Differentiation between benign and malignant breast lesions using quantitative diffusion-weighted sequence on 3 T MRI


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AIM: To investigate the capability and diagnostic accuracy of diffusion-weighted imaging (DWI) in differentiating benign from malignant breast lesions using 3 T magnetic resonance imaging (MRI).

MATERIALS AND METHODS: Women with suspicious or indeterminate breast lesions detected at MRI, mammogram and/or ultrasound were recruited for dynamic contrast-enhanced (DCE)-MRI and DWI prior to their biopsy. Image fusion of DCE-MRI with apparent diffusion coefficient (ADC) map was utilized to select the region of interest (ROI) for ADC calculation in the area that showed the most avid enhancement. DWI was performed using two sets of b-values at 500 and 1000 s/mm², respectively.

RESULTS: Fifty women were recruited and the final analysis comprised 44 breast lesions, 31 of which were malignant and 13 were benign. Significant results were obtained between ADC values of benign and malignant lesions (p < 0.001). The cut-off ADC values for benign and malignant lesions were 1.21 × 10⁻³ mm²/s for b = 500 s/mm² and 1.22 × 10⁻³ mm²/s for b = 1000 s/mm², respectively. The sensitivity of DCE-MRI alone was 100% with a specificity of 66.7%. When DCE-MRI was combined with b = 1000 s/mm², the specificity rose to 100%, while only mildly affecting sensitivity (90.6%). No significant correlation was found between ADC values and prognostic factors, such as lymph node metastasis, tumour size, oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status, and tumour grades.

CONCLUSION: The present study provides consistent evidence to support DWI as a diagnostic tool for breast lesion characterization. A combination of DCE-MRI with DWI is suggested to improve the sensitivity and specificity of lesion characterization.

Introduction

Breast cancer is the most common cancer in women worldwide. In Malaysia, breast cancer incidence is approximately 1 in 20, making it the most common cause of death due to cancer among Malaysian women. Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) is an...
established technique for detection, diagnosis, and staging of breast cancer. However, it has an inherently high sensitivity but only moderate specificity for characterization of breast lesions.\textsuperscript{1,2} The standard breast imaging protocol enables the analysis of the morphological and kinetic patterns of benign and malignant breast lesions detected at MRI. However, this standard protocol can result in a high false-positive rate of cancer detection leading to unnecessary biopsies.

Diffusion-weighted imaging (DWI) is a functional MRI technique utilizing the microdiffusion of water in the intra- and extracellular spaces. It has been shown to be useful in assessing breast lesions and has the capability to reflect the cellular density of a lesion without using contrast agent administration.\textsuperscript{13} Recent studies have shown that it is also capable in distinguishing between benign and malignant tumours by measuring apparent diffusion coefficient (ADC) values. Comparing ADC values has shown promising results in assessing tumour characterization and aggressiveness.\textsuperscript{4,5} Although ADC value is a valuable biomarker for detecting malignant lesions, it could not be used as a prognostic indicator for patients with breast cancer.\textsuperscript{6} No significant relationship was noted between the ADC values and traditional prognostic factors, such as tumour size, lymph node metastasis, and histologic grade.\textsuperscript{2}

High-field strength (3 T) MRI is becoming increasingly available in the clinical setting and is more readily utilized for the evaluation of breast cancer due to its higher spatial resolution, increase in signal-to-noise ratio, and shorter imaging time. DWI combined with conventional MRI at 3 T has the potential to increase the sensitivity and specificity of breast lesion assessment and may be incorporated into routine breast MRI evaluation of breast lesions. The number of unnecessary biopsies and/or surgeries may be reduced, hence reducing medical costs.

Confirmatory evidence of the usefulness of DWI in diagnosing and characterizing breast malignancy has recently been shown using a 1.5 T MRI unit.\textsuperscript{3} El Kouli et al.,\textsuperscript{3} was the first to show that adding quantitative DWI to conventional MRI at 3 T improved the diagnostic performance of MRI.\textsuperscript{6}

The aim of the present study was to investigate the diagnostic accuracy of DWI in the assessment of breast lesions and to provide further confirmatory evidence of the usefulness and the value of adding DWI as an adjunct to the standard breast imaging protocol using a 3 T MRI unit. Additionally, a further aim was to explore the capabilities of 3 T MRI, which can produce better spatial resolution at shorter imaging times for both DWI and dynamic enhancement sequences and hence improve lesion detection.

