The role of apparent diffusion coefficient (ADC) and relative ADC in the evaluation of breast masses

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Aims and objectives

The movement of water molecules in the biological tissues due to heat effect is called diffusion and Brownian motion. Diffusion weighted magnetic resonance imaging (DW-MRI) is a noninvasive technique used for measuring the diffusion of water molecules in the tissues. Apparent diffusion coefficient (ADC) maps provide quantitative information about water diffusion [1]. Biologic factors such as patient's age and body temperature, and technical factors such as b value, sequence parameters, location, and area of region of interest may affect and change ADC values in various parenchymal organs. Routine T1- and T2- weighted images have a limited role in the evaluation of breast masses.

Studies performed using apparent diffusion coefficient (ADC) with DWI for differentiating benign from malignant breast masses are reported in the literature [2,3]. An ADC value of the breast tissue is reported to be affected by the hormonal status and water content of the breast parenchyma. This may be the menstrual cycle in the premenopausal women or changing tissue components after the menopause or the hormone replacement. The diversity and intra-and interpersonal changes of breast tissue is reflected on ADC values. The wide range of ADC values and overlapping malignant and benign measurements still holds the need for a more reliable measurement. The normalized ADC, also known as relative ADC (rADC) is proposed to minimize the relativity of the ADC measurements, which is calculated by dividing the lesion ADC to the ADC value of the reference organ [3].

In this study, our aim is to evaluate the efficiency of apparent diffusion coefficient (ADC) and relative ADC (rADC) values for discrimination of benign and malignant breast lesions with diffusion-weighted magnetic resonance imaging (DW-MRI).
**Methods and materials**

All exams were performed with a 1.5-Tesla system (Magnetom Espree with Syngo MR B15 software; Siemens, Erlangen, Germany) by using bilateral 4-channels breast matrix coil with the patient in the prone position with a standardized protocol (Table 1). After bolus injection (injected at rate of 2.0 mL/s, 20 seconds delay) of contrast agent (Gd-DTPA, Magnevist; Bayer HealthCare, Bayer Schering Pharma) dynamic images were obtained. After the examination, subtraction of the unenhanced images from the first contrast-enhanced image on a pixel-by-pixel basis was performed by preset software. Premenopausal women were scanned during the second week of the menstrual cycle. ADC maps were automatically calculated by the vendor's preset algorithm by using the given b values (0 and 800 s/mm²) just after the sequences were completed.

**Patient selection**

Between June 2008 and September 2013, consecutive breast MRI examinations were retrieved from our database. Written informed consent was obtained before all breast MRI procedures. Institutional Ethics Committee had approved this retrospective study (No: 2013-539). Lesions with certain pathology result or with 2 years of follow up were included in the study. Patients with insufficient diffusion-weighted image quality, previous biopsy-surgery, neoadjuvant chemotherapy, and unilateral mastectomy were excluded.

**Image and Data Analysis**

Two breast radiologists (U.A.O.) and (A.O.) with 10 years of experience in an academic setting analyzed MRI results. The ADC maps were used to measure ADC values. Care was taken when positioning appropriate regions of interest (ROIs) to avoid cystic, calcific, hemorrhagic, and necrotic parts of the masses (Fig. 1 on page 5, Fig. 2 on page 5, Fig. 3 on page 6). The ROIs were at least 15 mm². The contralateral retroareolar central fibroglandular breast tissue was used as the reference tissue in the same series and ADC values were obtained (Fig. 4 on page 6). The mean value of ROI measurements on the same slice of breast was calculated for rADC values. The rADC values were calculated to eliminate the signal differences due to equipment, technical parameters, and tissue properties. The rADC values were obtained by dividing the mean values by the ADCmass measurements, and contralateral breast ADCcontralateral measurements respectively:

\[ rADC = \frac{\text{mean } ADC_{mass}}{\text{mean } ADC_{contralateral}} \]

**Statistical analysis**
All statistical analyses were performed using a commercially available software (NCSS (Number Cruncher Statistical System)) 2007 Statistical Software (Utah, USA). Independent-Samples T-Test and ROC curve were used to compare benign and malignant tumor ADC, rADC values. Sensitivity, specificity, positive predictive (PPV) and negative predictive values (NPV) for both ADC and rADC were calculated. Statistical significance was interpreted when P values were less than 0.05 (95% confidence interval).

Table 1. Routine breast MRI parameters

<table>
<thead>
<tr>
<th>Sequence</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Flip angle</th>
<th>Fatsat</th>
<th>Number of excitation</th>
<th>Voxel size (mm)</th>
<th>Orientation</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1w FLASH 3D</td>
<td>9</td>
<td>4.76</td>
<td>25</td>
<td>None</td>
<td>1</td>
<td>1.1x1.1x1.0</td>
<td>coronal</td>
</tr>
<tr>
<td>TIRM</td>
<td>3440</td>
<td>58</td>
<td>150</td>
<td>TI 170 ms</td>
<td>2</td>
<td>1.1x1.0x3</td>
<td>axial</td>
</tr>
<tr>
<td>Postcontrast</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1w FLASH 2D</td>
<td>129</td>
<td>4.6</td>
<td>80</td>
<td>None</td>
<td>1</td>
<td>1.3x1.0x3</td>
<td>axial</td>
</tr>
<tr>
<td>T1w VIBE</td>
<td>4.42</td>
<td>2.38</td>
<td>10</td>
<td>SPAIR</td>
<td>2</td>
<td>1.3x0.9x1.0</td>
<td>coronal</td>
</tr>
<tr>
<td>T2w TSE</td>
<td>9160</td>
<td>199</td>
<td>160</td>
<td>None</td>
<td>1</td>
<td>0.9x0.7x3</td>
<td>axial</td>
</tr>
<tr>
<td>DWI</td>
<td>12400</td>
<td>104</td>
<td>90</td>
<td>400</td>
<td>198X200</td>
<td>3</td>
<td>0-800</td>
</tr>
</tbody>
</table>
Fig. 1: Histopathologically proven invasive ductal carcinoma. Postcontrast T1w, and T2w TSE images. Enhancing spiculated mass, hypointense on T2 weighted images is shown.

