Value of MRI Perfusion in Discrimination between Benign and Malignant Breast Masses

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Abstract

Objective: Lesion detection at contrast material-enhanced breast Magnetic Resonance (MR) imaging is primarily based on a lesion's vascularity relative to normal breast tissue. MR imaging may be still be advantageous because it can be used not only to characterize the lesion in question but also to evaluate the remainder of the breast, potentially leading to identification of unsuspected multifocal disease. The primary benefit of a noninvasive test such as MR imaging undertaken prior to tissue diagnosis (i.e., with core biopsy or excisional biopsy) is that it can be used to determine which lesions are likely to be benign, so that mammographic or clinical follow-up could be used in place of tissue diagnosis. When a test is used in this capacity, it must be sufficiently sensitive that the negative predictive value is very high without sacrificing specificity. Standard evaluation criteria have not been optimized for evaluating Dynamic Contrast Enhanced breast MRI (DCE-MRI). Most evaluation criteria, especially morphologic criteria and Time-Intensity Curve (TIC) type, are subjectively interpreted. To reduce the subjectivity, quantitative analysis of the perfusion parameters may be of value in differentiation between benign and malignant breast lesions which is the aim of this study.

Material and Methods: 46 female patients (50 lesions), who underwent breast DCE-MRI. The lesions were analyzed using computer-assisted diagnosis CAD software to reproduce qualitative and quantitative kinetic data and the results correlated with histopathological results.

TIC of dynamic images were generated using (CAD) software. Seven parameters were calculated: Maximal contrast enhancement (ME), Maximum Relative Enhancement (MRE), Time to Peak (TTP), wash in rate, wash out rate, brevity of enhancement and Area Under the Curve (AUC).

Results: Fifty lesions were analyzed, thirty three (68.2%) of them were malignant and 17 (31.8%) were benign as proved by histopathology. Cut-off values used for differentiation between benign and malignant lesions show highest sensitivity for TTP and wash out rate about 83.3 3% and 80% respectively. The highest specificity was detected for wash out rate and MRE being 82.4% and 94.1%.

Conclusion: The routine DCE-MRI protocol can derive a qualitative assessment of kinetic curve type with high sensitivity for malignancy and reliable quantitative parameter (TTP, wash in rate and wash out rate) for better characterization of benign and malignant breast lesions with significantly higher specificity and overall diagnostic performance.

Key Words: Breast – Benign and malignant masses – MRI – Perfusion.

Introduction

BREAST cancer is one of the most common malignant diseases endangering women's health. Screening and early diagnosis has an important role in reducing the morbidity and mortality associated with breast cancer. Compared with mammography and breast ultrasonography, contrast material enhanced Magnetic Resonance (MR) imaging is a breast imaging technique that offers not only information on lesion cross-sectional morphology but also on functional lesion features such as tissue perfusion and enhancement kinetics [1].

Abbreviations:

MR: Magnetic Resonance
DCE-MRI: Dynamic Contrast Enhanced breast MRI.
TIC: Time Intensity Curve.
ME: Maximal Contrast Enhancement.
MRE: Maximum Relative Enhancement.
TTP: Time To Peak.
AUC: Area Under the Curve.
SI: Signal Intensity.
SPGR: Spoiled Gradient Recalled echo.
ROI: Region of Interest.
ROC: Receiver Operator Characteristic.
DCE-MRI is a perfusion MRI method that relies on the injection of a contrast agent, where T1-weighted magnetic resonance images are acquired dynamically before, during, and after bolus injection of a contrast agent. The data can be interpreted in terms of physiological tissue characteristics by applying the physical principles of tracer-kinetic modeling. This method has become standard in many applications [2].

Considering the contrast enhancement pattern during the dynamic series, three different phases can be distinguished: (1) The early phase (between contrast injection and the second postcontrast minute), (2) The post initial phase (3rd to 4th postcontrast minute), and (3) The late phase (later than the 4th postcontrast minute).

