The Egyptian Journal of Hospital Medicine (July 2018) Vol. 72 (3), Page 4113-4119

Role of Recent MR Imaging Modalities in Diagnosis of Problematic Breast Lesions

Maged M.A. Ghanem, Mohamed S.T. El-Feshawy, Ahmed M.S. Abdelmaksoud
Department of Radiodiagnosis, Faculty of Medicine-Al-Azhar University
Corresponding author: Ahmed M.S. Abdelmaksoud, **Mobile:** 01091530382; **Email:** ahhhmed488@gmail.com

ABSTRACT

Background: Breast imaging reporting and data system (BIRADS) III and IV lesions are considered indeterminate breast lesions and an imaging dilemma. Contrast enhanced MRI shows high sensitivity in detecting these lesions but with low specificity leading to unnecessary biopsy in some of them and high false positive rate. So there was a need for new imaging techniques to raise the specificity of MRI. One of these new imaging techniques is MRS which can improve breast cancer diagnosis especially in indeterminate breast lesions. IT is a noninvasive method that can be added to the DCE–MRI of the breast increasing only the time of examination but allow better characterization of lesions depending on their chemical composition.

Objective: To assess the diagnostic value of recent MR imaging modalities in diagnosis of problematic breast lesions categorized by mammography or sonomammography as (BIRADS III and IV) and correlation of these findings with available histopathological findings, clinical data or follow up.

Patients and Methods: Study was carried out in the Radiology Department of Al-Azhar University Hospitals. The work took place during the period between May 2017 and June 2018. A total of 35 patients, presented with breast lesions for characterization, were included in the study.

Results: We found that MRS measurement increased the specificity of the breast MRI in characterizing different breast lesions especially when it is combined with conventional dynamic MRI.

Conclusion: MRS is a noninvasive scan that can be added easily to standard breast MRI protocols as an adjuvant tool. Detection of choline peak using choline SNR can accurately differentiate benign from malignant breast lesions especially indeterminate breast lesions with high sensitivity and specificity especially by adding its results with the results of the standard DCE- MRI scan.

Keywords: Breast Imaging Reporting and Data System - Computed tomography - Dynamic contrast enhancement - Magnetic resonance

INTRODUCTION

Breast cancer is the most common cancer among women in Arab countries with a young age of around 50 years or even younger at presentation. Locally advanced disease is very common and total mastectomy is the most commonly performed surgery. Traditional approaches to assess breast lesions are routine screening methods, such as ultrasonography (US) and mammography. Mammography provides a widely available, reliable and cost-effective screening tool, however contraindicated in pregnancy and lactation, has decreased efficacy in patients with dense breasts, patients with silicone implant and patients that have previous surgery [(1)].

Breast US is routinely used as an adjunct to mammography to help differentiating benign from malignant lesions. The accuracy of US diagnostic methods is controversial because there is a considerable overlap of benign and malignant characteristics on US images and interpretation is subjective, dependant on the operator [(2)].

MRI is a helpful imaging modality in diagnosis of breast neoplasms and suspicious lesions (not for follow benign or malignant criteria, after lumpectomy to differentiate scarring from recurrence, female with positive family history of breast cancer, diffuse edema pattern). It is characterized by being noninvasive, more specific in lesion localization, superior contrast resolution, multiplanar capabilities, and imaging of physiological processes such as blood flow, perfusion, diffusion and metabolite concentrations which have provided an entire new world of insight into breast imaging [(3)].

The use of magnetic contrast agent is helpful in the evaluation of the breast lesions depending on the analysis of the uptake, and pattern of enhancement [(4)].

H-MRS allows noninvasive molecular analysis of biologic tissues and has been suggested as an adjunct to MR examination to improve the specificity of distinguishing benign from malignant breast masses classified according to BIRADS category. The diagnostic value of H-MRS is typically based on the elevation of choline compounds which are the markers of active tumor and aid in the discrimination between benign and malignant breast lesions mainly the BIRADS 3-5 masses [(1)].