Materials and methods

Patients

A prospective clinical breast MRI study was undertaken at the Biomedical Imaging Department of University Malaya Medical Centre between November 2009 and November 2011. DWI was included in the MRI breast protocol for women with indeterminate or suspicious breast lesions detected by mammogram and/or ultrasound. Institutional medical board ethical approval and written patient informed consent were obtained. Patients with inflammatory cancers or those receiving ongoing chemotherapy were excluded from the study. Histopathological diagnosis from samples obtained via core biopsy or excision surgery was used as the reference standard.

MRI image acquisition

Diagnostic MRI was performed on the General Electric Signa HDx 3 T MRI machine (GE Medical Systems, Milwaukee, WI, USA) using a double breast coil with the patient in a prone position. The MRI protocol was standardized in all cases. Prior to contrast medium administration, axial fat-suppressed T2-weighted images short tau inversion recovery (STIR; 5000 ms repetition time (TR), 35.1 ms echo time (TE); 40 × 40 cm field of view (FOV), 416 × 256 matrix; 4 mm section thickness; 83.3 kHz/pixel receiver bandwidth; total acquisition time of 5 min 41 s) were obtained. Axial diffusion-weighted images with spin-echo echo planar imaging was performed with the following parameters: for $b = 500$ s/mm$^2$, 8000 ms TR, 70.9 ms TE; 40 × 40 cm FOV, 80 × 128 matrix, 250 kHz/pixel receiver bandwidth, acquisition of time 2 min 24 s, number of excitations (NEX) 4; for $b = 1000$ s/mm$^2$, 8000 ms TR, 80.9 ms TE, 40 × 40 cm FOV, 80 × 128 matrix, 250 kHz/pixel receiver bandwidth, acquisition time of 2 min 24 s; NEX 4. In all patients, a bolus of intravenous contrast medium (gadopentetate dimeglumine) was administered at a dose of 0.2 mmol/kg body weight (Magnevist 0.5 mmol/ml), followed by 10 ml of saline solution (1%). Dynamic MRI (VIBRANT) with and without fat suppression was performed before and six times after injection of contrast medium. The parameters for dynamic MRI were as follows: 4.3 ms TR, 2.1 ms TE, 10° flip angle, 36 × 36 cm FOV, 256 × 256 matrix, 62.50 kHz/pixel receiver bandwidth, 1.6 mm section thickness, acquisition time of 5 min 30 s (46 s per dynamic sequence, one mask image and dynamic images obtained every minute for 6 min). Post-processing multiplanar reconstruction in sagittal and coronal planes and apparent diffusion coefficient images for b-values of 500 and 1000 s/mm$^2$ were obtained.

Image interpretation

The DCE-MRI images were interpreted by two radiologists (K.R., Y.F.) with 8–12 years of breast imaging experience. The objective morphological and dynamic kinetic data of the breast lesions were recorded based on the American College of Radiology (ACR) Breast Imaging Reporting And Data System (BI-RADS) MRI lexicon.\textsuperscript{8} The characteristics of lesions, which included the shape, size, location, enhancement pattern, kinetic curve, and secondary findings such as axillary nodal involvement, were documented. Image interpretation and appropriate MRI BI-RADS category was documented and scores were given based on morphological
The final assessment category for each lesion was similarly performed according to the authors' previous study. DCE-MRI characteristics were interpreted as explained by Kuhl et al. and correlated with BI-RADS MRI descriptors of malignancy.

For DWI sequence, post-processing included quantitative analysis of the ADC values at the region of interest (ROI). The size of the ROI was set at 0.5 cm for all lesions and three randomly selected ROIs were taken at areas demonstrating the most avid enhancement on DCE-MRI, avoiding areas of necrosis. An image fusion technique was used to aid ROI placement at these sites. Image fusion of contrast-enhanced dynamic phase sequences onto the ADC map was performed using OSIRIX 32 bit software (Figs 1 and 2). ROI placement was repeated three times for each lesion, and the average mean ADC values were taken at the b-values of 500 and 1000 s/mm², respectively.

**Statistical analysis**

Receiver operating characteristic (ROC) curve analyses were performed to assess the diagnostic performance of the ADC values in tumour characterization and determine suitable ADC cut-off points to separate benign and malignant lesions. As the distribution of ADC values were non-parametric, Mann–Whitney U-test was used to compare ADC values of benign versus malignant lesions, whereas Kruskal–Wallis test was used to compare ADC values in the different MRI enhancement curve types. A p-value of less than 0.05 was considered statistically significant. All analyses were performed using IBM SPSS statistical software version 20.0.

