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Original Research Article

Distinguishing Benign and Malignant Breast Mass using kinetic Curve of Dynamic contrast Enhanced MRI Scanning in Comparison with Histopathological Results

Ban Abbas Semander Al-Maammory* Huda Ali Rasool Hussain
College of Medicine, University of Babylon, Hilla, IRAQ

*E-mail:bansemander@gmail.com

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Abstract

MRI is now emerging as a very exciting and potentially powerful tool for the imaging of breast abnormalities in addition to the conventional modalities such as mammography and sonography. MRI imaging with its rich soft-tissue contrast and excellent tissue differentiation, thin-section, multiplanar capability, with no ionizing radiation, offers the possibility of better lesion characterization than can be obtained with conventional imaging methods. This study was conducted to assess the accuracy & the diagnostic value of the TSI - curve (kinetic curve) of DCI MRI in distinguishing benign and malignant breast mass in comparison with histopathological results. Sample of 40 female patients aged from 30-70 years with a mean age of 49 year having breast mass with clinical suspicion were subjected to mammographic and ultrasonic classification after clinical examination in the breast clinic and referred to the MRI unit. MRI were done and breast masses assessed according to their shape, pattern of enhancement and kinetic curve. Histopathological confirmation was obtained for all patients .twenty nine cases show kinetic curve of type 3 while type 2 curve in 9 cases and 2 cases revealed type 1 curve.by histopathological study, 28 case of type 3 curve are malignant, one case is benign. 4 case of type 2 are malignant and 5 cases are benign . Two cases of type 1 curve are benign . So MRI is good technique for assessment of breast masses and extension to other tissue and sensitive for detection of multifocal breast lesions and bilateral breast masses and local recurrence.

Key Words: **MRI** -magnetic resonance imaging, **DCE**= dynamic contrast enhancement, **TSI**- time signal intensity .

الخلاصة

التصوير بالرنين المغناطيسي يظهر الآن كأداة مثيرة للغاية، ويحتمل أن تكون قوية لتصوير اعتلالات الثدي بالإضافة إلى الطرائق التقليدية مثل التصوير الشعاعي والموجات فوق الصوتية. ان التصوير بالرنين المغناطيسي مع التباين الغني للأنسجة اللينة وتمايز الأنسجة الممتاز، شرائح رقيقة ،القدرة متعدد المستويات، مع خلوه من الإشعاع المؤين، يتيح إمكانية توصيف الآفة أفضل مما يمكن الحصول عليه مع أساليب التصوير التقليدية. اجريت هذه الدراسة لتقييم الدقة وقيمة التشخيص لمنحنى الحركية للتصوير بالرنين المغناطيسي باستخدام الصبغة في التمييز بين كتلة الثدي الحميدة والخبيثة بالمقارنة بالنتائج المرضية في الأنسجة. تم اخذ ٤٠ عينة من المرضى الإناث الذين تتراوح أعمارهم بين ٣٠-٧٠ عاماً مع متوسط عمر ٤٩ سنة مع وجود كتلة الثدي و الاشتباه السريري، حيث تعرضوا لتصنيف التصوير الشعاعي والموجات فوق الصوتية وبعد الفحص السريري في عيادة فحص الثدي تم تحويلهم لوحدة التصوير بالرنين المغناطيسي... حيث تم التصوير بالرنين المغناطيسي وتقييم كتل الثدي وفقا للشكل، ونمط اخذ الصبغه ومنحني الحركية. وكان الحصول على تأكيد الفحوصات المرضية للانسجة لجميع المرضى. وتبين تسعة وعشرين من الحالات اظهرت نوع منحنى الحركية ٣ بينما المنحنى نوع ٢ في ٩حالاتو حالتان كشفت عن منحنى نوع ١.وحسب الدراسة النسيجية تبين ان ٢٨ حالة من منحنى نوع ٣ خبيثة و حالة واحدة حميدة، ٤ حالات من النوع ٢ خبيثة و ٥ حالات حميدة وحالاتان نوع ١ حميدة. لذلك فان التصوير بالرنين المغناطيسي يعتبر تقنية جيدة لتقييم كتل الثدي وامتدادها للأنسجة الأخرى وحساسة للكشف عن آفات الثدي متعدد البؤر وكتل الثدي الثنائي والتكرار المحلي للورم.

