Diffusion-Weighted MRI for prediction of the response to neoadjuvant breast cancer treatment: our experience

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Authors: V. Di Fiore, M. Muzi, S. Ganino, L. Esattore, C. Canici, D. Tortora, A. Tartaro, A. R. Cotroneo; Chieti/IT
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Purpose

Background

In locally advanced breast cancer, a multimodal therapeutic approach, including neoadjuvant breast cancer treatment (NAC), surgery and adjuvant breast cancer treatment, possibly followed by radiation therapy, is required.

The assessment of tumor response to NAC has been shown to be essential for surgical planning and for the subsequent choice of chemotherapy regimen.

Magnetic Resonance Imaging (MRI) has proved highly accurate technique in the study of breast cancer neoadjuvant chemotherapy (NAC) in assessing the extent and disease activity. MRI is able to differentiate from residual tumor tissue alterations induced by treatment with reliability far superior to traditional method.

Diffusion-weighted MR imaging (DWI) has proved in recent years a qualitatively different technique in the diagnosis of malignancy, because of its inherent ability to evaluate the biological properties of tissues without the use of intravenous contrast medium and in times very short acquisition. Diffusion-weighted MR imaging (DWI) provides a quantitative analysis of the diffusivity in terms of apparent diffusion coefficient (ADC).

Purpose

To assess the role of Diffusion-weighted MR imaging (DWI) in the response of breast cancer to neoadjuvant chemotherapy (NAC), using the correlation between changes in the apparent diffusion coefficient (ADC) and pathologic findings.
Methods and Materials

PATIENT SELECTION

The work in an open-label uncontrolled. From February 2009 to May 2011, 25 patients with histopathologically confirmed breast cancer were included in the study.

The patients were subjected to NAC according to the scheme: 4 cycles of EC + 4 cycles of Taxotere +/- Herceptin.

MR PROTOCOL

All patients were subjected to DCE-MRI study integrated DWI (b values of 0-1000), before and after NAC, using a 1.5 T magnet.

<table>
<thead>
<tr>
<th>Technicals parameters</th>
<th>T1 Axial</th>
<th>STIR Axial</th>
<th>DWI Axial</th>
<th>THRIVE Axial</th>
<th>BLISS Sagittal</th>
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<td>FOV AP</td>
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<td>360</td>
<td>360</td>
<td>352</td>
<td>200</td>
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<td>360</td>
<td>360</td>
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<td>200</td>
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<td>3</td>
<td>4</td>
<td>1</td>
<td>1</td>
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<tr>
<td>RECON MATRIX</td>
<td>512</td>
<td>528</td>
<td>240</td>
<td>352</td>
<td>352</td>
</tr>
<tr>
<td>TE</td>
<td>8</td>
<td>70</td>
<td>88</td>
<td>2,4</td>
<td>3,6</td>
</tr>
<tr>
<td>TR</td>
<td>491</td>
<td>6243</td>
<td>9561</td>
<td>4,8</td>
<td>7,4</td>
</tr>
<tr>
<td>FLIP ANGLE</td>
<td>90</td>
<td>TI:165</td>
<td>90</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

*MR protocol*

For each lesion ADC values were measured before and after NAC using the following formula: ADC=(lnS0-lnS)/b

S0 = signal intensity obtained at b=0

S = signal intensity obtained at b=1000
ADC percentual variation was calculated according to the following formula: 
\[ \%ADC = \frac{ADC_{before} - ADC_{after}}{ADC_{before}} \times 100 \]
where ADC before and ADC after correspond to ADC values before and after treatment respectively.

The diagnostic performance of DWI (ADC values) was compared with the results of TRG classification.

**DWI-ADC analysis**

Two different methods have been used for DWI-ADC analysis: a Single ROI method where a single ROI was manually placed on the layer corresponding to the maximum longitudinal diameter of the lesion and Multiple ROIs method where three small ROIs (less than 100 pixels) were manually placed on different spots of the lesion to exclude necrotic or cystic areas. The average value was calculated for each measurement.

**DIMENSIONAL AND HISTOPATHOLOGICAL ANALYSIS**

The tumor response to treatment was assessed using the RECIST Criteria 1.1:

**RECIST CRITERIA 1.1**

- **Responders (R):** Complete Response (CR); Partial Response (PR; size reduction # 30%).
- **Non Responders (R):** Stable Disease (SD; neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD); Progressive Disease (PD; increase in size> 20%).

