axial T2WI , Axial T2 WI with fat suppression, Diffusion weighted image (DWI) (was done before contrast administration in axial plane at spin-echo sequence, at the following b-values (0,400,800 sec/mm2), ADC map was derived automatically in the MR system, and Dynamic T1 post contrast fat suppressed image (IV contrast (Dimeglumine Gadopentetate) injected using automatic injector, at a dose of 0.1 mmol/kg of body weight at a flow rate of 2 ml/s followed by flushing 25 ml of saline.

Image subtraction was obtained by subtracting each of the pre-contrast images from each post-contrast series images, creation of time to signal intensity curve for suspicious enhancing lesions and maximum intensity projection (MIP) views.

Image analysis was performed by 2 independent radiologists who were blinded to the final results. Size, signal intensity, enhancement pattern of each lesion was analyzed. Time–signal intensity curves were obtained on dynamic MR images by placing the region of interest (ROI) at the most enhancing area of the lesion. Fat suppression T2 WI was first examined to detect edema, postoperative seroma and hematoma. T1WI was also examined to detect fat within the lesion. Lesions were classified as enhancing lesion (a focus, a mass or an area of non-mass-like enhancement) and non-enhancing lesion. **A** focus is an area of enhancement measuring less than 5 mm in diameter. A mass is a three-dimensional, space-occupying lesion. It is usually visible on pre-contrast T1 or T2 weighted images. Masses were described in terms of shape, margin, and internal enhancement characteristics. Non-mass-like enhancement does not refer to enhancement of an area that was a mass nor was a focus, the enhancement categorized by distribution, internal enhancement pattern, and symmetric or asymmetric enhancement. Non enhancing lesion was categorized as benign changes.

Analysis of enhancement kinetics: 3 different phases were distinguished. The early phase (between contrast injection and the second post-contrast phase), the post-initial phase (3rd to 4th post-contrast phase) and the late phase (later than the 4th post-contrast phase). Types of curve were defined according to delayed phase as persistent Type I curve (continuous increase in signal intensity on each successive contrast enhanced images), plateau Type II curve (initial increase in signal intensity is followed by a flattening of the enhancement curve), and washout Type III curve (initial increase and subsequent decrease in signal intensity).

Regarding the morphologic analysis, the following features are considered to be suggestive of benign finding: non enhancing lesion, mass with a round, oval shape and well circumscribed margin; a high signal on T1 or T2 image, containing fat SI on T1WI and non-mass enhancements in focal or regional distribution. However, the presence of masses with irregular shape, irregular or spiculated margins, heterogeneous enhancement, and non-mass enhancement of a linear or segmental distribution especially those with clumped internal enhancement pattern, were considered as a feature suggestive of malignant finding. Persistent curve was defined as probable benign findings. On the other hand, washout curve was considered as probable malignant finding while the plateau curve was considered as intermediate finding and interpreted according to the morphological analysis.

Any associated finding (e.g. skin thickening or enhancement, chest wall invasion) and any lymphadenopathies were also reported.

Statistical analysis: was carried out using SPSS-26 (Statistical Packages for Social Sciences-version 26). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range. The significance of difference of different means (quantitative data) was tested using Students-t-test for difference between 2 independent means. The significance of difference of different percentages (qualitative data) was tested using Pearson Chi-square test (2-test) with application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the P value was ≤0.05.

RESULTS:

The study included 29 female patients with prior surgery for breast cancer with 42 detected lesions suspected as local recurrence. Age ranging from 21-66 years, mean (50.58±10.01years). Age of patients with malignant local recurrence was 51.4±13.16years (range 21-66 years,), whereas, age of patients with benign lesions was 50.15±8.61 years (range 33-63) years), with significant P value< 0.05.

Regarding location of detected lesions in relation to the operative tumor bed, 26 detected lesions were at operative tumor bed (20 benign postoperative lesions and 6 malignant local recurrence) and 16 lesions located at the same side away from the operative bed all of them were malignant local recurrence. These findings were statistically significant (P value < 0.0001), as showing in Table 1

Table 1: Shows location of lesions in relation to the operative tumor bed.