Suspicious lesions may also be characterized by their cellular chemistry obtained from proton MR spectroscopy (MRS). Proton MRS analyses of the breast have shown high levels of total choline-containing compounds at 3.2 ppm in malignant lesions but low levels in normal breast

Received:13/5/2018
Accepted:22/5/2018

tissues and benign lesions. In addition to being used for breast cancer diagnosis, In vivo single-voxel proton MRS may be a sensitive diagnostic tool in patients with breast cancer. Recent evidence suggests that MR spectroscopy, if incorporated into a standard MRI examination, may be effective in increasing the specificity and positive predictive value of lesion evaluation. For benign lesions where MRI is inconclusive, MRS may eliminate the need for biopsy by demonstrating the lack of a choline resonance [(5)].

With the addition of MR spectroscopy to breast MRI exam, the number of biopsies recommended on the basis of MRI findings decreased significantly. These results should encourage more women to take this potentially life-saving test [(3)].

AIM OF WORK

To assess the diagnostic value of recent MR imaging modalities in diagnosis of problematic breast lesions categorized by mammography or sonomammography as (BIRADS III, IV) and correlation of these findings with available histopathological findings, clinical data or follow up.

PATIENTS AND METHODS

The present study started on May 2017 till June 2018. The study included 35 patients; some of them are referred from surgical department and others are from out patient clinic. This study was composed of: Full history and clinical data: proper and full history from the patient taken including complaint, past history of (previous surgical interference, type of surgery, date of surgery, presence of reconstructive surgery, presence of hormonal replacement ……. etc). Mammography: was done for detection of micro calcification, architectural distortion and asymmetry in breast density. Ultrasonography: all cases were done on TOSHIBA APPLIO machine at Women Imaging Unite, Department of Radiodiagnosis, Al Hussein University Hospital) were done for detection of benign and malignant criteria and classification of the breast lesions as in (BIRADS) classification. **The study was approved by the Ethics Board of Al-Azhar University.**

Magnetic resonance mammography: (All cases were examined on ACHIVA PHILIPS 1.5 Tesla Machine at MRI unit, AL Hussein University Hospital) was done as following:

A- Preparation All metallic objects were removed from the patient's body including zippers and clasps because they can cause artifacts. I.V line were established, so that injection could done without movement of patient.

B- Patient position: The patient used to lie prone on the examination couch with her breast(s) in the breast coil(s) and the arms were placed along the body.

C- MRI Sequence: The routine protocol used for breast imaging that includes: Axial T1W and T2WIs. Axial T2 fat suppressed, STIR (Short Tau Inversion Recovery). Axial post-contrast fat suppressed T1 WI ± sagittal post-contrast T1 WI. Dynamic post-contrast MRI: for quantitative measurements of signal intensity changes, injection of a bolus of gadopentate dimeglumine (0.1 mmol/kg; magnevist, Bayer HealthCare) at a rate of 2 mL/s, followed by a 20 mL saline flush administered using an automatic injector. Both breasts were examined in the axial plane at 30 s, 1 min, 2 min, 3 min, 4 min, 5 min and 6 min after contrast injection, respectively. Time intensity curves (performed in all cases): Signal intensity measurements were performed prior to as well as following contrast administration in the preselected ROI which is usually drawn at the point of maximum enhancement. Diffusion weighted imaging (in some cases).

Diffusion study was performed prior to contrast administration not only to negate any possible effects of the presence of contrast agent may have on water diffusion within the tumor tissue but also to nullify any T2 shortening resulting from the contrast agent.

Proton MR Spectroscopy study: After all MRI sequences had been performed, single-voxel ^{1}H MRS was performed immediately after acquiring dynamic contrast-enhanced (DCE) MR images. Decisions about the placement of the MRS voxel were usually based on a review of the lesion morphology and the kinetics of contrast agent uptake while the patient is still in the magnet. Analysis of the chemical makeup of the lesion under study was then done using dedicated spectra. Single-voxel MR spectroscopy data were collected from a single rectangular volume of interest that encompasses the lesion. The position and size of the region of interest (ROI) was chosen to encompass each enhancing lesion limiting as much as possible the inclusion of non-enhancing parenchyma and surrounding fat. A curve fitting between 3.14 ppm and 3.34 ppm was finally applied to show Cho peak.