Introduction

Advancement in fighting cancer of the breast has been obvious by improvement of effective, less invasive techniques for diagnosis and treatment .MRI is diagnostic technique that uses a mixture of a huge magnet radio waves, and a supercomputer to create meticulous images of the body organs and structures, major improvement has been made in the development for the breast MRI [1].

Breast DCE-MRI is discovery widespread clinical application as an addition diagnostic method to Mammography and US. DCE-MRI offers spatial three-dimensional data and time-based resolution, and has revealed very high sensitivity for breast cancer [1,2].

It has been particularly valuable in indicating the extent of biopsy-proven cancers, specially invasive lobular carcinoma (ILC) and ductal carcinoma in situ (DCIS), which historically were not well imaged with other imaging techniques. In such situations, the MRI may be useful in guiding both the surgeon and the patient regarding the appropriate choice of breast conservation versus mastectomy [2-4].

The early enhancement rate of lesion in the post -contrast phase (also called as ‘‘slope of enhancement’’ or ‘‘enhance-ment velocity’’ works as a differential diagnostic measure, with malignant lesions showing faster and stronger enhancement than benign lesions [2].

Our study expressed a new technique to improve the extraction of kinetic types from dynamic enhanced-MRI breast lesions, which possibly will support radiologists in their interpretation [3].

Kinetic curve (fig.1) is categorized as type-1a if the lesion remains to enhance over the whole providing time. and It is named as type-1b if in the late post-contrast period the signal obtain is slowed down, producing a bowing of the curve. [5].

The curve is categorized as type 2 if the signal after the early increase is plateau. [5]

A curve type 3 is expressed in cases where there is rapid wash-out of contrast material taking place directly after the signal intensity highest [5].

Type 1 (1a and 1b) were more expected to be benign, while lesions with type 2 (suspicious) and with type 3a rapid wash-out of contrast have a tendency to be malignant [1,2].

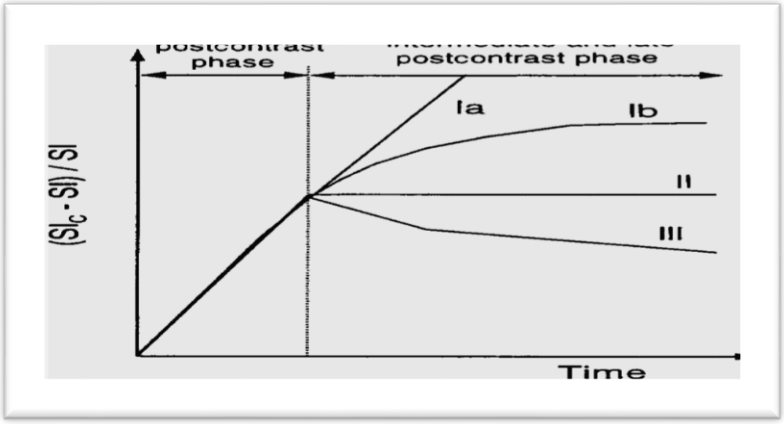


Figure 1. MRI enhancement kinetics (qualitative type). Diagram of the TSI- curve Types [6].

The "ACR BI-RADS "classification:-.

BI-RADS (table 1) is stands for "Breast Imaging Reporting And Data System" and was established by "American College of Radiology". designed to standardize breast imaging reporting and to reduce confusion in breast imaging interpretations. It also facilitates results monitoring and quality assessment.

