Diffusion-weighted imaging in prediction of the response to neoadjuvant treatment in breast cancer patients.

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Purpose

Potential advantages to neoadjuvant chemotherapy (NAC) in breast cancer patients include presurgical reduction of tumor volume and earlier treatment of possible occult micrometastatic disease with the breast mass acting as a "marker” for treatment effectiveness. NAC is offered primarily to patients with locally advanced breast cancer. However, current clinical trials are evaluating the use of NAC in multiple patient groups including those with smaller tumors.

Reliable assessment of treatment response has emerged as an important challenge in radiological research and techniques that can provide reliable response assessment during and at the end of therapy are in high demand.

The current method of radiological response assessment for breast cancer is the Response Evaluation Criteria in Solid Tumors (RECIST). This system provides a set of guidelines for lesion evaluation and measurement and for response categorization but it is essentially based on change in lesion size. RECIST may underestimate the antitumor efficacy of newer drug agents with cytostatic rather than cytotoxic effect.

Dynamic-contrast-enhanced (DCE) Magnetic Resonance Imaging (MRI) is known to enable the most accurate assessment of tumor response after neoadjuvant chemotherapy.

DCE-MRI provides reliable information about the evaluation of residual disease after NAC and about early assessment of treatment response. Several studies have demonstrated the ability of DCE-MRI to predict the pathological response at the end of therapy and the eventual response during neoadjuvant treatment.

Recently, diffusion MRI has been shown to offer interesting possibilities to provide the effectiveness of chemotherapeutic drugs.

DWI is an unenhanced functional MRI sequence that measures the mobility of water molecules and provides different and potentially complementary information to dynamic MRI. The water mobility in a tissue depends on number and morphology of the cells, of cells arrangement and of extra-cellular matrix in which the cells are embedded. The apparent diffusion coefficient (ADC) is the unit of measure used to quantify the water diffusion in a tissue.

Given that diffusion MRI is sensitive to structure at the cellular level and is able to recognize normal from malignant tissue, it has the potential to detect and quantify cellular changes that occur during NAC. Chemotherapeutic drugs cause cell death by different mechanisms such as apoptosis, mitotic catastrophe and necrosis. These changes are
reflected as an increase in the mobility of water due to the reduction in cell density, the damage of the cell membranes integrity, and to increase in extracellular space.

Several studies have correlated changes in ADC during neoadjuvant chemotherapy in breast cancer patients with radiological response. In general mean tumor ADC value has been found to increase both in responder and non responder patients but to increase more in responders.

The presumed ability of diffusion imaging to predict response to NAC may open a new approach in the assessment of response to neoadjuvant treatment. A single short functional sequence could give a reliable evaluation of the treatment effectiveness.

Moreover follow "in vivo" the modifications of cancer's mass in early stage of NAC allows to prognosticate the final outcome of chemotherapeutic treatment and to plan eventual second-line therapy in patients that don't show a valid response to treatment and/or avoid over-treatments in patients who instead are considered non responsive to chemotherapeutic regimens.

The purpose of this study was to explore the potential of diffusion imaging to predict the response to NAC in breast cancer patients.
Methods and Materials

From January 2011 to June 2012, all consecutive women with breast cancer undergoing NAC in the Breast Cancer Unit of our hospital were enrolled in this study.

Approval for the study was obtained from our institutional review board. Written informed consent was obtained from all patients before MRI.

Both Diffusion-Weighted (DW) MR Imaging and Dynamic-Contrast Enhanced (DCE) MR Imaging were performed before NAC, after three cycles of NAC and after the end of therapy.

All patients underwent the same MRI protocol including a diffusion sequence acquired using b values of 0 and 1000 sec/mm$^2$.

MRI protocol

MRI was performed with a 1.5 T unit with 23 mT/m gradient strength (Signa Excite; GE Medical System, Milwaukee USA) with women in the prone position using a dedicated bilateral four-channel breast coil (In Vivo, Orlando, Fla).

The following sequences were always acquired:

- STIR axial sequence [Repetition Time (TR) = 5900 ms, Echo Time (TE) = 68 ms, Echo Train Length (ETL) = 17, Bandwidth 41-67, 512x512 Matrix, Thickness = 4 mm, 0 Interval, Field-of-View (FOV) = 32-34 cm, Number of Excitation (NEX) = 1-2]

- DWI axial sequence [TR = 5150, TE = min, 256x256 Matrix, Thickness = 4 mm, 0 interval, FOV = 32-34 cm, NEX = 2]. DWI was acquired before dynamic sequences with a spin echo EPI sequence in the axial plane. Sensitizing diffusion gradients were applied sequentially in the x-, y-, and z- directions with b values of 0 and 1000 seconds/mm$^2$.