Image Interpretation: All lesions or areas of abnormal enhancement detected by MRI that could represent potential malignancies in both breasts were

evaluated, as regard: (A) Lesion assessment: 1-Mass was evaluated for its. Site (in which quadrant and its distance from nipple), size, shape (rounded, oval, lobulated or irregular), margin (smooth, irregular or speculated), enhancement pattern (homogenous, heterogeneous). 2- Non mass like enhancement was evaluated as the following: Its enhancement (focal, linear or ductal), distribution (segmental, regional, multiple, patchy or diffuse). 3- Kinetic curve assessment: as the shape of time/signal intensity curve: Whether it was consistent with type (1, 2 or 3) kinetic curve. 4- Diffusion study: whether the lesion showed (homogenous, heterogeneous or no) diffusion restriction and mean ADC value was measured. 5- Proton MR apectroscopy: the lesion was evaluated for presence of choline peak with evaluation of choline SNR. In this study a semiquantitative method was used, a threshold SNR of 2 was used for choline. Results were seemed positive when the signal to noise ratio was greater than or equal to 2 and negative in all other cases.

Statistical Methods:

The Shapiro-Wilk test was used to examine the normality of numerical data distribution. Normally distributed continuous data were presented as mean ± SD and non-normally distributed data as median (interquartile range). Categorical data were presented as number (%).

The diagnostic value of various radiological tools for discrimination between malignant and benign lesions was examined versus the result of histopathology (or follow-up) as the gold-standard test. The following diagnostic/predictive indices were calculated: sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and correct classification and misclassification rates.

Agreement between radiological tools was examined by calculation of the Cohen kappa coefficient (κ) and the bias and prevalence adjusted kappa coefficient (PABAK). The Cohen κ and PABAK are interpreted as follows:

The Cohen κ and PABAK:

Cohen κ or PABAK	Strength of agreement
< 0.20	Poor
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Good
0.81 - 1.00	Very good

RESULTS

Table (1): Clinical characteristics of patients

Variable	Value
Age (years)	45.6 ± 14.6 (range, 18 – 76)
Clinical presentation	
Breast pain	1 (2.9%)
Breast lump	24 (68.6%)
Nipple discharge	2 (5.7%)
Postmastectomy follow-up	4 (11.4%)
Skin redness and edema	4 (11.4%)
Lesion site	
UOQ	9 (25.7%)
LOQ	2 (5.7%)
LIQ	4 (11.4%)
Retroareolar	9 (25.7%)
Axillary tail	1 (2.9%)
Multiquadrant	3 (8.6%)
Scar site	7 (20.0%)
Lesion size	
1 cm	3 (8.6%)
1.1-2 cm	15 (42.9%)
2.1-3 cm	7 (20.0%)

Table (2): Sonomammographic findings.

Sonomammographic findings	Value
Suspicious lesion	15 (42.9%)
Benign-looking lesion (with positive family history of cancer breast)	7 (20.0%)
Distorted architecture	6 (17.1%)
Suspicious scar	3 (8.6%)
Inflammatory changes	2 (5.7%)
Suspicious postoperative seroma	2 (5.7%)

Table (3): BIRADS classification by sonomammography

BIRADS classification	Value
BIRADS III	18 (51.4%)
BIRADS IV	17 (48.6%)

Table (4): Accuracy of the Sonomamography BIRADS classification.

	Malignancy status		
BIRADS class	Malignant	Benign	Total
BIRADS IV	10	7	17
BIRADS III	0	18	18
Total	10	25	35
Statistic	Value	Lower 95% CI limit	Upper 95% CI limit
Correct classification (accuracy)	80.0%	66.7%	93.3%
Sensitivity	83.7%	67.4%	100.0%
Specificity	87.5%	52.1%	85.8%
Positive predictive value (PPV)	58.8%	35.4%	82.2%
Negative predictive value (NPV)	100.0%	100.0%	100.0%

Table (5): MRI findings.

