

ORIGINAL ARTICLE

Diffusion-weighted magnetic resonance imaging for pretreatment prediction and monitoring of treatment response of patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy

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Abstract

Background. For patients with locally advanced breast cancer (LABC) undergoing neoadjuvant chemotherapy (NACT), the European Guidelines for Breast Imaging recommends magnetic resonance imaging (MRI) to be performed before start of NACT, when half of the NACT has been administered and prior to surgery. This is the first study addressing the value of flow-insensitive apparent diffusion coefficients (ADCs) obtained from diffusion-weighted (DW) MRI at the recommended time points for pretreatment prediction and monitoring of treatment response. **Materials and methods.** Twenty-five LABC patients were included in this prospective study. DW MRI was performed using single-shot spin-echo echo-planar imaging with b-values of 100, 250 and 800 s/mm² prior to NACT, after four cycles of NACT and at the conclusion of therapy using a 1.5 T MR scanner. ADC in the breast tumor was calculated from each assessment. The strength of correlation between pretreatment ADC, ADC changes and tumor volume changes were examined using Spearman's rho correlation test. **Results.** Mean pretreatment ADC was $1.11 \pm 0.21 \times 10^{-3}$ mm²/s. After 4 cycles of NACT, ADC was significantly increased ($1.39 \pm 0.36 \times 10^{-3}$ mm²/s; $p=0.018$). There was no correlation between individual pretreatment breast tumor ADC and MR response measured after four cycles of NACT ($p=0.816$) or prior to surgery ($p=0.620$). **Conclusion.** Pretreatment tumor ADC does not predict treatment response for patients with LABC undergoing NACT. Furthermore, ADC increase observed mid-way in the course of NACT does not correlate with tumor volume changes.

Neoadjuvant chemotherapy (NACT) is currently standard treatment for women with locally advanced breast cancer (LABC) [1]. But, the response to NACT is highly individual and use of patient tailored treatment regimes are needed for improved outcome and survival for these patients [1]. Thus, non-invasive biomarkers that can predict treatment response either prior to the onset of treatment or early in the course of treatment would be of great clinical benefit.

In *in-vivo* diffusion-weighted magnetic resonance imaging (DW MRI), the signal intensity reflects local

microstructural characteristics of water diffusion over distances comparable to the cell diameter [2]. Presence of cell membranes, vessels, fibers or macromolecules restricts water diffusion. The complex water diffusion in tissue can be assessed quantitatively using the apparent diffusion coefficient (ADC). ADC is calculated from DW MRI by acquiring at least two MR images with different degrees of diffusion-weighting (b-values) [2]. As a quantitative parameter ADC reflects not only diffusion but also perfusion of microvessels and for b-values less than

100 s/mm² perfusion contribution has been shown to dominate [3–5]. By omitting low b-values the ADC is considered to be flow-insensitive since perfusion contribution is minimised and the ADC approximates true diffusion [5].

As tissue properties of malignant breast lesions differ from those of normal breast tissue or benign lesions, ADC has been recognized as a potential parameter of diagnostic and prognostic value [6]. Effective cancer treatments induce apoptotic and/or necrotic cell death. Depending of death mechanism, cell swelling or loss of membrane integrity occurs in the early phases of treatment, followed by lethal disruption of cell structures and loss of cell activity. The alteration in cell density and barriers to water diffusion can be assessed using DW MRI and studies have shown the potential for tumor ADC alteration being a surrogate marker for chemotherapy and/or radiotherapy response. In preclinical studies, increased tumor ADC occurring within hours to days after initialization of treatment was positively correlated with treatment response [7–9]. In clinical studies of LABC it has been shown that ADC increase precede tumor size reduction and that these ADC changes can be observed already after the first cycle of NACT [10,11]. A longitudinal study of breast tumor ADC from onset of treatment until completion of the third cycle of NACT showed a continuously increasing ADC value [11]. In a study including 11 LABC patients ADC measurements prior to the onset of treatment and after the full course of NACT indicated that ADC was a sensitive indicator of tumor response [12]. These previous DW MRI studies of LABC have been focusing on evaluating early changes in tumor ADC and have all been using flow-sensitive ADC values.