The histopathological examination after surgery has been the Gold Standard. Response to treatment was assessed, on the surgical specimen, according to the Mandard's classification based on tumor regression degree (TRG-Tumor Regression Grade):

**MANDARD'S CLASSIFICATION**

- **Responders (R):** TRG1: Complete Regression, no presence of residual malignant cells; TRG2: Presence of rare malignant cells in the fibrous tissue; TRG3: Increase of residual tumor cells with fibrosis predominant.
- **Non Responders (R):** TRG4: Residual malignant cells more than fibrous tissue; TRG5: No regressive changes.
STATISTICAL ANALYSIS

Statistical analysis has been evaluated using MedCalc Statistical Software, Mariakerke, Belgium.

Student’s T-test (independent samples) has been used to evaluate # % of maximum longitudinal diameter and ADC # % before and after NAC to establish differences between R and NR for both measurement method.

Diagnostic performance of each variability (sensibility, specificity and diagnostic accuracy) has been evaluated with ROC curves which allowed to identify a cut-off value corresponding to the highest sensibility and specificity value.

Correlation among accuracy of different methods has been established analysing ROC curves according to Hanley and McNeil's method.

Kendall’s test (tau) has been used to evaluate correlation between diameter and ADC # % (single ROI and multiple ROIs method) and different TRG groups according to Mandard's classification and between ADC values (before and after NAC) and lesion receptor state.

A P value of less than .05 was considered to indicate a significant difference.
Fig. 1: Single ROI method

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Fig. 2: Multiple ROIs method

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Results

POPULATION

- 18 patients and 20 lesions (mean age 41.3 years, range 27-67 years)
- 15 cases of invasive ductal carcinoma (IDC) (two of which associated with foci of intraductal and intralobular carcinoma in situ, 3 cases of ductulo-lobular infiltrating carcinoma (IDLC) and 2 cases of infiltrating lobular carcinoma (ILC) (one of which associated with intraductal and intralobular carcinoma in situ). Fig. 3 on page 12
- surgery: 5 mastectomies, 5 quadrantectomies, 7 segmentectomies and 1 lumpectomy
- Receptor state (15: ER; PgR; Her 2/neu; 5 :triple neg)
- Sentinel lymph node: 5 positive cases (axillary lymphadenectomy). Fig. 4 on page 12

MORPHO-DYNAMIC STUDY

- Diameter evaluation : $\Delta \% \ Ø=(\Ø_{before}-\Ø_{after}/\Ø_{before} \times 100)$
- 15 mass-like - 5 non mass-like
- 8 cases of multifocal/multicenter disease, 11 cases of unifocal disease, 1 case of bilateral disease.

<table>
<thead>
<tr>
<th>MR - DCE</th>
<th>mean lesion diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before NAC</td>
<td>36,2 ± 20,25</td>
</tr>
<tr>
<td></td>
<td>(range 10-80)</td>
</tr>
<tr>
<td>After NAC</td>
<td>11,79 ± 13,82</td>
</tr>
<tr>
<td></td>
<td>(range 0 - 55)</td>
</tr>
</tbody>
</table>

Mean lesion diameter before and after NAC Fig. 5 on page 13 Fig. 6 on page 14

<table>
<thead>
<tr>
<th>RECIST criteria 1.1</th>
<th>Complete Response (CR)</th>
<th>Partial Response (PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders (n = 17)</td>
<td>2</td>
<td>15</td>
</tr>
</tbody>
</table>

Responders

<table>
<thead>
<tr>
<th>RECIST criteria 1.1</th>
<th>Steady Disease (SD)</th>
<th>Progressive Disease (PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Responders (n = 3)</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Non Responders
<table>
<thead>
<tr>
<th>TRG</th>
<th>n°</th>
<th>Tot.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Non responders</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

**Mandard's classification**

<table>
<thead>
<tr>
<th></th>
<th>before-NAC ADC (x 10^-3 mm^2/sec)</th>
<th>after-NAC ADC (x 10^-3 mm^2/sec)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single ROI method</td>
<td>892,27</td>
<td>1234,42</td>
<td>0,0007</td>
</tr>
<tr>
<td>Multiple ROIs method</td>
<td>899,95</td>
<td>1295,06</td>
<td>0,0122</td>
</tr>
</tbody>
</table>