- Three-dimensional (3D) FSPGR (Fast Spoiled Gradient Echo) fat sat coronal sequence [FA (Flip - Angle) = 15°, TR <30 ms, TE <5 ms, NEX = 0.5, Thickness = 2-3 mm, 0 Interval, 512x512 Matrix, FOV = 34-38 cm] before and five times after intravenous administration of 0.1 mmol/kg of Gd-DTPA (Gadopentetate dimeglumine). Contrast medium was injected with a 10 seconds of timing delay into the antecubital vein with a 18-20 G needle at a flow rate of 2 ml/s followed by a flush of 20 ml of saline solution

- 3D FSPGR sagittal post-contrast sequence (TR<30, TE<5, FA=15°, 512x512 Matrix, Thickness = 2-3 mm, 0 Interval, FOV = 22-26 cm, NEX = 2)

- 3D FSPGR axial post-contrast sequence (TR<30, TE<5, FA=30°, 512x512 Matrix, Thickness = 2-3 mm, 0 Interval, FOV = 34-38 cm, NEX = 2).
Acquisition time of this complete MRI protocol was 18-20 minutes.

**MRI analysis**

We used dynamic-enhanced imaging as a reference for detecting breast lesions.

All malignant lesions were measured in the three orthogonal axis. The greater diameter was considered for statistical analysis.

In cases of multifocal or multicentric cancer only the largest lesion was considered for data analysis.

The dynamic and diffusion images were evaluated in a dedicated workstation (GE Healthcare®, Advantage Windows 4.1), in consensus, by two radiologists with a large experience in breast imaging.

The ADC distribution is shown in an axial ADC color map, in which the red color represents the high ADC value and the blue color represents the low ADC values.

ADC maps were automatically calculated by the software using the following formula: 

\[
ADC = \frac{(\ln S_0 - \ln S)}{b}
\]

(where \(S_0\) is signal intensity obtained at \(b = 0\) and \(S\) is signal intensity obtained at \(b = 1000\)), directly applied by the program.

Using dynamic images as a reference, in diffusion images the ROI was manually placed in the target lesion in the slice where the lesion showed the larger diameter.

The placement of the ROI was also confirmed by agreement of the two radiologists.

**Data analysis**

After the end of treatment patients were classified on MRI as responder (R) and non responder (NR).

Based on RECIST criteria a complete response (disappearance of lesion) or a partial response (decrease of tumor volume of more than 30%) were defined as a response. Stable and Progressive disease were defined as non response.

Pre-treatment Apparent Diffusion Coefficient (ADC) and percentage increase in ADC after three cycles of NAC and before surgery were compared in responder and non-responder patients.
Results

117 female patients (mean age 49.0, range 30-68) were included in our study.

After the end of treatment 27 patients were classified as non responder and 90 as responder. Among responder 36 patients showed a complete response.

Before NAC mean ADC value of lesion was $0.99 \times 10^{-3}$ mm$^2$/s. Particularly mean ADC value for NR and R were respectively $0.96 \times 10^{-3}$ mm$^2$/s and $1.04 \times 10^{-3}$ mm$^2$/s.

After three cycles of NAC the percentage increase of ADC value for NR and R were respectively 7.7% and 29.8%. For patients with complete response the percentage increase was 36.0%.

Before surgery the percentage increase of ADC value for NR and R were respectively 11.1% and 42.0%. For patients with complete response the percentage increase was 42.3%.

Table 1: percentage increase of ADC value during and at the end of NAC in Responder and Non Responder patients

<table>
<thead>
<tr>
<th></th>
<th>% increase of ADC value after three cycles of NAC</th>
<th>% increase of ADC value before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>29.8</td>
<td>42.0</td>
</tr>
<tr>
<td>Non responder</td>
<td>7.7</td>
<td>11.1</td>
</tr>
<tr>
<td>Complete response</td>
<td>36.0</td>
<td>42.3</td>
</tr>
</tbody>
</table>

From the third cycle of treatment Responders show a percentage increase of ADC value greater than 20%. Among Responders, patients with complete response show a significantly higher percentage increase after three cycles.