For rectal and brain tumors, a strong negative correlation between pretreatment ADC and ultimate tumor response has been found [13,14]. Variation in treatment response has been suggested to be directly related to tumor morphology where tumors with low pretreatment ADC, indicating high viability, show favourable response compared to tumors with high ADC values, indicating necrosis.

The purpose of this study was to assess the value flow-insensitive pretreatment tumor ADC for prediction of treatment response in LABC patients undergoing NACT. For patients with LABC the European Society of Breast Imaging recommends MR examinations to be performed before start of NACT, when half of the NACT has been administered and prior to surgery [15]. Whereas the second MR is aimed at examining the effect of NACT, the purpose of the final MR examination is the evaluation of residual disease. Thus, a secondary objective was to evaluate the predictive value of including DW MRI at these recommended time points.

Material and methods

Patients and treatment

Between April 2007 and March 2008, 25 patients with LABC (stage 2 and 3) were included in this study. One of these women had bilateral disease. The mean age of the study population at time of inclusion was 51.2 years (range; 37–72 years). The patients received NACT followed by surgery with local or loco-regional radiotherapy. None of the patients had received any treatment before the inclusion to this study. The study was approved by the regional ethics committee and the protocol review committee of our institution. Written informed consent was obtained from all participants.

MR examination

MR examination was performed prior to onset of NACT (MR0), after four cycles of NACT (MR1) and prior to surgery (MR2). A total of 65 MR examinations were carried out in this study. MR data from all patients at all time points was not obtained due to non-compliance (n=6), non-cooperation (n=3) or technical problems (n=1).

All MR examinations were performed using a 1.5 T MR system (ESPREE, Siemens, Erlangen, Germany) and a dedicated phased-array bilateral breast coil (CP Breast array coil, Siemens). Patients lay in the prone position and cotton pads were put inside the breast coils to reduce motion artefacts during acquisition of the data. MR parameters for the four sequences included in the study protocol, i.e. sagittal turbo spin-echo T1-weighted MRI, axial turbo spin-echo T2-weighted MRI, single-shot spin-echo echo-planar DWI and 3D-axial dynamic contrast-enhanced MRI, are shown in Table I. The DCE MRI was acquired every 85 s with gadopentetate dimeglutamine (Magnevist®, Schering, Berlin, Germany) being administered at a dosage of 0.1 mmol/kg body weight followed by a 10 ml saline flush.

Data analysis

Breast tumor volumes. Breast tumor volumes were obtained from the contrast enhancement images of the breasts. An in-house written semi-automated threshold based segmentation method similar to the one used by Partridge [16] was implemented in Interactive Data Language (IDL v6.3, Research System Inc., Boulder, CO). Initially, axial DCE MR images were reformatted to produce sagittal and coronal images series of both breasts. By using these three images series a volume of interest including contrast enhancing areas was defined. Contrast enhancement was calculated on a pixel-by-pixel basis for all pixels

Table I. MR protocol.

MR parameter	MR sequence			
	Sagittal TSE T1-w MRI	Axial TSE T2-w MRI	Axial single-shot SEEP DWI	3D-axial DCE MRI
Echo time (ms)	9.4	80	10300	1.43
Repetition time (ms)	666	4570	126	4.37
Inversion time (ms)			190	
Flip angle (degree)				12
Slice thickness (mm)	4	3	4	1
Slice gap (mm)	1	0	2	
Number of slices	30	50	26	160
Number of excitations	1	1	3	1
Field of view (mm × mm)	220 × 220	340 × 340	360 × 195	320 × 320
Image matrix	256 × 256	512 × 512	192 × 104	384 × 307 × 160
Bandwidth (Hz/pixel)	220	220	1240	345
Turbo factor	5	17		
Generalized autocalibrating partially parallel acquisitions				2
B-values (s/mm ²)			100, 250, 800	

TSE, turbo spin-echo; SEEP, spin-echo echo-planar.

contained within the selected volume. Tumor pixels were segmented from normal breast tissue by using a threshold excluding pixels with less than 80% enhancement within 3 minutes after contrast administration. This enhancement threshold was reduced after MR1 and MR2 to account for lower contrast uptake after NACT. By using a second threshold benign lesions with continuous increasing contrast enhancement were removed. Pixels where contrast enhancement was reduced by more than 80% between 3 and 7 minutes after contrast administration were anticipated to be blood vessels and were removed from the tumor volume. A visual inspection of the segmented volume was performed in order to prevent overestimation of the tumor volume. This interactive inspection included removal of pixels containing noise or enhancing blood vasculature and pathological skin thickening. The tumor volume was calculated by multiplying the number of segmented tumor tissue pixels by pixel spacing and slice thickness.