This means that the time course is evaluated by simply looking at the curves (SI vs. time plots) and deciding whether, after the early phase, the SI continues to increase considered as Type I TIC, or stays the same (plateau) considered as Type II, or decreases (washout) considered as Type III [3]. Software is available that also quantifies the SI loss (if it is present) relative to peak enhancement, the time point of peak enhancement, the washout rates [4]. This study aimed to use a kinetic model with DCE-MRI to improve the specificity and decrease the subjectivity of the diagnosis of breast cancer as compared with the time-signal intensity curves method.

Material and Methods

Patients:

This study was performed on 46 female patients, their age ranged from 19 to 85 years with average age 45.7±14.9, referred to MRI Unit at Radiology Department of Assuit University Hospital from May 2015 to May 2016 for MRI examination with a provisional diagnosis after clinical examination and radiological assessment by mamography and ultrasonography. Tru-cut needle biopsy under ultrasound guidance was done for suspicious lesions. Lesions considered benign if have no changes in imaging for 2 years.

Prior to examination an intravenous route was assured usually through the cubital vein. The patient was then placed in the prone position with both breasts placed adequately in double breast coil (4-channels phased array coil).

Methods:

MRI protocol:
- Axial T1 weighted fast spin echo sequence: (TR=542ms, TE=13ms, slice thickness 3mm, matrix 340 X 512).
- Axial T2 weighted fast spin echo sequence: (TR=4000ms, TE=85ms, slice thickness 3mm, matrix 340 X 512).
- Axial T2WI with fat suppression sequence: (TR=4180ms, TE=72ms, slice thickness 3mm, matrix 340 X 512).
- Dynamic study: The breast was axially scanned with dynamic CE MR-mammography using fat-suppressed 3D spoiled gradient recalled echo (SPGR) sequences [TR:17-21ms, TE:1.7-2.1ms, flip angle: 10, and FOV: 160mm]. One sequence before and seven sequences after contrast medium injection (Magnevist) (0.1mmol/kg) was administered as a bolus injection after the first sequence, followed by flush with 20ml saline. After the dynamic series, image subtraction was performed to suppress the signal from fat, and enhancing lesions were identified on the subtracted images. To verify the presence of a contrast-enhancing lesion and to exclude subtraction artifacts, we also re-identified the lesions on the non-subtracted images.

Qualitative analysis:

The Region of Interest (ROI) was selected so that it should be as large as possible but small enough to exclude the fibrotic or necrotic areas of a tumor or surrounding tissue. Only the area with the strongest enhancement within a lesion was chosen for drawing the ROI, time-intensity curve of dynamic images were generated using (CAD) software (CAD vue Version 2.2.9, iCAD) as percentage enhancement (y-axis) versus time (x-axis) of a Region of Interest (ROI) placed in the detected lesion.

Quantitative analysis: In dynamic studies, 7 MR parameters were calculated from the signal intensity before application of contrast medium (SI0) and from the signal intensities determined in the first (SI1), second (SI2), third (SI3), fourth (SI4), and fifth (SI5) measurement at 90 s intervals after administration of contrast medium in the chosen ROI. Those parameters were ME (maximal contrast enhancement), MRE (maximum enhancement relative to the first postcontrast enhancement), TTP (time point at which maximal uptake occurs), wash in rate (rate of contrast material uptake), wash
out rate, brevity of enhancement, AUC (area under the curve). The kinetic criteria that relate to the different phases are as follows:

**1- Criteria relating to the early postcontrast phase:**
In the early post-contrast phase, wash in rates (or enhancement velocities) are quantified using the following equation:

\[
\frac{\text{SI post-contrast} - \text{SI pre-contrast}}{\text{SI pre-contrast}} \times 100
\]

Where Signal Intensity (SI) post-contrast is the SI of the lesion in the first post-contrast image (usually, 60-120s after injection, in our study after 90s), and SI pre-contrast is the SI of the lesion before contrast. This value provides the relative (percentage) SI increase of a lesion that is reached within the early post-contrast phase.

**2- Criteria relating to the post-initial and late post-contrast phase:** While the SI changes in the early post-contrast phase are usually quantified (percent signal change), those that occur in the post-initial and late post-contrast phase are virtually always evaluated qualitatively.