MRI findings	Value
Suspicious enhanced lesion	15 (42.9%)
Benign-looking lesion	9 (25.7%)
Enhanced rim	1 (2.9%)
Non mass-like enhancement	7 (20.0%)
Inflammatory changes	1 (2.9%)
Thick nodular enhancement	1 (2.9%)
Seroma	1 (2.9%)
MRI kinetic curve	
Type I	13 (37.1%)
Type II	18 (51.4%)
Type III	4 (11.4%)
DCE-MRI classification	
Benign looking finding (type I curve)	13 (37.1%)
Suspicious finding (type II &type III curves)	22 (62.9%)

Table (6): Accuracy of MRI and the MRI kinetic curve (DCE-MRI).

	Malignancy status		
MRI	**Malignant**	**Benign**	**Total**
Suspicious finding with Type II/III kinetic curve	10	12	22
Benign looking /Type I kinetic curve	0	13	13
Total	10	25	35
Statistic	Value	Lower 95% CI limit	Upper 95% CI limit
Correct classification (accuracy)	85.7%	50.0%	81.4%
Sensitivity	92.3%	67.4%	100.0%
Specificity	83.3%	33.5%	69.9%
Positive predictive value (PPV)	45.5%	24.6%	66.3%
Negative predictive value (NPV)	100.0%	100.0%	100.0%

Table (7): MR spectroscopic findings.

Choline peak by MR spectroscopy	Value
Negative (no choline peak, small peaks, SNR less than 2)	22 (62.9%)
Positive (choline peak, SNR >2)	13 (37.1%)

Table (8): Accuracy of the MR spectroscopy choline peak.

	Malignancy status		
MR Spectroscopy	**Malignant**	**Benign**	**Total**
Positive choline peak	10	3	13
Negative choline peak	0	22	22
Total	10	25	35
Statistic	Value	Lower 95% CI limit	Upper 95% CI limit
Correct classification	91.4%	82.2%	100.0%
Sensitivity	100.0%	67.4%	100.0%
Specificity	92.3%	69.0%	96.5%
Positive predictive value (PPV)	76.9%	54.0%	99.8%
Negative predictive value (NPV)	100.0%	100.0%	100.0%

Table (9): Final diagnosis by histopathology or follow-up for at least 1 year

Ultimate diagnosis	Value
Invasive ductal carcinoma	8 (22.9%)
Invasive lobular carcinoma	1 (2.9%)
Inflammatory carcinoma	1 (2.9%)
Fibroadenoma	10 (28.6%)
Necrotic tissue/fat necrosis	2 (5.7%)
Abscess	2 (5.7%)
Fibrosis /granulation tissue	5 (14.3%)
Cyst	1 (2.9%)
Mastitis	3 (8.5%)
Seroma with inflammatory changes	2(5.7%)

DISCUSSION

MRI is an important supplementary modality to sonomammography in the evaluation of the breast. Breast MRI is the most sensitive imaging modality for breast cancer detection in both primary and recurrent breast cancer. The sensitivity ranges between 89 and 100%. The specificity of breast MRI has been reported to be overall ranging between 20 and 100%, with more recent studies yielding 70–90% [(6)].

However it is not widely used as alternative to breast biopsy because of its unsatisfactory specificity. To improve the specificity of breast MRI, several studies focused on either lesion shape or enhancement kinetics. Higher specificity was achieved by integrating the morphologic and kinetic characteristics of lesions detected with MRI. Yet they weren't satisfactory. So, efforts have been directed toward developing new pulse sequences and evaluation methods that improve lesion characterization [(7)].

Magnetic resonance spectroscopy of the breast can be used to measure the level of choline, which is a marker of malignancy. MR spectroscopy can provide high specificity to differentiate between benign and malignant lesions, which is complementary to the high sensitivity provided from contrast enhanced MR imaging [(8)].

In this study we investigated the accuracy of choline peak as a malignancy marker in characterization of suspicious breast lesions detected by ultrasound or mammography and classified as BIRADS III and VI. Then, these lesions were correlated with histopathological data and/or follow up results.

In our study the choline peak was searched for at the frequency of 3.2 ppm. The SNR of choline peak was automatically calculated as the ratio of choline peak amplitude to noise amplitude.