**Results**

Out of the 50 women (age range 28–65 years) with breast lesions recruited for the MRI study, six were excluded due to poor image acquisition, which led to technical misinterpretation and ROI placement. Out of a total of 44 breast lesions, 31 were malignant and 13 were benign.

There were 26 invasive ductal carcinomas (IDC), two malignant phyllodes tumours, two invasive lobular carcinomas (ILC), and one mucinous carcinoma. The benign breast lesions were nine fibroadenomas, two fibrocystic disease, one benign proliferative lesion, and one fibroadenomatoid mastopathy. Mann–Whitney U-tests demonstrated significant differences between the ADC distribution of benign and malignant lesions in the b = 500 and b = 1000 groups (p < 0.001 at b-values of 500 and 1000 s/mm²; median ADC at b = 500 was 1.01 mm²/s for malignant and 1.55 mm²/s for benign lesions; and median ADC at b = 1000 was 0.92 mm²/s for malignant and 1.49 mm²/s for benign lesions).

At b = 500 and b = 1000, the same three outliers were demonstrated, comprising of a malignant phyllodes tumour and a mucinous carcinoma in the malignant category and one fibroadenoma in the benign category (Figs 3 and 4). The malignant phyllodes tumour demonstrated high ADC values (b = 500, ADC = 1.58 × 10⁻³ mm²/s; b = 1000, ADC = 1.45 × 10⁻³ mm²/s), as did the mucinous carcinoma (b = 500, ADC = 1.74 × 10⁻³ mm²/s; b = 1000, ADC = 1.63 × 10⁻³ mm²/s). The fibroadenoma had an abnormally low ADC value (b = 500, ADC = 0.87 × 10⁻³ mm²/s; b = 1000 ADC = 0.89 × 10⁻³ mm²/s) (Table 1).

The ROC curve at b = 500 yielded an area under the curve (AUC) of 0.897, while at b = 1000, the AUC was 0.919 (Fig 5). The cut-off value for benign and malignant lesions was 1.21 × 10⁻³ mm²/s (a lower value was more suggestive of malignancy, while values above this cut-off suggested benignity) for imaging done at b-value of 500 s/mm² with a sensitivity of 87.5% and specificity of 91.7%. At b = 1000 s/mm², the cut-off value for benign and malignant lesions was 1.22 × 10⁻³ mm²/s with a sensitivity of 90.6% and specificity of 91.7%.

With regards to the curve types obtained on DCE-MRI, all patients with a type 1 kinetic curve were benign, whereas 90.9% of patients with a type 3 kinetic curve were malignant. The bar chart shows the DCE-MRI kinetic curves versus percentage distribution of benign and malignant histopathological (HPE) results (Fig 6). Lesions demonstrating a type 2 kinetic curve were somewhere in between, leaning more towards malignant, of which only one-third was benign.

In an attempt to increase the accuracy, DCE-MRI BI-RADS classification were combined with the ADC values, setting the criteria to require both tests to return a positive result to denote malignancy. Hence, out of the four possible outcomes of combining DCE-MRI with ADC, only one (malignant in both instances) was taken as being malignant. At the b = 1000 (which showed a better AUC than b = 500), the combined DCE-MRI and ADC specificity increased to 100% with no reduction in sensitivity from b = 1000 value alone (Table 2).

Overall, in terms of tumour size, six lesions were <2 cm, 31 lesions were between 2–4.9 cm, and seven lesions were >4.9 cm. The benign lesions ranged from 1.4–5.1 cm and the malignant lesions ranged from 1.7–8.8 cm. Out of 31 malignant lesions, 17 were ER positive, 16 PR positive, and 18 HER2 positive. Fifteen patients had lymph node metastasis. Out of the 26 invasive ductal carcinomas, two lesions were grade 1, nine were grade 2, and 14 lesions were categorized as grade 3 tumours. No significant trend was demonstrated in the ADC values of these biomarkers, tumour size, or grade.

Significant results were obtained between types 1, 2, and 3 curve enhancement patterns (p = 0.015 at b = 500 and p = 0.008 at b = 1000), in which the mean and median ADC values were significantly higher in cases with a type 1 curve and lower in cases with types 2 and 3 curves.

**Discussion**

The assessment of breast lesions on MRI is based on the morphological criteria, enhancement kinetic pattern, and the T2 characteristic of breast lesions. Characterization of the detected lesions can be difficult as imaging features have been shown to demonstrate considerable overlap.
between benign and malignant lesions. Hence, in equivocal circumstances, an additional feature to characterize suspicious lesions could be helpful in order to decrease the number of invasive breast procedures.