It is a scheme for putting the outcomes from mammography. screening (for breast cancer diagnosis) into small

number of "well–defined categories" although BIRADS started out for practice with breast screening mammography, it was later adapted for use with MRI and US as well.

Table 1: BIRADS classification

Final Assessment Categories			
	Category	Management	Likelihood of cancer
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examinations	n/a
1	Negative	Routine screening	Essentially 0%
2	Benign	Routine screening	Essentially 0%
3	Probably Benign	Short interval-follow-up (6 month) or continued	>0 % but ≤ 2%
4	Suspicious	Tissue diagnosis	4a. low suspicion for malignancy (>2% to ≤ 10%) 4b. moderate suspicion for malignancy (>10% to ≤ 50%) 4c. high suspicion for malignancy (>50% to <95%)
5	Highly suggestive of malignancy	Tissue diagnosis	≥95%
6	Known biopsy-proven	Surgical excision when clinical appropriate	n/a

BI-RADS-MRI lexicon was produced in 2003 as a part of the ACR's Breast Imaging Reporting and Data System Atlas [6,7].

Grading BI-RADS

1- Normal
2- Benign
3- Probably Benign / Imaging follow up or tissue
4- Probably Malignant . /tissue biopsy
5- Malignant . / tissue biopsy

Patient and Methods

During the period from December 2016 to July2017, 40 women with suspected breast cancers referred from the breast clinic at the Hilla- teaching general hospital to the MRI unit where breast DCE-MRI done.

We classified our patients into 3 age groups ,group 1(30-39 year) group 2 (40-49 year) and group 3 (50 and above) all patients ages range from 30-70 years with a mean age of 49years. Marital state, obstetrical history and breast feeding, family history of breast cancer or other, previous breast problems, and history of contraceptive pills or any HRT. were added to the data of each patient.

Patients complain and Clinical presentation, physical breast examinations were performed Mammography and US were done for all .patients and FNAC were done for most patients of the suspected malignant masses.MRI done for patients with BI-RADS III, IV and V were carried out using Philips-MR System Achevia machine 1.5 Tesla unite magnet strength.

Every patient was examined in a prone position on the MR table with her both breasts emerge within a special breast coil and bilateral breasts where examined according to the following breast MRI protocol : 3 mm slice thickness and 1mm gap was applied in certain sequences staring with T2 axial,T1axial, DWI, T2 fat suppression and sometimes coronal T2 (when needed) , then a dynamic study with IV contrast; gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA) 0.1-0.2mmol/ kg with20ml normal saline ; by injector devise and post

contrast sequence of bilateral 3D spatial and temporal resolution (eTHRIV) and (VISTA).

The total examination time takes about 40-60 minutes for each patient, then the curve is displayed by choosing the area of maximum enhancement or ROI(region of interest) and data were transformed to the work station where they were studied carefully and reported by an expert specialist ; who described the site, morphology, multiplicity of the lesion , pattern of enhancement and the type of curve displayed for each detected mass as well as extension of the lesion, any axillary LAP and/ or chest wall invasion and finally gave the conclusion by applying the BIRADS classification .

Histopathological studies following excisional biopsies and/ or mastectomy were obtained 31cases show malignant cell and 9 cases show benign cells .

Results

Patients referred to MRI unite with the age distribution as follow 22.5% of patients of group 1 (30-39year) , 32.5% within group2 (40-49year) and 45 % were group3 (50 year and above) . the higher frequency of breast cancer was(51.6%) seen in group 3 and lowest frequency was (16.1%) seen in group 1 .

Our study show that patients referred with different breast clinical presentation , Painless palpable mass was the predominant features of 29 patients " 68 % " of cases .

According to anatomical distributions of breast masses, the UOQ (upper outer quadrant) of breast have more predominance of malignancy seen in 62.5 % of breast cancer in our samples.

A comparison between the mean size and standard deviation between MRI and US is shown a mean size measured by US was 18.2 mm while MRI mean size of breast masses was 25.5mm .

