Region of interest standardisation for diffusion-weighted imaging of breast malignancies

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Aims and objectives

Diffusion Weighted Imaging (DWI) is currently used in addition to the standard DCE-T1 and T2 series in breast MRI. DWI acquires the diffusion or motion of hydrogen protons in a voxel due to Brownian motion and is most often quantified in the apparent diffusion coefficient (ADC). Diffusion is affected by the tissue properties and obstacles (for example lipophilic cell membranes) and restricted in tissues with a high cellular density. In malignant lesions, the cells are more densely packed and the extracellular space is reduced, in comparison to benign lesions and normal breast tissue. Therefore, diffusion is restricted in malignant lesions. [1]. Apart from differences in the DWI acquisition protocols and postprocessing approaches [2-4], the method of region of interest (ROI) delineation also has a decisive influence on the ADC. This leads to different outcomes affecting the differentiation between malignant and benign breast lesions. [5]

In most clinical DWI studies published up to now ROIs have been drawn circular or ellipsoidal, or freeform to enclose as much of the lesion as possible while staying within the hyperintense lesion on DW images. [6-10] Alternatively, the brightest part of the lesion on the DW images is captured in the ROI [11-14], the hypointense part at the ADC map [15] or inside the solid portion of the lesion. [16-19] It was recently shown that the selection of subregions within lesions with high, intermediate or low ADCs influences the differentiation between benign and malignant lesions. [20] In that particular study the ROIs were not standardized in terms of either size or shape.

Therefore, the purpose of this study was to compare the reproducibility and diagnostic use of three alternative methods comparing the ADC values in ROIs standardized by fixing both size and shape, to cover the whole lesion.
Methods and materials

**Patient population:** In this retrospective study 41 consecutive women (ages 22-75, mean age 47) with 50 mass enhanced breast lesions (44 malignant and 6 benign), with an area of # 0.8 cm$^2$ were included between November 2008 and February 2011. Mean lesion size was 2.0 cm$^2$ (0.8-8.9 cm$^2$). Lesions smaller than 0.8 cm$^2$ and non-mass enhancement lesions were excluded to reduce partial volume effect. Exclusion criteria were: Cystic lesions, previous breast malignancy, breast surgery or breast radiation. Final diagnosis was acquired by mastectomy (24), lumpectomy (16), core needle biopsy (6) or follow-up MRI for at least 2 years (4).

**Data acquisition:** All MRI examinations were performed using a 1.5 Tesla (T) system (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany). Patients were placed in prone position. The MRI protocol consisted of transversal Dynamic Contrast Enhanced (DCE) T1-weighted, DW-images with b-values of 0, 50, 200, 500, 800 and 1000 s/mm$^2$ and pre-contrast ADC maps were automatically calculated from the b=0 and b=1000 s/mm$^2$ DWI series by dedicated software (AEGIS, Hologic, Mariborough, USA).

**Data analysis:** Three observers independently drew four types of ROIs: observer 1 was a medical student, observer 2 was a resident radiology, observer 3 was a radiologist with 6 years of experience in breast radiology. Observer 1 chose the largest cross section MRI slice, based on the lesion diameter on DCE-T1 (Figure 1). All observers placed ROI1 as an oval shape on that same slice, to encompass most of the lesion, while staying within its borders on the subtracted DCE-T1 series, and copied ROI1 to the DW images with b-values of 0 and 1000 s/mm$^2$. Only b-values 0 and 1000 s/mm$^2$ were used because that b-value combination showed the best discrimination between malignant and benign in a previous meta-analysis on DWI breast lesion evaluation. [5] ROIs 2, 3 and 4 with standard size and shape were positioned on b-values 0 and 1000 s/mm$^2$ as well. Possible position mismatch was corrected: DW images guided by their position (ROI2) or ADC outcome (ROI3,4) (Figure 2). ROI2 was a standardized circle of 0.3 cm$^2$ positioned in the middle of the lesion. ROI3 and ROI4 were also circular with fixed areas of 0.3 cm$^2$ and 0.6 cm$^2$ respectively and positioned inside ROI1 such that the lowest mean ADC was obtained.

**Statistical analysis:** For statistical analysis IBM SPSS Statistics 22 was used. The intra- and inter-observer variability were calculated using the Intraclass Correlation Coefficient (ICC). Dual axis plot was made for ROI1, to visualize the agreement of the size of ROI1. Differences between the mean ADC values of benign and malignant breast lesions were tested for significance by a sample t test. The mean ADC values were calculated by combining the results of all three observers, whereby the first set of measurements by...
observer 1 was used. The area under the curve (AUC) was calculated using receiver operating characteristic (ROC) analysis for the mean ADC values of all observers and each ROI. P-value of less than 0.05 was considered to indicate statistically significant difference.
**Fig. 1:** ROI1 positioned at largest cross section on the DCE-T1 series, subtracted and inverted.

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Fig. 2: ADC map for ROI1-4 projected on the $b = 0 \text{ s/mm}^2$ DW-Image of an invasive ductal carcinoma.

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Results

Breast lesions:

Forty-four (88%) out of the 50 breast lesions were malignant. Malignant breast lesions were invasive ductal carcinoma (41) or invasive lobular carcinoma (3). The size of ROI1 for malignant lesions varied between 0.8 cm$^2$ and 8.4 cm$^2$. For the 6 benign lesions (12%) the size varied between 0.8 cm$^2$ and 6.3 cm$^2$. The benign lesions consisted of five fibroadenomas (1 histologically proven, 4 with follow-up MRI) and one chronic mastitis.