DWI utilizes the microscopic thermally induced behaviour of molecules moving in a random pattern also known as Brownian motion. The random microscopic motion of water protons determines image contrast, in which low diffusion of water molecules corresponds to lower signal loss and hyperintense areas, and high diffusion corresponds to a higher signal loss and hypointense areas. DWI is quantified by ADC values, which is a calculated measure of water diffusion through the tissues. ADC values vary between malignant and benign breast masses, whereby the ADC values of malignant breast lesions are usually lower than those of benign lesions, indicating restricted water diffusion and increased cellularity. The ADC values of benign lesions are higher, reflecting normal cellularity and no restriction of water movement. Nevertheless, there is overlap as benign breast changes can mimic malignancies.

Breast lesions <5 mm and those with central necrosis or with rim enhancement <5 mm are difficult to delineate on

Figure 1 Left breast invasive ductal carcinoma (grade 2). (a) Axial DWI showed diffuse hyperintensity within the carcinoma compatible with diffusion restriction. (b) The lesion was peripherally hypointense on the ADC map. (c) At DCE-MRI, the lobulate lesion showed heterogeneous enhancement and (d) displayed rapid uptake of contrast medium with early washout enhancement pattern (type 3 curve). (e–f) Technical post-processing and ADC quantification. (e) The IDC showed peripherally hypointense signal on the ADC map and (f) image fusion technique of DCE-MRI sequence on the ADC map with ROI placement for the lesion. The lesion gave a mean ADC value of $0.82 \times 10^{-3}$ mm$^2$/s at $b = 1000$ s/mm$^2$. 

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DWI or may lead to inaccurate ADC value calculations. According to Liberman et al., there is a low likelihood for lesions <5 mm to be cancerous. In the present study, the targeted lesions were set above 1 cm in size. The smallest lesion was a 1.4 cm fibroadenoma.

The role of DWI and the capabilities of using ADC values on the 1.5 T unit to differentiate benign and malignant breast lesions have been demonstrated in previous studies. Lesion detection is improved by using higher magnetic field strength MRI due to its higher spatial resolution and increased signal-to-noise ratio. It also shortens the imaging acquisition time. Previous studies have compared the visibility of MRI breast lesions and ADC values at 1.5 and 3 T, and concluded that there were no significant differences in the ADC values of these lesions. However, with regards to lesion visibility, 3 T MRI was found to be better at detecting smaller lesions. The present study obtained statistically significant differences between benign and malignant lesions, for both b-values of 500 s/mm² and 1000 s/mm² (p < 0.010) and the present results are comparable to other studies performed at 1.5, 3, and 3 T.

In previous studies, ADC value calculations were obtained using various methods, either randomly or using single or double readers. In the present study, OSIRIX 32 bit software was used to perform image fusion of the dynamic contrast phase with the ADC map to determine the ROI for the ADC measurement. The most avid area of enhancement, and thus the most solid component of tumour, was selected as the ROI. This prevented areas with

Figure 2 Left breast fibroadenoma at the upper outer quadrant. (a) The lesion was hyperintense on DWI and hypointense on the ADC map (b). (c) DCE-MRI demonstrated a well-defined, oval heterogeneously enhancing lesion with non-enhancing septa. (d) Time signal intensity analysis demonstrated a gradual progressive enhancement pattern (type 1 curve). (e–f). Technical post-processing and ADC quantification. (e) The fibroadenoma was hypointense on the ADC map and (f) image fusion of DCE-MRI sequence on the ADC map showing a mean ADC value of $1.36 \times 10^{-3}$ mm²/s at b = 1000 s/mm².
tumour necrosis from being included in the ADC calculation, which could give rise to false or higher ADC reading. Significant results were obtained between ADC values of benign and malignant lesions (p < 0.001). The cut-off ADC values for benign and malignant lesions were determined as $1.21 \times 10^{-3}$ mm$^2$/s for $b = 500$ s/mm$^2$ and $1.22 \times 10^{-3}$ mm$^2$/s for $b = 1000$ s/mm$^2$, respectively. One malignant phyllodes tumour was found with high ADC values at both $b = 500$ and 1000 s/mm$^2$, measuring $1.58 \times 10^{-3}$ mm$^2$/s and $1.45 \times 10^{-3}$ mm$^2$/s, respectively. The

Figure 3 Box plot showing the mean ADC values for various benign and malignant lesions at $b = 500$ s/mm$^2$. HPE, histopathological result.