Tumor volumes were calculated from DCE MRI at all the three time points. Tumor response was assessed as tumor volume changes normalized to individual baseline tumor volumes.

ADC values. Postprocessing of the DW MRI was performed using the commercially available nICE software package (Nordic NeuroLab, Bergen, Norway). ADC-maps were calculated using a mono-exponential approach based on DW MRI with b-values of 100, 250 and 800 s/mm². Mean ADC of individual breast tumors were obtained by manually drawing a region of interest (ROI) in the ADC-maps inside a solid part of the tumor avoiding adipose tissue, areas

of necrosis and muscle. A native 800 s/mm² DW MR image and a subtraction image from DCE MR from the same anatomical location as the ADC-map were used to guide placement of the ROI, since areas of high signal enhancement in DCE MRI and high signal intensity on the native 800 s/mm² DW MR images both are known characteristics of tumor tissue [5]. Figure 1 illustrates placement of the ROI in the ADC-map of the first patient included in this study.

ADC values were calculated from DW MRI acquired prior to and following four cycles of NACT. If there was no contrast enhancement in areas previously occupied by the tumor on the second MR examination, no ADC value was calculated. Changes in ADC values were assessed as percentage changes of ADC values between MR0 and MR1.

Statistical analysis

All statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). The non-parametric Spearman's rho was applied to all performed correlation tests. Comparison between pretreatment ADC values and ADC values obtained after four cycles of NACT was performed by the two-sided paired samples Student's t-test. Significance level was set at 5% in all statistical analysis.

Results

Breast tumor volumes

Mean pretreatment tumor volume for all 25 patients was 26.25 cm³ (range, 1.60–83.96 cm³). Three of the patients had only MR0, 4 had MR0 and MR1, and

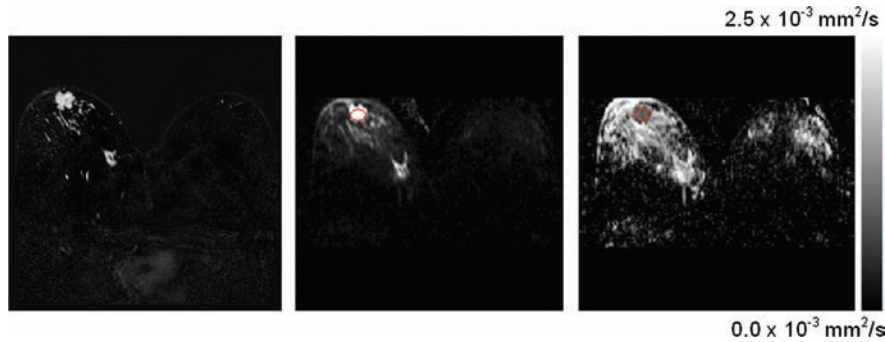


Figure 1. Placement of the region of interest (red circle) in the ADC-map (right) from the first breast cancer patient included in this study together with the corresponding native 800 s/mm² DW MR image (middle) and the subtraction image from DCE MRI 3 minutes after contrast injection (left).

18 had MR0, MR1 and MR2. Consequently, number of patients used for calculation of tumor volume changes between baseline and MR1 and baseline and MR2 was 22 and 18, respectively. One of these patients had bilateral disease and volumes of the right and left breast were calculated separately. Normalized tumor volumes from the three MR examinations for all patients are shown in Figure 2. In this study mean breast tumor volume after four cycles of NACT was reduced by 81.3%, but inter-patient variation was large. Tumor volume changes ranged from radiological complete remission with no remaining enhancing regions to a 17.5% reduction in tumor volume. At MR2 tumor tissue was detected in seven patients.