MRS findings would be defined as positive if the SNR of the choline resonance peak was >=2, AND as negative in all other cases. We used the same SNR cut off value used by ***Bartella et al.*** [3].

A study by ***Basara et al.***[9] using qualitative approach analyzed 77 patients considering choline peak positive when it is at least 2 times higher than base line shows sensitivity 79% and specificity 82%.

In the review of ***Baltzer et al.***[10] the authors reported no difference between qualitative and quantitative methods.

In a study by ***Kousi et al.***[11], they evaluated breast lesions pre and post contrast by MRS and revealed that MRS accuracy, specificity and sensitivity in detecting malignant lesions was increased after contrast administration especially in small or non mass lesions to allow proper voxel localization. In controversy to their study ***Aydin et al.*** [1] stated that MRS especially done before contrast administration should significantly increase sensitivity and PPV for characterization of BIRADS III and IV lesions.

In our study we evaluated the lesions with MRS after contrast administration, actually this was helpful to accurately localize lesions and allow proper voxel placement.

Breast cancer incidence and death rates generally increase with age. During 2008-2012, the median age at the time of breast cancer diagnosis was (61). This means that half of women who developed breast cancer were 61 years of age or younger at the time of diagnosis. The median age of diagnosis is younger for black women (58) than white women (62) [12]. The age of cases included in our study ranged from 18 to 76 years old with the mean age being 54.6 and the standard deviation "SD": 14.6. However our study didn't reflect actual prevalence, it only represents patients referred to MRI for suspicious breast lesions and indeterminate lesions to avoid unnecessary biopsy.

BIRADS III and IV lesions are a clinical dilemma as they need either follow up or biopsy. Since 80% of lesions determined in the breast are benign upon biopsy, we need new methods for evaluation of these lesions to avoid unnecessary breast interventions. MR spectroscopy is a promising new MRI technique which can be used to improve the diagnosis of breast lesions classified according to BIRADS category to decrease rate of unnecessary breast interventions in BIRADS IV and avoid cost of follow up in case of lesions categorized as BIRADS III.

Our study included 35 lesions, 18 were classified as BIRADS III lesions and 17 were classified as BIRADS IV lesion, these classifications were by sonomammography. 25 lesions were benign (71.4%) (7 of them were initially classified as BIRADS IV lesions by sonomammography and 18 were classified as BIRADS III lesions), and 10 were malignant (28.6%) (All of them BIRADS IV lesions). So, 51.4% were categorized as BIRADS III lesions and 48.6% categorized as BIRADS IV.

Non mass like enhancement was present in 7 cases out of 35 lesions in our study. All of them turned out to be benign. None of them showed choline peak, yet three of them were suspicious by DCE-MRI. So biopsy might have been avoided in 42% of non mass enhanced lesions if we follow the choline spectroscopy results and this agree with ***Bartella et al.*** [3] who stated that MR spectroscopy has a sensitivity of 100% and a specificity of 85% for of enhanced non mass lesions. For 25 lesions with unknown pathology MRS significantly, increased the PPV of biopsy from 20% to 63%. If biopsy was performed for only lesions with positive choline peak, biopsy might have been avoided for 17 (68%) of 25 lesions, and no cancers would have been missed [3].

However, non mass enhanced lesions have multiple normal glandular tissue in-between area of abnormal enhancement, so lipids in this glandular tissue may produce sidebands echoes that interfere with signal produces from MRS voxel making problems in choline resonance. So, skills are mandatory to select adequate voxel size that includes much of the lesion and less glandular tissue [3].

In our study there were 8 cases (representing 22.8 % of studied population) with postoperative breast evaluation. 3 of them presented with suspicious scar, and 3 of them with solid lesion at lumpectomy site, and 2 suspicious postoperative seroma with adjacent architecture distortion. We concluded that MRS is useful method in increasing MRI specificity in these patients. One patient had recurrence and MRS could accurately diagnose it, in which there was choline peak with SNR about 2.4, while there were no choline peak in the other 7 lesions. This was concordant with the pathology result that confirmed their benign nature. So MRS was able to exclude recurrence in 7 patients and voiding unnecessary biopsy. In controversy to DCE-MRI alone which raise the suspicion in four of them which turned out to be benign with MRS and pathology. In these 7 cases MRS was able to downgrade the BIRADS category of DCE-MRI, thus raising the specificity of DCE –MRI.