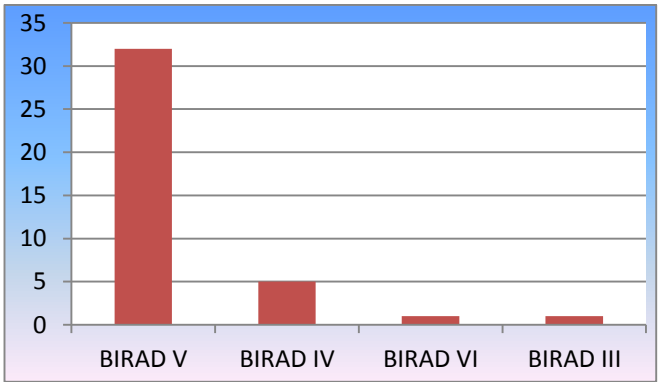
There was significant difference between US and MRI in size of breast mass ($P<0.05$).

LAP had been found in 20 patients of our sample , all take malignant curves (type 3 curve) . in histopatology 9 patients proved to be malignant and other 11 patients had benign reactive enlarged lymph nodes (55%).with high false positive rate as 11 .

MRI BIRADS classification **:**32cases were classified as BIRADS V, 5 cases as BIRADS IV ,one case was BIRADS VI and 2 was BIRAD III as shown in table 2 and figure 2.

Table 2. MRI BIRADSclassification in the study sample.

	BIRAD classification	NO.	%
1	BIRAD V	32	80
2	BIRAD IV	5	12.5
3	BIRAD III	2	5
4	BIRAD VI	1	2.5
Total		40	100



Graph 2: MRI BIRADS classification in the study sample

MRI diagnostic validity of MRI " BIRADS" in correlation with cytological diagnosis as shown in(table 3)were performed Sensitivity, specificity, accuracy and positive predictive value were calculated according to cytology and were 93.5 %, 55.5%, 85 % and 87.87 % respectively.

Table 3: The MRI findings by BIRAD of patient group with and without CA breast in correlation to Histopathology result

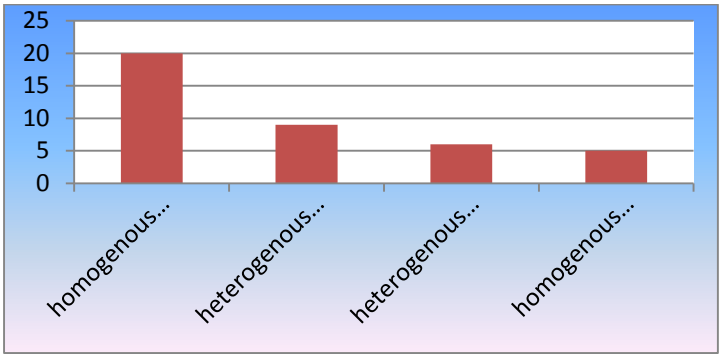
		Histopathology		Total
		Patients with Ca	Without ca	
MRI examination	Positive	29	4	33
	Negative	2	5	7
Total		31	9	40
Accuracy			85%	
Sensitivity			93.5%	
Specificity			55.5%	
PPV			87.87%	
NPV			71.4%	
P value		0.003	P<0.05	

P. value of MRI –BIRAD =0.003 (p<0.05 is significant)

MRI enhancement pattern predominating 50% of cases with homogeneous intense enhancement and 22.5 % with heterogeneous intenseenhancement this shown in table 4 and graph 3.