Location	Benign		Malignant		Total		P value
	N.	%	N.	%	N.	%	
At tumor operative bed	20	100	6	27.2	26	61.9	<0.0001
Away from operative bed	0	0	16	72.7	16	38	
Total	20	100	22	100	42	100	

Regarding the type of enhancement of detected lesions, 25 lesions were mass with heterogeneous enhancement (19 lesions proved to have local recurrences, while 6 lesions proved as benign postoperative changes) and this finding was statistically significant (P value < 0.0001). Mass with smooth marginal enhancement was found in 5 lesions, all of them proven as benign postoperative changes (100% sensitivity and 100% specificity for detection of benign lesions). Another 4 lesion show non-mass like enhancement (3 lesions proved to be local recurrences, while 1 lesion proved as benign postoperative changes). The remaining 8 lesions were not enhancing in dynamic study (all of them were proved pathologically to have

postoperative scar and area of fibrosis (benign postoperative changes), so non enhancing lesions have (100%) sensitivity and (100%) specificity for detection of benign lesions, All of these findings were shown in Table 2.

Table 2: Shows correlation between the type of enhancement and detection of recurrent malignant tumor.

Type of enhancement		Benign		Malignant		Total		P value
		N.	%	N.	%	N.	%	
Mass	Heterogeneous enhancement	6	30	19	86.3	25	59.5	<0.0001
	Marginal enhancement	5	25	0	0	5	11.9	
Non-mass-like enhancement		1	5	3	13.6	4	9.5	
No enhancing Lesions		8	40	0	0	8	19	
Total		20	100	22	100	42	100	

Regarding the margin of lesions, irregular margins were found in 26 lesions (11 local recurrence and 15 benign postoperative changes), regular smooth margins were seen in 11 lesions (8 proved as benign postoperative changes and 3 proved as local recurrence), spiculated margins were seen in 5 lesions (4 local recurrence and 1 postoperative scaring), these findings were statistically significant (P value 0.031), as shown in (Table 3).

Table 3: Shows correlation between the margins of the lesions and detection of recurrent malignant tumor.

Margins of the lesions	Benign		Malignant		Total		P value
	N.	%	N.	%	N.	%	
Irregular	11	55	15	68.1	26	61.9	0.031
Regular	8	40	3	13.6	11	26.1	
Spiculated	1	5%	4	18.1	5	11.9	
Total	20	100	22	100	42	100	

Regarding the types of kinetic curve on DCE-MRI: Type I (persistent) curve was noted in 12 lesions (2 local recurrence and 10 benign postoperative changes). Type II (plateau) curve was noted in 9 lesions (7 local recurrence and 2 benign postoperative changes). Type III (wash out) curve was noted in 13 lesions (all of them local recurrence). The remaining 8 lesions were not enhancing so no kinetic curve can be obtaining. These findings were statistically significant (P value <0.0001), as shown in (Table 4).

Table 4: Shows correlation between type of kinetic curve and detection of recurrent malignant tumor.

DCE-MRI Kinetic curve assessment	Benign		Malignant		Total		P value
	N.	%	N.	%	N.	%	
Not enhancing	8	40	0	0	8	19	
Type I	10	50	2	9	12	28.5	
Type II	2	10	7	31.8	9	21.4	
Type III	0	0	13	59	13	30.9	<0.0001
Total	20	100	22	100	42	100	

According to the overall findings of DCE-MRI interpretation and in comparison, with the histopathological results for each lesion, one true malignant lesion was misdiagnosed as benign lesion, and 2 true benign lesions were misdiagnosed as a malignant (Table 5). So DCE-MRI study has an overall sensitivity of 95.5%, specificity of 90%, positive likelihood Ratio 9.55, Negative Likelihood Ratio 0.05, Positive Predictive Value (PPV) of 91.3%, Negative Predictive Value (NPV) of 94.7% and an accuracy rate of (92.86%) in differentiation between benign postoperative changes and recurrent malignant tumors.

Table 5: DCE-MRI in relation to histopathological results among the patients.

DCE-MRI	Histopathological result						P value
	Benign		Malignant		Total		
	N.	%	N.	%	N.	%	
Benign	18	9%	1	4.5	19	45.2	
Malignant	2	10	21	95.4	23	54.7	<0.0001
Total	20	100	22	100	42	100	

The final diagnosis of the 42 breast lesions was: 22 (52.3%) malignant lesions, (17 invasive ductal carcinoma, 2 ductal carcinoma insitu (DCIS) and 3 invasive lobular carcinoma).
The 20 (47.6%) benign lesions (8 fibrosis, 5 granulation tissue, 4 fat necrosis, 2 seroma and 1 diffuse skin thickening and edema).
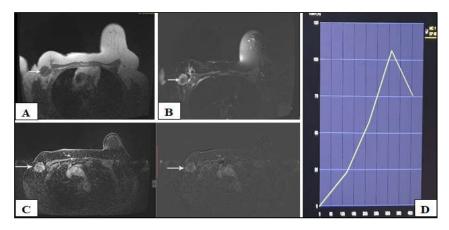 Figure 1 and 2 show MR images of 2 patients included in the study.