The MR imaging and DCE-MRI suggested pathology whether benign or malignant had been correlated with histopathological results. The Receiver Operator Characteristic (ROC) analysis was used to determine the optimum cut off value for the studied diagnostic markers. \(p\)-values less than 0.05 was considered statistically significant.

**Results**

Out of 46 studied patients their age ranged from 19 to 85 years with average age 44.8 ± 14.8, 33 patients (67.4%) of them were malignant and 17 (32.6%) were benign as proved by histopathology with (48.77 years) as median age of breast cancer which was significantly higher than in age group of patients with benign lesions (39.2 years).

Among the malignant lesions 27 of them (78.8%) diagnosed as invasive ductal carcinoma (IDC-NOS) Fig. (1) apart from one case diagnosed a mucinous type. Two cases (6.1%) were diagnosed as Ductal Carcinoma in Situ (DCIS) Fig. (2). One case diagnosed as squamous metaplasia. The remaining three cases were diagnosed as miscellaneous (one lymphoma and the other borderline malignant phylloid tumours Fig. (3).

Eight cases of the benign lesions (47.1%) diagnosed as fibroadenoma. Three cases (17.6%) diagnosed as fibroadenosis. Three cases diagnosed as abscess one of them of tubercullos type. One case diagnosed as intraductal papilloma and another diagnosed as sclerosing adenosis Fig. (4). One case diagnosed as chronic granulomatous mastitis.

The calculated sensitivity and specificity of the DCE-MRI according to curve type only in the characterization of benign and malignant lesions are 90.9% and 52.9% respectively with accuracy about 78%.

**Table (1): Percentage of curve type according to the pathological diagnosis.**

<table>
<thead>
<tr>
<th>Curve type</th>
<th>Malignant</th>
<th>Benign</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>9.1</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>33.3</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>57.6</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table (2): The mean values for different kinetic parameters for benign and malignant lesions compared with pathological diagnoses.**

<table>
<thead>
<tr>
<th>Pathological diagnoses</th>
<th>Malignant</th>
<th>Benign</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME</td>
<td>332.54+308.82</td>
<td>160.5+163.07</td>
<td>0.013*</td>
</tr>
<tr>
<td>MRE</td>
<td>20.19+23.84</td>
<td>8.49+10.18</td>
<td>0.019*</td>
</tr>
<tr>
<td>TTP</td>
<td>165.34+118.86</td>
<td>360.87+144.57</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Winitrate</td>
<td>18.69+78.43</td>
<td>2.99+1.19</td>
<td>0.416</td>
</tr>
<tr>
<td>Woutrate</td>
<td>1.05+1.59</td>
<td>0.12+0.19</td>
<td>0.002**</td>
</tr>
<tr>
<td>Brevity</td>
<td>545.54+1343.67</td>
<td>216.36+244.47</td>
<td>0.318</td>
</tr>
<tr>
<td>AUC</td>
<td>97334.7+123946.16</td>
<td>25133.47+68679.43</td>
<td>0.011*</td>
</tr>
</tbody>
</table>

\(p\)-value <0.05* \(p\)-value <0.001**

**Table (3): AUC (area under the ROC curve) and cutoff of studied markers.**

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRE</td>
<td>0.594</td>
<td>&gt;11.04</td>
</tr>
<tr>
<td>TTP</td>
<td>0.838</td>
<td>&lt;286.5</td>
</tr>
<tr>
<td>Winitrate</td>
<td>0.697</td>
<td>&gt;3.27</td>
</tr>
<tr>
<td>Woutrate</td>
<td>0.857</td>
<td>&gt;0.22</td>
</tr>
<tr>
<td>Brevity</td>
<td>0.627</td>
<td>&gt;0</td>
</tr>
<tr>
<td>AUC test</td>
<td>0.674</td>
<td>&gt;10096</td>
</tr>
</tbody>
</table>