Table 4: MRI enhancement pattern of breast masses

	MRI pattern of enhancement	N0	%
1	Homogenous intense	20	50
2	Heterogeneous intense	9	22.5
3	Heterogeneous moderate	6	15
4	Homogenous moderate	5	12.5
Total		40	100



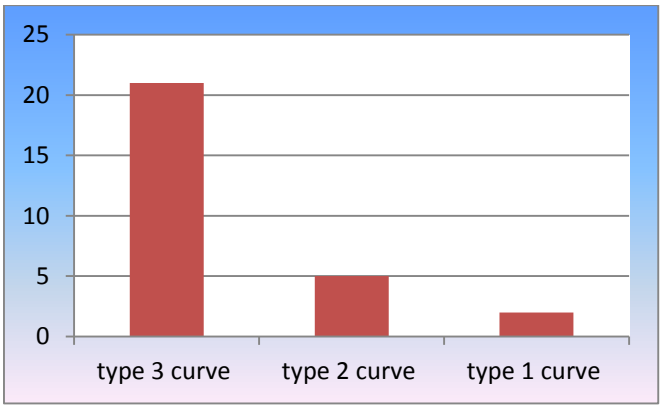
Graph 3: MRI enhancement pattern of breast masses

Kinetic analysis and temporal resolution curves found in our cases are shown in table 5 (a)and fig. 4 (a)displayed type 3 curve in 73.5 % type 2 curve in 20.6% and type 1 curve in 5.9% in unifocal breast mass .

While in table 5(b) and fig.4(b) type 3 curve was 66.7 % and type 2 curve was 33.3 % in multifocal breast mass .

Table 5(a): MRI kinetic analysis and temporal resolution of unifocal breast mass

	kinetic analysis and temporal resolution	*No*	%
1	Type 3 curve	25	73.5
2	Type 2 curve	7	20.6
3	Type 1 curve	2	5.9
Total		34	100

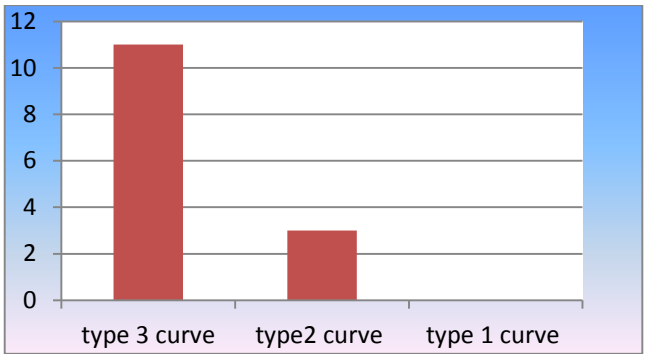


Graph 4 (a): MRI kinetic analysis and temporal resolution of unifocal breast mass

In our study six cases had more than one foci of breast cancer, two cases were ipsilateral multifocal and four cases were bilateral breast carcinomas , all had been detect by MRI and proved by histopathology

Table 5 (b): MRI kinetic analysis and temporal resolution of multifocal breast mass.

	kinetic analysis and temporal resolution	No	%
1	Type 3 curve	4	66.7
2	Type 2 curve	2	33.3
3	Type 1 curve	-	-
Total		6	100



Graph 4 (b): MRI kinetic analysis and temporal resolution of multifocal breast mass.

and according to the accuracy , sensitivity and specificity were 90 % , 90.3 % and 88.8 % in respectively of DCE-MRI kinetic curve in correlation to histopathological result (table 6).

Table 6: The MRI findings by Kinetic curve of patient group with and without CA breast in correlation to Histopathology result

		Histopathology		Total
		Patients with Ca	Without ca	
MRI examination	Positive	28	1	29
	Negative	3	8	11
Total		31	9	40
Accuracy			90%	
Sensitivity			90.3%	
Specificity			88.8%	
PPV			96.5%	
NPV			72.8%	
P value		0.0002	P<0.02**	

P. value of MRI kinetic curve = 0.0002 … (p<0.02 is highly significant)

Histopathological confirmations were available for all 40 patients . (31 cases show malignant cells (table 7) and 9 show benign cells (table 8)).