Size of ROI1:

ROI 1 is a manually positioned oval of freehand size, to encompass most of the lesion, while staying within its borders on subtracted DCE-T1 series, and copied to the DW images using b-values of 0 and 1000 s/mm$^2$. Figure 3 shows high agreement in the size of ROI1 (the only ROI with an unfixed size) amongst the three observers.

Inter- and intra-observer variability:

Listed in Table 1 are the inter- and intra-observer correlations for the mean ADC values obtained in the 50 breast lesions using the 4 ROI methods. A strong agreement (>0.7) was found for all ROIs between the readers and good intra-observer correlation (>0.8). Overall, ADC reproducibility in ROIs 2 to 4 was similar to that in the entire lesion (ROI1).

ADC values for each ROI:

Table 2 shows the mean (±sd) ADC values of benign and malignant lesions for each ROI method of all 3 observers. Significant differences in ADC values of benign and malignant breast lesions were not observed in the entire lesion (ROI1) or in its center (ROI2) but did apply to the minimum ADC subregions of fixed size and shape: ROI3 (p=0.008) and ROI4 (p=0.044).

ROC analysis:

In Table 3 and Figure 4 the ROC analyses for the mean ADC values of the 3 observers are shown. ROC analysis showed the highest AUC for ROI3, 0.706 (95%CI: 0.549-0.864), consistent with the above mentioned best differentiation between benign and malignant lesions obtained with the small ROI minimum ADC fixed circle method (P=0.008).
Images for this section:

![Graph showing Size of ROI1 (cm²) for all observers.](image)

**Fig. 3:** Size of ROI1 (cm²) for all observers.

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Fig. 4: ROC curve for all ROIs.

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<table>
<thead>
<tr>
<th></th>
<th>ROI1</th>
<th>ROI2</th>
<th>ROI3</th>
<th>ROI4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-observer ICC</td>
<td>0.871 (0.804-0.920)</td>
<td>0.876 (0.811-0.923)</td>
<td>0.741 (0.606-0.839)</td>
<td>0.810 (0.707-0.883)</td>
</tr>
<tr>
<td>Intra-observer ICC</td>
<td>0.923 (0.868-0.955)</td>
<td>0.876 (0.787-0.928)</td>
<td>0.928 (0.860-0.961)</td>
<td>0.922 (0.862-0.956)</td>
</tr>
</tbody>
</table>

Table 1: Intraclass correlation coefficient (Confidence Interval, CI), absolute agreement, two way mixed, single measures for the mean ADC values of the 4 ROIs in the 50 breast lesions examined.
**Table 2:** Mean ADC values (sd) (x10-3 mm2/s) of malignant and benign lesions of all 3 observers and p-values.

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<table>
<thead>
<tr>
<th>ROI</th>
<th>Mean ADC values of Malignant lesions (±sd)</th>
<th>Mean ADC values of Benign lesions (±sd)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>ROI1</td>
<td>0.958 (±0.433)</td>
<td>1.002 (±0.542)</td>
<td>0.699</td>
</tr>
<tr>
<td>ROI2</td>
<td>1.171 (±0.371)</td>
<td>1.238 (±0.295)</td>
<td>0.466</td>
</tr>
<tr>
<td>ROI3</td>
<td>0.873 (±0.246)</td>
<td>1.050 (±0.357)</td>
<td>0.008</td>
</tr>
<tr>
<td>ROI4</td>
<td>1.002 (±0.266)</td>
<td>1.141 (±0.315)</td>
<td>0.044</td>
</tr>
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**Table 3:** Area under the curve for all ROIs and confidence interval.

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<table>
<thead>
<tr>
<th>ROI</th>
<th>Area under the ROC curve (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI1</td>
<td>0.540 (0.385-0.694)</td>
</tr>
<tr>
<td>ROI2</td>
<td>0.613 (0.482-0.744)</td>
</tr>
<tr>
<td>ROI3</td>
<td>0.706 (0.549-0.864)</td>
</tr>
<tr>
<td>ROI4</td>
<td>0.655 (0.507-0.803)</td>
</tr>
</tbody>
</table>
Conclusion

The purpose of this study was to compare the reproducibility and diagnostic use of the currently most widely applied ROI method featuring coverage of the entire lesion, to three alternative methods comparing the ADC values in ROIs standardized by fixing both size and shape. Any of the alternative ROI methods, featuring either fixed-size ROIs in the middle of the lesion (ROI2, 0.3 cm$^2$) or ones at lowest ADC (ROI3, 0.3 cm$^2$; ROI4 (0.6 cm$^2$), yielded strong inter- and intra-observer agreements, similar to those of ROI1.

In conclusion, these preliminary results showed that the ADC values derived from fixed size and shape ROIs covering the geometric center of breast lesions or subregions of minimal ADC are equally reproducible as whole lesion ROIs. Our very small proof-of-principle study indicates that minimum ADC subregions of fixed size and shape allow for improved differentiation between malignant and benign lesions. These results should be validated in a larger group of breast lesions and in prospective study.
Personal information

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References