Imaging

Responder Patient
**Fig. 1:** A, Axial MIP before NAC: malignant mass in the right breast. B, Diffusion sequence before NAC: ROI is drawn around the perimeter of the lesion. C, ADC map before NAC: the lesion shown an ADC value of 1.08 x10-3 mm2/s

**References:** Bioimaging and Radiological Sciences, Catholic University of Sacred Heart, Policlinico Gemelli - Rome/IT

*Fig. 1 on page*
**Fig. 2:** A, Diffusion sequence at the third cycle of treatment: ROI is drawn around the perimeter of the lesion. B, ADC map at the third cycle of treatment: the lesion shown an ADC value of $1.51 \times 10^{-3} \text{ mm}^2/\text{s}$

**References:** Bioimaging and Radiological Sciences, Catholic University of Sacred Heart, Policlinico Gemelli - Rome/IT

*Fig. 2 on page 13*
Fig. 3: Axial MIP at the end of therapy: the mass has disappeared

References: Bioimaging and Radiological Sciences, Catholic University of Sacred Heart, Policlinico Gemelli - Rome/IT

Fig. 3 on page 14

Non Responder Patient
Fig. 4: A, Axial MIP before NAC: malignant mass in the left breast. B, Diffusion sequence before NAC: ROI is drawn around the perimeter of the lesion. C, ADC map before NAC: the lesion shown an ADC value of 0.88 x10^{-3} \text{mm}^2/\text{s}.

References: Bioimaging and Radiological Sciences, Catholic University of Sacred Heart, Policlinico Gemelli - Rome/IT

Fig. 4 on page 15
Fig. 5: A, Axial MIP at the third cycle of treatment. B, Diffusion sequence at the third cycle of treatment. C, ADC map at the third cycle of treatment, the ADC value was 0.93 x10-3 mm2/s

References: Bioimaging and Radiological Sciences, Catholic University of Sacred Heart, Policlinico Gemelli - Rome/IT

Fig. 5 on page 16.
Fig. 6: A, Axial MIP at the end of therapy. B, Diffusion sequence at the end of therapy. C, ADC map at the end of therapy, the ADC value was $1.01 \times 10^{-3}$ mm$^2$/s.

References: Bioimaging and Radiological Sciences, Catholic University of Sacred Heart, Policlinico Gemelli - Rome/IT

Fig. 6 on page 17
Fig. 1: A, Axial MIP before NAC: malignant mass in the right breast. B, Diffusion sequence before NAC: ROI is drawn around the perimeter of the lesion. C, ADC map before NAC: the lesion shown an ADC value of 1.08 x10-3 mm2/s

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**Fig. 2:** A, Diffusion sequence at the third cycle of treatment: ROI is drawn around the perimeter of the lesion. B, ADC map at the third cycle of treatment: the lesion shown an ADC value of 1.51 x10^-3 mm²/s

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Fig. 3: Axial MIP at the end of therapy: the mass has disappeared

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Fig. 4: A, Axial MIP before NAC: malignant mass in the left breast. B, Diffusion sequence before NAC: ROI is drawn around the perimeter of the lesion. C, ADC map before NAC: the lesion shown an ADC value of 0.88 x10^{-3} mm^2/s

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**Fig. 5:** A, Axial MIP at the third cycle of treatment. B, Diffusion sequence at the third cycle of treatment. C, ADC map at the third cycle of treatment, the ADC value was 0.93 x10-3 mm2/s

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Fig. 6: A, Axial MIP at the end of therapy. B, Diffusion sequence at the end of therapy. C, ADC map at the end of therapy, the ADC value was 1,01 x10⁻³ mm²/s

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Conclusion

The study showed a significant difference in the rate of increase in the ADC value during the neoadjuvant treatment between Responders and Non Responder. Responder patients have a percentage increase of ADC value greater 20% from the third cycle of treatment and reach percentages of increase of around 40% at the end of treatment.

Non Responder patients have a low percentage of increase in the ADC value since the third cycle (< 10%) that does not change significantly at the end of treatment.

An important consideration concerns patients with complete response that at the third cycle showed an ADC value increase (36%) significantly higher than Responder.

These results demonstrate that diffusion imaging early can predict the response to NAC both in terms of responder and non-responder but also in terms of complete response.

The combined use of DW-MRI and DCE-MRI has the potential to improve the diagnostic performance in monitoring NAC. Our study confirm that diffusion imaging is a valid method in predicting response to treatment in breast cancer patients. ADC value seems to be an important predictor of responder patients even in the initial stages of treatment.
References


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