Table 7: Histological classification of breast cancer in the study sample

	Histological classification of breast cancer	No	%
1	Invasive ductal ca.	20	64.5
2	Ductal ca in situ	4	12.9
3	Mixed invasive lobular and ductal ca.	3	9.7
4	Invasive lobular ca.	3	9.7
5	Inflammatory Ca.	1	3.2
Total		31	100

Table 8:. histological classification of benign breast masses in our sample .

	Histological classification of benign breast lesion	NO.	%
1	Hyperplasia or fibrocystic dysplasia	3	33.3
2	Fibroadenoma	3	33.3
3	Radial scar	1	11.1
4	Reactive lymph node	1	11.1
5	Fat necrosis	1	11.1
Total		9	100

MRI – validity :- as shown in (table 9) of both MRI- BIRAD and MRI- kinetic curve

Table 9: show MRI BIRAD or MRI- kinetic curve / Cytology validity of study sample

Yield*	Sensitivity	Specificity	Accuracy	PPV
BIRAD –MRI	93.3	55.5	85	82.86
Kinetic curve only	*90.3*	*88.8*	*90*	*96.5*

*NB, return to methodology analytical statistic

The sensitivity of MRI in detecting cancers proved by histopathological diagnosis in comparison with conventional imaging; including mammography , US and combined modality yields is expressed a combined mammography , US and MRI sensitivity of 100% while combined US and mammography sensitivity of 83.87%.

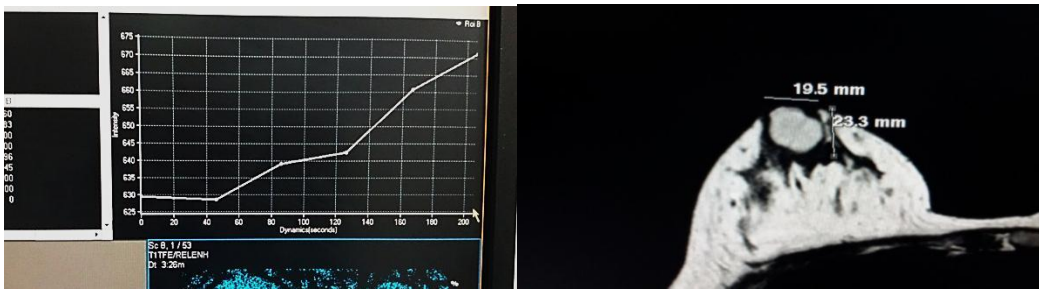


Figure 5: (DCE-MRI " type1 kinetic curve").

Patient with well defined homogenous enhancement breast mass , BIRAD III ,with DCE-MRI type1 kinetic curve . proved to be Fibroadenoma in histopathology .

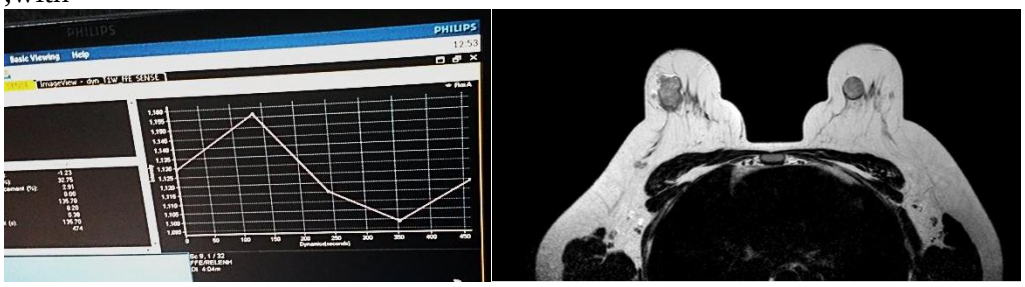


Figure 6 : (DCE-MRI " type 3 kinetic curve ") non contrast MRI. Bilateral breast cancer in T2 WI . both show type 3kinetic curve

Discussion

We assess the diagnostic accuracy and impaction of breast DCE- MRI with the kinetic curve for early detection of breast cancer to take good surgical planning and appropriate treatment .This aim will affected by many factors including the selection of good sample size , appropriate indications [6] ,good technical factors like : strength of the field, thin slice , suitable surface coil , pulse sequences ,and efficient staff . [8,9]

Also depend on criteria used on the interpretation of the image which must include morphology of the lesion , pattern of enhancement and kinetic analysis with histopathological results . [8 ,10]

After selected 40 patients depend on the technical factors and protocol selection as well as the interpretation criteria; morphology and its pattern of enhancement. all were comparatively analogous to those cases used by Hey wang K. el al and Nunes LW et al . [8,10] .