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**Fig. 2:** DWI and ADC map of the same lesion on Figure 1, invasive ductal carcinoma. Restricted diffusion of the lesion, high signal intensity on DWI and low signal intensity on ADC map is demonstrated. ADC value of the lesion is 0.881x10-3 for b: 800 s/mm2.

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**Fig. 3:** Benign epithelial hyperplasia. DWI, ADC map and postcontrast T1w images. Enhancing lobulated mass with ADC value 1.814x10-3 for b: 800 s/mm2.

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**Fig. 4:** Left breast, opposite side breast normal parenchymal ADC value measurement of the patient with invasive ductal carcinoma shown in Figure 1 and 2. DWI, ADC map, postcontrast T1w, T2w TSE images. ADC value of the normal parenchyma is $1.934 \times 10^{-3}$ for $b:800 \text{ s/mm}^2$. rADC value of the lesion is $0.881 \times 10^{-3}/1.934 \times 10^{-3}=0.45$.

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Results

A total of 126 patients were retrospectively included in the study (63 malignant and 63 benign breast lesions). Malignant lesions were invasive ductal carcinoma (43 patients), ductal carcinoma in situ (6 patients), invasive ductal and invasive lobular carcinoma (4 patients), invasive lobular carcinoma (8 patients), tubular carcinoma (1 patient) and mucinous carcinoma (1 patient). Benign lesions were fibroadenoma (14 patients), intraductal papilloma (4 patients), benign phylloides tumor (1 patient), mastitis (3 patients), intramammary lymph node (2 patients), fat necrosis (2 patients), fibrocystic changes, adenosis, sclerosis, fibrosis (28 patients), at least 2 year follow up benign lesions (9 patients).

The difference between ADC values of malignant \((0.975 \times 10^{-3} \pm 0.297)\) and benign \((1.614 \times 10^{-3} \pm 0.398)\) lesions was statistically significant \((p=0.0001)\). The difference between rADC values of malignant (mean 0.878) and benign (mean 0.521) lesions was statistically significant \((p=0.0001)\). The difference between normal tissue of the opposite side breast ADC values was not statistically significant \((p=0.246)\). The sensitivity, specificity, PPV, and NPV for ADC values (cut off value 1.264) were 92.06%, 85.71%, 86.6%, 91.5%, and for rADC values (cut off value 0.687), 76.19%, 84.13%, 82.8% and 77.9%, respectively (Fig. 5 on page 9).

Figure 3. ROC Curve, sensitivity, specificity of ADC and rADC values.
Fig. 5: ROC Curve, sensitivity, specificity of ADC and rADC values.

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Conclusion

Diffusion weighted imaging in breast imaging has gained importance recently and various reports have been published concerning the ADC values. ADC provides a parametric value which allows objective assessment in the evaluation of breast masses. However different technical parameters may cause slight differences among the centers. Our study revealed that differentiation of benign vs. malignant breast lesions by calculating ADC and rADC values leads to high accuracy with high sensitivity, specificity, PPV, and NPV.

In different studies, ADC values allowed discrimination between malignant and benign lesions with a diagnostic accuracy of 95%, with $1.25 \times 10^{-3}$ for $b$: 850 s/mm² and $1.44 \times 10^{-3}$ for $b$: 600-1.18x$10^{-3}$ for $b$: 1000 s/mm² threshold values, 80% for $b$: 600 s/mm² and 77.5% $b$: 1000 s/mm² sensitivity and 95% specificity respectively [2, 4]. Partridge et al. demonstrated that both malignant masses (mean $1.25 \pm 0.29x10^{-3}$) and malignant lesions with nonmasslike enhancement (mean $1.41 \pm 0.22x10^{-3}$) had lower mean ADC than benign masses (mean $1.74 \pm 0.46x10^{-3}$) and benign lesions with nonmasslike enhancement (mean $1.61 \pm 0.33x10^{-3}$) [5]. In a study of Sahin et al. revealed mean ADC value $1.9 \pm 0.45x10^{-3}$ for benign lesions, $0.86 \pm 0.26x10^{-3}$ for malignant lesions with 88.5% sensitivity and 100% specificity [6]. In this study the ADC threshold for malignant lesions was $1.26x10^{-3}$ for $b$: 800 s/mm² in accordance with the results of Bogner and colleagues.

In the recent literature, the reported ADC values range between 0.86 to $1.41x10^{-3}$ [2, 6]. This range of ADC values limit the use of a certain threshold in the routine practice. The ADC values are affected by the b values, the magnet strength, tumor biology and internal characteristics of the tumor cellular structure. In this study, the cystic, calcific, hemorrhagic, and necrotic parts of the masses were avoided, and the post- biopsy cases (the hemorrhage would lower the ADC value) were not included to obtain more reliable ADC results that reflect the inner structure of the tumor mass. The rADC measurements may help to standardize the ADC values and our results showed a cut off value of 0.69 for malignant lesions with a sensitivity of 76%, specificity 84%.

Relative ADC measurements require a standard normal breast tissue measurement which limits its use due to intrinsic differences among different breast compositions. Another limitation of this study is that, our results are mainly based on invasive ductal and lobular pathology, while lacking specific data of various other types of malignancies.

**In conclusion**, both ADC and rADC values are efficient in discriminating between benign and malignant breast lesions with high sensitivity, specificity, PPV, and NPV.
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