Figure 1: 59 years old female with history of R. mastectomy for breast cancer 7 years ago present with pain and palpable lump at lateral aspect of mastectomy bed
A. T1WI.
B. fat suppression T2WI.
C. dynamic contrast subtraction image.
D. time intensity curve. There rounded heterogeneously enhancing mass with irregular margin at lateral aspect of mastectomy bed in region of axillary fold, the mass show low SI in T1 and T2 with type III washout kinetics curve. Histopathology reveals recurrent malignant tumor (invasive ductal carcinoma).
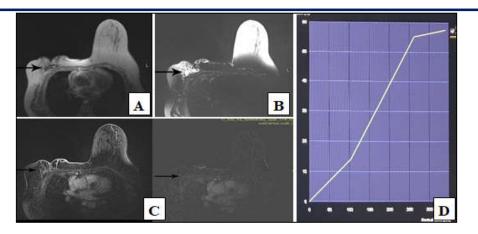
Figure 2: 56 years old female with history of Rt. mastectomy for breast cancer 2 years ago present with suspectious lesion at lateral aspect of mastectomy bed on routine follow up US.

A. T1WI.

B. fat suppression T2WI.

C. dynamic contrast with subtraction image.

D. time intensity curve. There is heterogeneously enhancing lesion of irregular shape and margin located at lateral aspect of the operative scar, showing intermediate SI on T2 weighted image, low SI in T1, with type I kinetic curve in dynamic study. Histopathological reveals granulation tissue with fibrosis.

DISCUSSION:

MR imaging is useful in evaluation of the postoperative breast, in the case of suspected local recurrence when the conventional imaging techniques (i.e., mammography and US) are inconclusive or in conflict with the physical examination or other clinical indicators as distortion of normal breast architecture leads to difficulty in distinguishing between normal postsurgical changes and locally recurrent breast cancer [8].

In current study of 42 detected lesions, 22 proved as true recurrent malignant tumor, the most frequent malignant tumor recurrence were invasive ductal carcinoma (17 lesions) which represented (40.5%) from total detected lesions and (77%) from malignant tumor recurrence lesions, while 20 lesions were benign postoperative changes and the most frequent benign postoperative lesions were fibrosis which represented (19.4%) of total detected lesion and (40%) from the benign postoperative changes, these results were similar to the results of Saleh OI et al. [9] and Li et al [10] studies.

In the current study MRI misdiagnose 2 benign lesions as a malignant, and 1 malignant lesion as a benign. An overlap is noted between the morphological characteristics and the enhancement kinetics of some malignant and benign lesion leading to improper diagnosis of these lesions. The 2 false positive lesions were presented as focal areas of non-mass enhancement with type II time-signal intensity curve on kinetic analysis, excisional biopsy done

for them and both were reported pathologically as a granuloma with no evidence of malignant cells infiltration. These results were in agreement with that of Saleh OI et al. [9]. While Hyunkyung et al. [11] stated that 7 false positive cases among a total number of sixteen cases showing suspicious features and explain it due to short post radiation period (12 month) as the scarring tissue enhanced after the operation by 6 month without radiation and up to 18 month after the radiotherapy.

The current study shows that DCE-MRI have a sensitivity of (95.5%), a specificity of (90%), and overall accuracy rate of (92.86%) in differentiation between benign postoperative changes and recurrent malignant tumors and these results were in concordance with previously reported studies (Saleh OI et al. [9], Drukteinis et al [12], Dershaw et al [13] and Brennan et al [14]). A study done by EL-Adalany et al [15] states that DCE-MRI had (100%) specificity in differentiating postoperative changes from recurrent tumor, but this difference was not significant.

Fibrosis is a common sequela of radiation therapy in the breast. Fibrotic masses can be irregular, often with spiculated margins [16]. Distortion of the surrounding breast architecture can also be seen. These findings overlap with those of cicatrizing tumors, one of the challenges in evaluating the postoperative breast is therefore the differentiation between postoperative or post-radiation therapy scarring and tumor

recurrence[17]. Previous studies done by Drukteinis et al [12] and Devon et al [17] stated that MR imaging has been shown to be useful in differentiating fibrosis and granulation scar tissue from tumor recurrence; in particular, non-enhancing areas have a high NPV for malignancy (88-96%).