The predominant clinical presentation in our study sample was a painless palpable mass seen in 68% of cases and the anatomical distribution 62.5% were found in the UOQ in harmonization with other studied that show the tumor location is higher in the UOQ(50-58%) among multiple population , including United Kingdom ,Chinese and Danish . [11,12 , 13,14]

Also go with Hadi A.M. study who found that 58.06% of malignant breast lesions situated at the UOQ [15] .and practically comparable with Ellsworth et al ,who demonstrate an increased levels of genomic instability of outer breast quadrants . [16]

Tumor size in MRI has a mean of 25.5mm , while the mean size with US measurement was 18.2 . About 7.3 mm increase of the mean size in MRI and this is relatively in agreement with the other studies made by N. Hylton [17] Weather all PT [18] and Wasif N.et al. [19] who observed that MRI is more accurate in assessing the size and extent in patients with recent diagnosis of breast cancer.

LAP had been seen in 20 patients . 9 cases show malignant infiltration proved pathologically while benign reactive lymph nodes were seen in 11 cases .MRI showed type 3 "malignant curve " so high false positive rate (55 %) which mean that the kinetic analysis is not useful in detecting malignant lymph node infiltration .

However the morphology may be helpful in suspecting the nature of LAP such as the malignant nodes show peripheral enhancement in dynamic CE- MRI, while benign reactive enlarged lymph nodes show fatty center that appear hyperintense signal on non enhanced T1 weighted image . [5].

MRI is more sensitive in identifying multifocal and / or bilateral breast cancers ; in complete agreement with a study by Sardanelli F, et al who conclude that MRI has additional sensitivity than mammographyfor the discovery of multiple malignant centers in fibroglandular or dense breasts and mammography overlooked larger and more invasive cancer lesion than MRI.[3,5 , 20 ,21]

In our study there was one case show false positive results according to MRI – kinetic curve as the patient presented with nipple discharge and pain , mammographywas inconclusive due to dense breast and US expressed prominent glandular tissue with non homogenous echo texture and was categorized as BIRADS III , in DCE-MRI show type 3 kinetic curve, but in histopathology there was no malignant cell .

In connection with clinical data the patient was at second half of her cycle (proliferative phase) so this condition is explained by the hormonal effect on enhancement pattern and temporal resolution of the normal tissue of the breast , this result go with available literatures that displayed false positive nodular of diffuse or nodular enhancement occur mainly in the 1st and 4th weeks during the cycle .[22,23]

In our study the kinetic analysis , done to all patients . where type 3 shown in 29

patients and type 2 in 9 cases and type 1 in 2 cases of unifocal & multifocal cases.

Type 3 and type 2 curves displayed in 73.5% and 20.6% respectively and type 1 curve found in 5.9% in patients with unifocal breast cancer and 66.7% type 3 and 33.3 % type 2 in multifocal breast cancer masses.

29 cases of type 3 (28 case show malignant cell on histopathology and one case not), 9 cases with type 2 (three of them show malignant cells and other six show benign cells in histopathology) while 2 cases of type 1 show benign cells .this is comparable with many studies that reported the importance of the curve shape in differentiating between benign and malignant lesions .