Figure 4 Box plot showing the mean ADC values for various benign and malignant lesions at $b = 1000$ s/mm$^2$. HPE, histopathological result.
other malignant phyllodes tumour in this study had a low ADC value as expected at both b-values, measuring $1.15 \times 10^{-3}$ mm$^2$/s and $1.03 \times 10^{-3}$ mm$^2$/s, respectively. Some studies have reported that it is not unusual to find high-grade invasive tumours with ADC values that are higher than expected. It is likely that these types of tumours may have microstructures that promote water diffusion.19,20

In the present study, the sensitivity of DCE-MRI alone was 100% with a specificity of 66.7%. When DCE-MRI was combined with $b = 1000$ s/mm$^2$, the specificity rose to 100%, while only mildly affecting sensitivity (90.6%). These results are comparable with the meta-analysis from previous studies conducted on 1.5 T MRI.3 However, larger sample sizes would be needed to reproduce these results in a more generalized patient population in the future.

Only one study found in the literature attempted to correlate quantitative DWI and DCE kinetic characteristics. The study by Partridge et al.21 showed that lower ADC values were associated with more suspicious kinetics. Incorporating ADC and the worst curve type (type 3) significantly improved the accuracy in the prediction of malignancy as compared to utilizing either variable alone, suggesting that DWI provides distinct and complementary information to DCE-MRI for lesion characterization.21 Significant results were also obtained between types 1–2 and type 3 curve enhancement pattern ($p = 0.015$ at $b = 500$; $p = 0.008$ at $b = 1000$).

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Mean ADC value ((b = 500 \text{ s/mm}^2))</th>
<th>Mean ADC value ((b = 1000 \text{ s/mm}^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign (FA, FCD, BPL, FM)</td>
<td>13</td>
<td>29.54</td>
<td>1.51</td>
<td>1.46</td>
</tr>
<tr>
<td>IDC – low grade</td>
<td>2</td>
<td>4.55</td>
<td>1.06</td>
<td>0.91</td>
</tr>
<tr>
<td>IDC – intermediate grade</td>
<td>9</td>
<td>20.45</td>
<td>0.89</td>
<td>0.89</td>
</tr>
<tr>
<td>IDC – high grade</td>
<td>15</td>
<td>34.09</td>
<td>1.01</td>
<td>0.92</td>
</tr>
<tr>
<td>Malignant phyllodes</td>
<td>2</td>
<td>4.55</td>
<td>1.37</td>
<td>1.24</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>2</td>
<td>4.55</td>
<td>1.04</td>
<td>0.93</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>1</td>
<td>2.27</td>
<td>1.74</td>
<td>1.63</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>100</td>
<td>–</td>
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</tr>
</tbody>
</table>

FA, fibroadenoma; FCD, fibrocystic disease; BPL, benign proliferative lesion; FM, fibroadenomatoid mastopathy.

Figure 5 ROC curves demonstrating AUC for DCE-MRI, ADC alone, and DCE-MRI+ADC combined methods in detecting breast malignancy.
In a series of 67 women with invasive cancer, Kim et al.\textsuperscript{22} did not show a statistically significant correlation between ADC value and prognostic factors, i.e., tumour size, tumour grade, and hormone receptor status, i.e., ER, PR, and HER2. They concluded that although the ADC value was a helpful parameter in the detection of malignant breast lesions, it could not predict patient prognosis. Yoshikawa et al.\textsuperscript{23} demonstrated a correlation between ADC and histological type.\textsuperscript{23} The present study did not establish a significant correlation when comparing tumour grades, tumour size, hormone receptor status, and lymph node metastasis to ADC values. The poor correlation of ADC values with prognostic factors of the malignant tumours in this study may be due to the small sample size.

The present study was limited by a small number of grade 1 carcinomas. There were only two grade 1 breast carcinomas. These data are a reflection of the current presentation of breast carcinoma in Malaysia, which is diagnosed at an advanced stage in the majority of cases. This had been reported to be attributed to the lack of awareness among local women to attend regular and early breast screening.\textsuperscript{24}

In conclusion, the present study provides further confirmatory evidence of the usefulness of quantitative DWI assessment in the characterization of breast lesions using 3 T MRI. The utilization of image fusion to determine the ROI placement for the ADC was also demonstrated to yield more accurate measurement of ADC values. The results from the present study and previous literature provide consistent evidence to support DWI as a diagnostic tool for breast lesion characterization and as a useful adjunct to standard breast MRI protocols in aiding the diagnosis of breast cancer.\textsuperscript{4,6,21} Based on the present study, a combination of DCE-MRI with DWI is suggested to improve the sensitivity and specificity of lesion characterization in breast MRI.

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