**Table (4): Perfusion parameters in two studies for patient with breast cancer before and after 3 cycles of neoadjuvant chemotherapy.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ME</th>
<th>MRE</th>
<th>TTP</th>
<th>Wash in rate</th>
<th>Wash out rate</th>
<th>Brevity of enhancement</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>252.5</td>
<td>12</td>
<td>60.78</td>
<td>3.47</td>
<td>3.26</td>
<td>156.16</td>
<td>12136</td>
</tr>
<tr>
<td>After</td>
<td>106</td>
<td>4.57</td>
<td>72.82</td>
<td>4.91</td>
<td>0.42</td>
<td>26.05</td>
<td>12361</td>
</tr>
</tbody>
</table>
Fig. (1): Female patient 38 years old had right breast cancer for which right mastectomy was done and presented with left breast edema. MRI study revealed: (A) Axial T1WI shows increase skin thickness of left breast and on the scar site of the right breast. There is a hypo intense lesion at the axillary tail of left breast, (B) Axial STIR shows hyperintense edema of left breast and the left breast lesion being small, hyperintense with speculated margin, (C) DCE axial image with subtraction shows mild lesion enhancement, (D) MIP axial image, (E) Type II TIC with red color of the lesion in color coded map. The quantitative assessment was TTP 215.37s, wash in rate 4.14 I/s and washout rate 0.75I/s. MRI diagnosis is BIRADS V. Histopathological diagnosis was IDC.
Fig. (2): Female patient 30 years old presented with right breast mass. MRI study revealed: (A) Axial T2WI shows two well-defined hypointense soft tissue masses, larger one shows irregular speculating margin, (B) Axial T1WI shows two well-defined hypointense soft tissue masses, smaller one with smooth outline, (C) Axial MRI MIP image shows mild increased vascularity at the inner side of the breast near by two enhanced lesions, (D) Axial DCE-MRI image without subtraction shows homogenous enhancement of two breast lesions, (E) Axial DCE-MRI image with subtraction, color coded map with type III curve for large lesion and type II curve for the smaller lesion. Quantitative assessment for larger lesion above the malignant values and the smaller one has washout rate value (0.28/s). MRI diagnosis: Two BI-RADS IV lesions for biopsy. Pathological diagnosis: Invasive Ductal Carcinoma (IDC) for larger lesion and Ductal Carcinoma in Situ (DCIS) for the smaller one.
Fig. (3): Female patient 20 years old with right breast mass. MRI study revealed: (A) Axial T1WI shows well-defined hypointense soft tissue mass at the right breast with smooth lobulated margin, (B) Axial T2WI shows the lesion being slightly hyperintense, (C) Axial MIP image, (D) Axial DCE image with subtraction shows homogenous enhancement of the lesion, (E) Axial contrast enhanced image at 7:00 minute with subtraction and its color coded map (the lesion with red color suggesting malignancy), type I curve and its quantitative assessment TTP 215.45s, wash in rate about 6.681 I/S, wash out rate about 0.75 I/S. MRI diagnosis is BI-RADS IV lesion for biopsy. Histopathological examination reveals borderline malignant phylloide tumor.
Fig. (4): Female patient 45 years old presented with left breast lump. MRI study revealed: (A) Axial T1WI shows well-defined hypointense soft tissue mass seen in outer of left breast measuring about 1 X 0.5cm with smooth regular outline, (B) Axial T2WI shows hypo intense lesion not surrounding by edema, (C) Axial STIR, the lesion being hyperintense, (D) DCE-study with subtraction image shows faint enhancement with type 1 time-intensity curve and TTP about 299.05 s, wash in rate 4.77 I/S and wash out rate 0.11 I/S. MRI diagnosis: Benign featuring left breast mass BIRADS II and pathological diagnosis is sclerosing adenosis.
Discussion

The prevalence of breast cancer has continued to rise in recent years, and the individuals affected have been getting progressively younger. Screening and early diagnosis has an important role in reducing the morbidity and mortality associated with breast cancer. MRI is an emerging tool and has the highest sensitivity of current breast imaging techniques. It has been increasingly used in the screening of high-risk individuals, diagnosing occult cases, staging and assessing the response to chemotherapy [5].

Angiogenesis is the process by which new blood vessels are formed. Once tumors grow beyond a diameter of 1-2mm, passive diffusion is no longer sufficient to support the viability of malignant cells, and neovascularization becomes a necessity [6].