ADC values

Mean pretreatment breast tumor ADC was $1.11 \pm 0.21 \times 10^{-3} \text{ mm}^2/\text{s}$ (range, $0.80\text{--}1.50 \times 10^{-3} \text{ mm}^2/\text{s}$,

$n=21$). After four cycles of NACT the mean ADC was $1.39 \pm 0.36 \times 10^{-3} \text{ mm}^2/\text{s}$ (range, $0.87\text{--}2.11 \times 10^{-3} \text{ mm}^2/\text{s}$, $n=15$) yielding a significant increase of 23.8% ($p=0.018$). Mean area of the ROIs was 118.2 mm^2 (range, $28.1\text{--}221.5 \text{ mm}^2$) and 55.3 mm^2 (range, $28.1\text{--}137.1 \text{ mm}^2$) for MR0 and MR1, respectively.

In addition to patients excluded due to lack of follow-up MR (MR1: $n=3$, MR2: $n=7$), all DW MRI data from one patient was excluded from the dataset because movement artifacts precluded interpretation of the DW MRI. Finally, DW MRI data from MR1 and MR2 of the last four patients included in this study were excluded due to alterations in DW MRI parameters. For the patient with bilateral disease, contrast enhancing areas in the left breast were too small for ADC measurements. Furthermore, for two of the 21 patients showing radiological complete response without any remaining contrast enhancing areas in the DCE MRI after four cycles of NACT, no ADC was calculated.

Pretreatment ADC (mean ± 1 SEM) as function of tumor volume changes after four cycles of NACT (MR1) and prior to surgery (MR2) are shown in Figure 3A and B, respectively. No significant correlation between pretreatment ADC values and radiological assessed treatment response after four cycles of NACT ($r=-0.540$, $p=0.816$, $n=21$) or prior to surgery was found ($r=-0.130$, $p=0.620$, $n=17$).

Changes in ADC from MR0 to MR1 and tumor volume changes from MR0 and MR1 are shown in Figure 4. No correlation was found between these parameters ($r=0.047$, $p=0.869$, $n=15$).

Discussion

In this study including 25 LABC patients undergoing NACT, no correlations between pretreatment breast tumor ADC and radiological assessed treatment response was found. These results are in accordance with results briefly reported for breast tumors

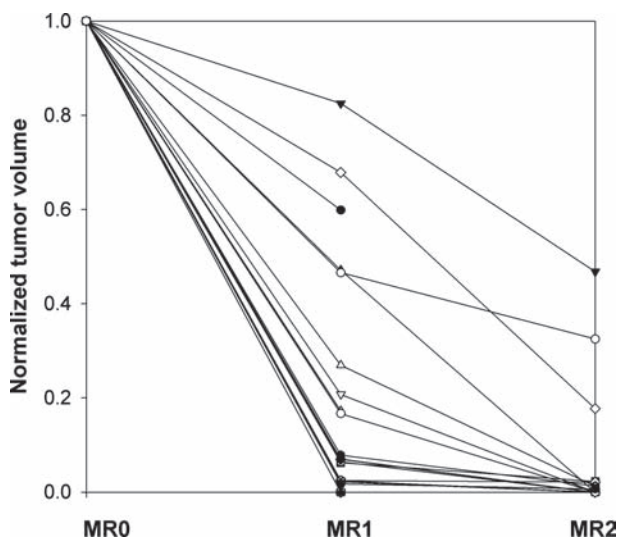


Figure 2. Normalized breast tumor volumes prior to onset of neoadjuvant chemotherapy (NACT) (MR0: $n=25$), after four cycles of NACT (MR1: $n=22$) and prior to surgery (MR2: $n=18$).