In the current study 8 lesions were detected and reported as postoperative fibrosis in tumor bed, in all of them MRI showed an area of architectural distortion and no enhancement was observed on dynamic post-contrast study. Five lesions were proved pathologically as granulation tissue (granuloma), 3 of them show mild enhancement with type I kinetic curve and the remaining 2 lesions were misdiagnosed by MRI to be recurrent malignant tumor as one of them showed spiculated margin, heterogeneous enhancement and Type II time signal intensity curve, and the other case showed irregular margin, heterogeneous enhancement and Type II time signal intensity curve.

Fat necrosis is a common and challenging pitfall in interpretation of post-breast conservative surgery and MR imaging. However, when identified appropriately, this finding can be placed in the BI-RADS 2 or BI-RADS 3 category. The margins and the enhancement pattern of fat necrosis may be indistinguishable from recurrent malignant tumor. The clue for the diagnosis of postoperative fat necrosis is the presence of fat on T1WI [12, 18]. In current study, the present of fat in the detected lesion which appear as high signal on T1WI was present in 5 lesions which were proved pathologically to be fat necrosis, these result is in agreement with EL-Adalany et al [15] and Mansour et al [19] studies.

Postoperative seromas are common following breast surgery; in this study 2 lesions (4.76%) were showed to be postoperative seromas, both have high signal on STIR images, regular smooth margins, showing thin smooth marginal enhancement and Type I curve and this was in agreement with Drukteinis et al [12], Devon et al [17] studies which stated that postoperative seromas have high signal intensity (fluid signal) on T2-weighted images and Smooth, thin rim enhancement.

In the current study we had 4 lesions show non-mass-like enhancement, 3 lesions shows as an area of clumped non mass-like enhancement at MRI, one of them showed Type II time signal intensity curve and the remaining 2 cases showed Type III time signal intensity curve. Biopsy from these 3 lesions revealed recurrent ductal carcinoma. These results were in agreement with several previously reported studies (Drukteinis et al [12], Devon et al [17] and Kinoshita et al [18]. these studies showed that ductal and clumped non-mass-like enhancement has high positive predictive values for malignancy of up to (85%) and (60%), respectively. The remaining small focal area of non-mass-like enhancement at the lumpectomy site with Type I kinetics curve. Follow-up of this lesion by ultrasound and dynamic contrast enhanced MRI revealed that the lesion have stationary course along this year with no development of any malignant changes. Drukteinis et al [12] and Dershaw et al [13] stated that a minimal or small focal area of enhancement or thin linear non-mass-like enhancement can be seen for up to 18 months (in some cases even longer) without nodularity or an associated mass and they consider it probably benign and appropriate for 6-month MR imaging follow-up. While Saleh OI et al.[10] stated that 7 cases presented as focal, regional or linear areas of non-mass enhancement and all of them proved as recurrent ductal carcinoma.

Regarding to the kinetics curve types obtained on DCE-MRI, the result was highly significant statistically, as all lesions (100%) of type III kinetic curve were proved pathologically as malignant tumor recurrence. Lesions demonstrating a type II kinetic curve were somewhere in between but mainly malignant (77.8%) and (22.2%) were benign, while type I were mainly benign in (83.3%), versus (16.7%) malignant lesion. These results were in agreement with Saleh OI et al. [10] EL-Adalany et al [15] and Tan et al [20] studies.

The recurrence of the tumor in surgically treated breast usually occurs at the surgery bed, adjacent to the operative margin, However it may recur elsewhere in the breast, axilla or in chest wall [21]. Recurrence away from operative bed in multifocal and multicentric lesions is detected by MRI in our study in 6 cases and 16 lesions proved histopathologically as recurrent malignant tumor were detected away from operative bed. This is one of the advantages of the MRI over the US which usually misses these multifocal and multi-centric lesions [22]. In comparison with Saleh OI et al. [9] study the tumor recurrent was more commonly occur at lumpectomy site. This difference occurs because they include only the patients after breast conservative surgery and exclude the post mastectomy patients.

CONCLUSION:

Dynamic contrast enhanced MRI is a valuable tool in evaluation of postoperative breast as it has high sensitivity and specificity in differentiation between benign postoperative changes and locally recurrent malignant tumor. The DCE-MRI is an examination technique that offers not only information on lesion cross sectional morphology but also on functional lesion features such as tissue perfusion and enhancement kinetics.

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