**MR DWI - ADC** [Fig. 7 on page 15 Fig. 8 on page 16]

At the end of NAC a significative increase of mean ADC value was seen for both Single and Multiple ROIs methods. [Fig. 9 on page 17 Fig. 10 on page 18]

Fig. 9: Mean ADC percentage variation in Single ROI method

*References: "G. d'Annunzio" University of Chieti, SS Annunziata Hospital of Chieti - Chieti/IT*
Fig. 10: Mean ADC percentage variation in Multiple ROIs method

References: "G. d'Annunzio" University of Chieti, SS Annunziata Hospital of Chieti - Chieti/IT

The next table summarizes the data reported by comparing the three considered methods:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p</th>
<th>AUC</th>
<th>Cut-off</th>
<th>Sensibility</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ% diameter</td>
<td>0.0053</td>
<td>0.821</td>
<td>&gt; 47%</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(82%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ% ADC multiple ROIs</td>
<td>0.0001</td>
<td>0.857</td>
<td>&lt; 37%</td>
<td>100%</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(86%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ% ADC single ROI</td>
<td>0.0001</td>
<td>0.893</td>
<td>&lt; 30%</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(89%)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 1: ADC single/multiple ROIs method: diagnostic performances

References: "G. d'Annunzio" University of Chieti, SS Annunziata Hospital of Chieti - Chieti/IT
Both Single and Multiple ROIs methods have demonstrated a higher sensitivity compared to the #% of the maximum longitudinal diameter (100% vs. 83%). There were no statistically significant differences between the three evaluation methods. Fig. 11 on page 19.

It was also assessed the correlation between the three evaluation methods and Mandard's TRG classes. The analysis showed that there is a direct correlation between the positive #% of the maximum longitudinal diameter and the different TRG classes ($p = 0.0013$ and $\tau = 0.527$), indicating that with decreasing of the maximum longitudinal diameter there is a statistically significant decrease in the TRG class. Fig. 12 on page 20.

<table>
<thead>
<tr>
<th></th>
<th>$p$</th>
<th>$\tau$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$% diameter/ TRG</td>
<td>0.0013</td>
<td>0.527</td>
</tr>
<tr>
<td>$\Delta$% ADC single ROI/ TRG</td>
<td>0.0008</td>
<td>-0.540</td>
</tr>
<tr>
<td>$\Delta$% ADC multiple ROIs/ TRG</td>
<td>0.0434</td>
<td>-0.322</td>
</tr>
</tbody>
</table>

**Table 2:** TRG correlations

**References:** "G. d'Annunzio" University of Chieti, SS Annunziata Hospital of Chieti - Chieti/IT
Fig. 3: Histologic lesions distribution

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Fig. 4: Breast surgery performed

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Fig. 5: MR morpho-dynamic study before and after NAC in a Responder patient
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Fig. 6: Morpho-dynamic study before and after NAC in a nonResponder patient

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Fig. 7: MR DWI/ADC single ROI method before and after NAC

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Fig. 8: MR DWI/ADC multiple ROIs method before and after NAC

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**Fig. 9:** Mean ADC percentage variation in Single ROI method

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![Mean ADC percentage variation in Single ROI method](image)

**Fig. 10:** Mean ADC percentage variation in Multiple ROIs method

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![Mean ADC percentage variation in Multiple ROIs method](image)

**Table 1:** ADC single/multiple ROIs method: diagnostic performances

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<td>Δ% ADC multiple ROIs/ TRG</td>
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<td>-0.322</td>
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</table>

**Table 2:** TRG correlations

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![ROC curves comparison](image_url)

**Fig. 11:** ROC curves comparison
Fig. 12: Correlation with TRG
Conclusion

- Conventional MRI is considered the gold-standard for the assessment of breast cancer before and after chemotherapy.

- DW MR has shown a significant increase of mean ADC value after NAC for both measurement methods (Single ROI/Multiple ROIs). Changes in ADC values were more significant in Responders than in Non Responders.

- The significant changes in ADC values after NAC suggest that this parameter imaging can be considered a useful biological marker to assess breast cancer response to chemotherapy.

- The correlation between changes of ADC and tumor response degree seems very promising, especially considering that DW MR requires short acquisition time and does not need intravenous contrast medium administration.

- Final aim could be DW MR exclusive application (without conventional DCE MR protocol) for analysing patients who underwent NAC.
References


Personal Information

v.difiore@rad.unich.it

m.muzi@rad.unich.it