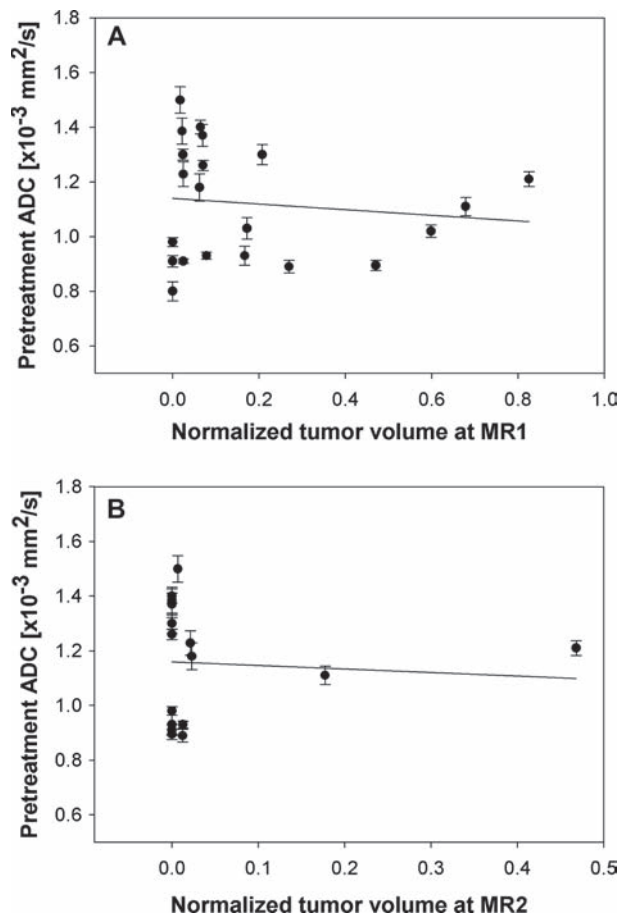


Figure 3. Pretreatment breast tumor ADC (mean $\pm$ SEM) as function of normalized tumor volume after four cycles of neoadjuvant chemotherapy (NACT) (MR1) (A) and prior to surgery (MR2) (B). Spearman's rho correlation showed no significant correlation between pretreatment ADC and tumor volume changes neither after four cycles of NACT ($r = -0.540$, $p = 0.816$, $n = 21$) or prior to surgery ($r = -0.130$, $p = 0.620$, $n = 17$).

by Manton [17], but contrasts other recent DW MRI studies of primary rectal carcinomas [13], brain gliomas [14] and colorectal hepatic metastasis [18] showing a strong negative correlation between pretreatment tumor ADC and tumor shrinkage during therapy. The differences in treatment response have been suggested to be related to the amount of necrosis in a given tumor and the fact that necrotic tumors often are hypoxic, acidotic and poorly perfused, all being factors that could explain their resistance to treatment [13,14]. In this study, only one breast tumor classified as containing necrotic areas based on an elevated pretreatment ADC value. This tumor showed a favorable response to treatment. Further studies are needed in order to address if structural differences between tumor types and mechanisms underlying tumor development may explain the conflicting results.

Mean pretreatment breast tumor ADC in our study was $1.11 \pm 0.21 \times 10^{-3} \text{ mm}^2/\text{s}$. It has recently

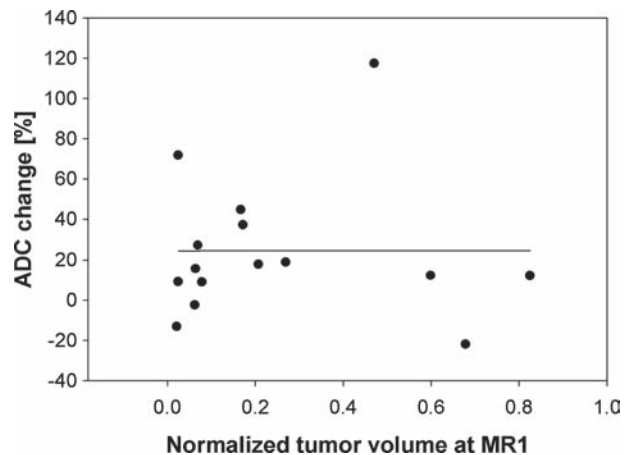


Figure 4. ADC change between pretreatment values (MR0) and after four cycles of neoadjuvant chemotherapy (NACT) (MR1) as function of normalized tumor volume after four cycles of NACT ($r = 0.047$, $p = 0.869$, $n = 15$).