Imaging can provide a noninvasive means of detecting angiogenesis within and about the perimeter of the whole tumor, while giving functional information.

In this study, the mean age was 44 years and it was higher in malignant group (53.5 years) than in benign group (40.2 years). This is in agreement with American Cancer Society 2015 reported risk of developing breast cancer increases with age thus, the risk of developing invasive breast cancer at fifty is about 2.3% comparing with 1.4% at age of forty [7].

According to the present study, the most frequent malignant lesion was invasive ductal carcinoma represented 78.8% while the most frequent benign lesion was fibroadenoma represented 47.1%. Cennet & Erkin et al., have also made similar observation. On the other hand, Li et al., showed in their study that invasive ductal carcinoma account for 56% and fibroadenoma account for 20% [8].

The shapes of the time-signal intensity curves of benign and malignant lesions differed significantly; in benign breast lesions, the predominant signal intensity time curve was type I. It was found in (9 out of 17 benign breast lesion) 52.9% of all benign breast lesions. A type II curve was identified in (6 of 17) of pathologically proved benign lesions, a type III curve was obtained in 11.8% (2 of 17) of benign lesions. In malignant lesions, a type I curve was seen in (3 of 33) 9.1% malignant cases, type III curve was seen in 57.6% (19 of 33) malignant breast lesions, while a type II curve occurred in 33.3% (11 of 33) of malignant proved breast lesions. The distributions proved significantly different (p-value 0.001). The diagnostic indices for time intensity course were sensitivity, 90.9%; specificity, 52.9% and diagnostic accuracy 78%.

According to Yin Yang et al., [9] for TIC classification, the conventional method resulted in relatively high sensitivity, but was also limited by low specificity, as reported in almost all the previous studies [9-12].

The lower specificity in our study may accounts for increase in the number of benign lesions in type II curve including inflammatory breast lesions, sclerosing adenosis and highly vascular fibroadenomata. There is a considerable overlap in signal characteristic and enhancement kinetics between different lesions according to their vascularization and proliferative changes which not necessarily imply malignancy [13,14].

Pharmacokinetic modelling is based on the analysis of the enhancement kinetics to characterize tissue perfusion. This modelling offers many advantages over the classic qualitative assessment of DCE study. It provides quantitative parameters that reflects the physiological and anatomical information about the lesions. They allow characterization of breast lesions and enable the assessment of treatment response to neoadjuvant therapy of breast cancer.

In this study, there is a significant difference between the benign and malignant lesions in Maximum Enhancement (ME), Maximum Relative Enhancement (MRE), and wash out rate that all of them show significant higher values in malignancy than in benign lesions. (TTP) shows significantly lower value (earlier enhancement peak) in malignant lesions than benign do.

This is in agreement with Karahaliou, Vassiou et al., [15] who conclude that the peak enhancement pattern is diagnostically important and one of the criteria assessed in clinical practice and also suggest that time-to-peak and wash out pattern are also diagnostically important, while combining information from the three patterns can significantly improve differentiation of malignant from benign masses.

In our study, the calculated sensitivity, specificity, NPV and PPV for the suggested cut-off values used for differentiation between benign and malignant lesions show highest sensitivity for TTP and wash out rate about 83.33% and 80% respectively. The highest specificity was detected for wash out
rate and MRE being 82.4% and 94.1%. Karahaliou, Vassiou et al., [15] suggest accuracy about 87.7% for wash out rate and 78.9% for TTP.

Two recent study using the same protocol as our study, the first Navaei-Lavasani, Fathi-Kazerooni et al., [16] they suggest that the (TTP, wash in rate, wash out rate, SI max) as quantitative parameters can be used as potential indicators for differentiating between benign from malignant suspicious breast tumors. Their results were similar to ours that they found that benign tumors showed lower values in (MRE) in comparison with malignant tumors. For benign tumors, longer time elapses to reach the peak of relative time intensity curve (TTP) malignant tumors showed faster wash-in rate and faster wash-out-rate.

According to Aksoy, Kiliçoğlu et al., [17] the (TTP) values were significantly shorter for malignant lesions (p=0.01). No other semi-quantitative parameter showed statistically significant differences between benign and malignant lesions. They also suggest that curve type was significant in discriminating malignancy.