So according to our study MRS was a useful method in differentiating tumor recurrence from postoperative changes. Our result was concordant with ***Tharwat et al.***[4] who investigated 16 patients comprising 32% of the studied population with history of previous surgery for breast cancer presented with suspicion of recurrence.

8 cases out of the 16 patients had recurrence and MRS study was able to diagnose them accurately, while it was able to exclude recurrence in 6 of the 16 patients as no choline peak was detected. Yet, 2 patients out of the 16 showed false positive results (inflammatory lesions with minimal atypia displaying non-mass like enhancement) with detectable choline peak and choline SNR of 2.1.

However the sensitivity was 100%, specificity of 75% and overall accuracy of 88% in evaluation of postoperative breast.

In controversy, MRS study of the choline peak as marker of malignancy revealed a higher precision in classification of false positive, but the true positive score was worse than in DCE classification 2.

The most common benign entity in our study was fibroadenoma representing 28.6 % of cases. Other entities include; fat necrosis/necrotic tissue 5.7%, complicated cyst 2.9%, mastitis 8.5 %, breast abscess represented 5.7 %, while post-operative granulation tissue, scarring, represented 14.3 %, and seroma with inflammatory changes 5.7 %

MRS gave false positive results in three of these cases according to biopsy and follow up one of them was fibroadenoma, the 2nd was abscess and the 3rd was inflammatory changes with minimal atypia.

The most common malignant entity in our study was invasive ductal carcinoma representing 22.9% of cases included in our study while invasive lobular carcinoma represents 2.9% and inflammatory carcinoma 2.9% (one patient). MRS was able to accurately diagnose all of them.

In conventional dynamic MRI 62.9% of cases were suspicious (BIRADS IV) while only 37.1% benign (BIRADS III and II).

According to our result in the conventional dynamic MRI without MRS accuracy was 65.7 % and specificity was only 52 % with false positive rate about 48 %. The positive predictive value was 45.5%. There was 12 false positive cases with MRI without spectroscopy, two of them were necrotic tissue, 5 of them was atypical fibroadenoma, 4 cases were granulation tissue, postoperative scarring and 1 inflammatory lesion with minimal atypia.

While after adding MRS the accuracy was 91.4% and the specificity with MRS increased to 88 %. With false positive rate decreased to 12 %. The positive predictive value increased to 76.9 %. It was able to detect 10 malignant cases all of them have positive choline peak with SNR equal to or more than 2, no choline peak was detected in 22 cases all of them were benign while only 3 cases showed false positive choline peak.

From our data, combining DCE -MRI breast with MRS using choline peak as a malignancy marker increased specificity of MRI in diagnosis of BIRADS III and IV Lesions. So avoid unnecessary biopsy in BIRADSIV lesions and avoid cost of follow up in BIRADS III lesions.

Our study included 35 female patients who presented with different breast complaints. They had mammography, ultrasound, DCE-MRI and MRS done. The findings of each modality was compared to the histopathological and follow up results in order to be able to detect sensitivity, specificity and accuracy of each of them. These results have helped in detecting the effectiveness of using DCE-MRI and MRS in characterization of suspicious breast lesions (BIRAD III & BIRAD IV).

In our study over all sensitivity of sonomammography, DCM-MRI and MRS was 83.7%, 92.3%, and 100% respectively while their specificity was 59%, 52%, 88% respectively, which is compatible with ***Geraghty et al.*** [13].

CONCLUSION

MRS is a non-invasive scan that can be added easily to standard breast MRI protocols as an adjuvant tool. Detection of choline peak using choline SNR can accurately differentiate benign from malignant breast lesions especially indeterminate breast lesions with high sensitivity and specificity especially by adding its results with the results of the standard DCE- MRI scan.

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