been recommended to avoid using low b -values ($< 100 \text{ s/mm}^2$) for calculation of ADC since perfusion of microvessels may contaminate the diffusion signal for these low b -values [5]. Previous breast tumor DW MRI studies have been using $b = 0 \text{ s/mm}^2$ in combination with b -values of 300 s/mm^2 [12], 500 s/mm^2 and/or 1000 s/mm^2 [11,19,20], 700 s/mm^2 [10], 750 s/mm^2 [21] and multiple $b \leq 1000 \text{ s/mm}^2$ [17,20,22]. This is the first study reporting flow-insensitive breast tumor ADCs omitting low b -values for ADC calculations. Such flow-insensitive ADC values are anticipated to be different from flow-sensitive ADC values where directionality of micro-perfusion will contribute to the diffusion signal. Despite differences in selected b -values, breast tumor ADC values found in this study are in the same range as ADC values reported by other diffusion studies of malignant breast lesions [10,11,19–22]. This indicates limited perfusion contribution for these tumors. It should be noted that information on tumor vasculature obtained using low b -values may be of increased importance when anti-angiogenic treatments are included as part of the NACT regimen for LABC patients [3,7].

ADC values obtained using a single ROI can be affected by tumor heterogeneity and artifacts in the DW MRI due to patient movement, chemical shift and partial volume effects. In this study partial volume effects were minimized by using DCE MRI enhancement pattern and the native $b = 800 \text{ s/mm}^2$ DW-MR images as guidance for ROI placement, and thereby ensuring placement of the ROI within a solid part of the tumor and avoiding tumor borders. Large pretreatment tumor volumes allowed ROI translations within the tumor, ensuring ROI placement in an area with low ADC variability.

In this study mean ADC increased by 23.8% following four cycles of NACT compared to baseline values. No correlation between these ADC changes and tumor volume changes calculated at the same time point was found. Effective therapeutic interventions have shown to induce increased water diffusion due to loss of cell membrane integrity and increased extracellular extravascular space [8]. The increase in tumor ADC in our study is likely attributed to this response mechanism and is in accordance with other recent clinical breast diffusion studies showing increasing tumor ADC as function of time after onset of NACT [10,11,17]. But, reduced ADC at the end of NACT has been reported for responding primary rectal carcinomas. This drop has been suggested to be attributed to loss of necrotic fraction [13]. In contrast to our results and the results of a study evaluating ADC changes after two cycles of NACT [17], increase in ADC has been found to correlate positively with treatment response in breast tumors [11]. Compared to our study, these ADC changes were obtained earlier in the course of NACT i.e. after the three first cycles. Thus, if changes in tumor ADC can predict treatment efficacy with high sensitivity and specificity early after onset of NACT, the second MRI aimed at examining the effect of NACT should be performed earlier in the full course of NACT to permit an early change to second-line treatment and spare patients unnecessary toxicity, physiological morbidity and delay of initiation of effective treatment.

A possible shortcoming in our study is the use of a single ROI for obtaining tumor ADC. Histogram analysis of the entire breast tumor may be used to reduce uncertainties related to ADC measurements and also to provide more accurate information about the heterogeneity in tumor ADC. In a study investigating the predictive power of ADC values of rectal cancer treated with a combination of NACT and radiotherapy [23], emphasis were put on the potential of achieving increased predictive value by using histogram analysis. Significant difference in ADC values of non-responders and responders was only obtained when histogram analysis was applied in contrast to using mean ADC values. Segmentation of tumor volume followed by histogram analysis is however very time consuming and not clinically applicable.

In our study treatment response was evaluated using tumor volume changes, obtained by semi-automatic segmentation of DCE MRI, similar to the segmentation algorithm used by Partridge [16]. Segmentation of tumor tissue is technically challenging and may also be operator dependant. However, recent studies evaluating semi-automatic segmentation of tumor tissue based on DCE-MR images have shown that such methods can provide reproducible and accurate tumor volumes [24]. This study also

showed that the use of Response Evaluation Criteria In Solid Tumors, which is based on changes in the longest diameter, is less sensitive than 3D volumetric tumor measurements.

Our results showed that the inclusion of DW MRI as part of the diagnostic pretreatment evaluation and after four cycles of NACT for LABC patients undergoing NACT yielded no prediction of treatment efficacy.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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