Most lesions included in this study (99%) had a histologically proven diagnosis. Lesions that were biopsied were likely to be malignant. This likely enriched the numbers of patients in the type II and type III categories. Also, the threshold values for kinetic curve categories that we determined are likely to be specific to the pulse sequence parameters and MRI scanners that were used in this study. Although we assumed that the assessment of kinetic parameters might offer greater reproducibility by virtue of its simplicity and quantification, especially when developed across multiple sites in a large-scale clinical trial.

Conclusion:
Quantitative assessment of the type of contrast enhancement kinetic curve on breast DCE-MRI resulted in significantly higher diagnostic performance for establishing or excluding malignancy compared with assessment based on the standard qualitative method. Reliable quantitative parameter (TTP, wash in rate and wash out rate) can be used for better characterization of benign and malignant breast lesions with significantly higher specificity and overall diagnostic performance.

Recommendations:
Further studies needed to evaluate the value of those quantitative parameters in assessment the response of breast cancer to neoadjuvant treatment.

References


Value of MRI Perfusion in Discrimination between Benign & Malignant Breast Masses

دور الرنين المغناطيسي بإستخدام خاصية الأرواء في التمييز بين تكتلات الثدى الحميدة والخبيثة

في جميع أنحاء العالم سرطان الثدى هو السرطان الأكثر شيوعا بين النساء ويتكون سرطان الثدى 22.9% من السرطانات الخبيثة في النساء.

يتم تقييم وتشخيص سرطان الثدى عن طريق التصوير الشعاعي للثدى تقييماً بالأشعة السينية لتقييم المرض الذي يعاني من أعراض ولأغراض الفحص الدوري على حد سواء ومع ذلك وحتى عندما يُؤدي النتائج الإيجابية للتصوير الشعاعي للثدى ما بين 79% و90% نتائج الإجراء من هذه الإجراء من مصادر مختلفة ضعف التدقيق خطاً من المراقب وحجم وطبيعة أعراض الثدى لا سيما في الثدى ذو الكثافة العالية.

يستخدم بشكل روتيني الموجات فوق الصوتية كمقياس أساسية لفحص الجسم والتصور الشعاعي للثدى في تقييم كل الثدى الملتزمة.

في السنوات الأخيرة وقد أظهرت نتائج العديد من الدراسات إلى أن تقنيات التصوير بالرنين المغناطيسي لها إمكانات قوية لتحسين حساسية وخصوصية تشخيص وتقدير سرطان الثدى ولا سيما تلك التي تتطلب في إدارة عوامل التباين وقد أجريت في المرضى المختارة لتقييم وتشخيص أورام الثدى بعد خضوع المادة البيئية وحساب ديناميكيتها في الأورام الحميدة والخبيثة عن طريق الرنين المغناطيسي وحساب درجة الأورام الخبيثة تحدد طبيعة الأورام الدموية المغنية للورم.

الهدف من الدراسة:

دور الرنين المغناطيسي بإستخدام خاصية الأرواء في التفرقة بين تكتلات الثدى الحميدة والخبيثة ومقارنة النتائج بالفحص الخلاوي لعينة عن طريق إجراء أو بعد إجراء العملية.

وعقد إشتم الدراسة على 61 مريضة (فحص 50 كثافة بالثدى) ثم فحصهن بإستخدام الرنين المغناطيسي التقليدي وإستخدام خاصية الأرواء وحول المادة البيئية ومقارنة النتائج لتحليل الأساسي عن طريق أنف عينة من نسيج الورم.

وقد أدت الدراسة أن جميع المواد والبيئات السارة إلى الأورام الحميدة أفضت إلى قيم محسنة في الأورام الحميدة فضلاً عن معدلات ROC التفرقة بين الأوراق الحميدة والخبيثة >0.58 0.028 من منطقة تحت المنحنى بالرمز 0.8382838080٪ و80٪ على Wash Out Rate, TTP و MRE و Wash Out Rate التوالي. وقد أُكتشفت على خصوصية 80٪ و70٪ و100٪ على التوالي.