So use of this curve is dramatically increase the discrimination between benign and malignant lesions , type 3 is more suspicious of malignancy where type 2 is either indicator of malignancy or benign while the last type (type1)is associated with benign lesions.Schnall et al .[24]

Kuhl et al. expressed the importance of determining enhancement curve shape as a method to add specificity to breast contrast-enhanced MRI. And have demonstrated the importance of the accuretly measuring TSI- curve shape, not as a morphological replacement , but to be evaluated in combination with morphology. [25]

In our study the DCE-MRI sensitivity in detecting breast cancer found to be 93.5% in correlation with histopathological diagnosis that was agreement to most studies that show the sensitivity of MRI for detection of breast cancer is very high ,with 90 % the value being reported [26,27] .

It also increased the sensitivity of other combined modalities(MRI , mammography& US) up to 100 % versus sensitivity of mammography of 51.6 % and sensitivity of US 67.7% while sensitivity of combined (mammography and US) together did not exceed 83.87% in our sample.

MRI and cytology diagnostic validity including MRI sensitivity, specificity, accuracy and positive predictive value were 93.5%, 55.5%, 85 % and 87.87 % respectively and is well comparative with related articles. As there is overlap in enhancement appearances between benign and malignant lesions, dependence on a kinetics assessment alone is not recommended.

While The specificity of breast MRI is improvedwhen both morphologic and kinetic features are evaluated in the interpretation . [21]

It has been supposed that MRI is a very sensitive technique for discovering even small cancers that cannot be detected by conventional imaging modalities in complete agreement with most of other literatures and studies . [5, 10 , 28 , 29]

Our outcomes document that DCE- MRI is obviously superior to both mammographyand US for early recognition and grouping ofbreast cancers.

Conclusion

Dynamic breast MRI produce information on both aspects cross-sectional morphology and functional lesion features such as vascularity/perfusion and vessel permeability.

According to kinetic curve The shape of TSI- curve is an import criterion in differentiating benign and malignant enhancing lesions .

3 types of kinetic curve ,type Iassociated with benign lesion , type II curve which is indictor of either benign or malignant lesion and type III for more suspicion of malignancy.

All these done to increase the accuracy of imaging modalities to be use in the early detection of breast cancer and to avoid unnecessary surgical intervention (mastectomy ,or even exceptional biopsy for benign lesion).

DCE-MRI is more accurate than US for assessing the size and extent of breast cancer presenting as a mass ; consequently assessing the efficacy of local staging and planning surgical treatment .

DCE-MRI has a useful role in detecting local recurrence .

Recommendation

With our study results about breast masses MRI the following guidelines have emerged:

1. Analysis of TSI-kinetics is done after the evaluation of the lesions' morphology in post contrast images. So If morphology is indeterminate or suggests a benign lesion, we recommend a TSI- curve analysis. where

If morphology is suggestive of malignancy , we do not evaluate kinetics for reasons explained earlier.

2. If a washout time course is detected and the morphology suggests a benign or indeterminate lesion, biopsy must be performed on the lesion. A washout constitutes an absolute indication to perform biopsy on a lesion

3. , On the other hand ,Lack of a washout phenomenon may not be used to prove absence of malignancy.

4. If the enhancement rate is suggestive (rapid) , but morphology suggests a benign lesion , then a type I TSI- curve supports the diagnosis of a benign lesion and may be used to preclude the performance of biopsy.

Because of the world wide promising role of breast MRI; we recommend an breast MRI uses as complementary modality with other tradiotional ones .. and also establishment of a specialized unit for breast MRI. This will allow proper selection of high risk group population that improves early detection of breast cancer and hence better prognosis.

We recommended also few points To increase specificity of breast MRI ,first is proper selection of patients time of examination so not done for populations with a low prevalence of breast cancer, like young patients with no risk factors, and second thing is try to obtains proper timing for premenopausal women. to avoid normal diffuse and nodular enhancement occurs during all phases of the cycle especially in the 1st and 4th weeks.To . Increase the specificity that is preferred between day 7 and day 14 as this period has the least false-positive of their menstrual cycles.

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