Diffusion weighted MR derived apparent diffusion co-efficient values as a biomarker for treatment response in breast cancer

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PURPOSE: With an increase in the number of patients receiving neoadjuvant chemotherapy (NACT) for breast cancer and multiple emerging drug agents, reliable early assessment of therapy response would provide considerable benefit to patient care by facilitating tailored treatment for individuals. In this study, we sought to evaluate the performance of tumor apparent diffusion coefficient (ADC) values in predicting response early in the course of chemotherapy, for patients with breast cancer. We also assessed the effect of tumor marker clip placement on the ADC value.

METHODS: 15 patients with pathologically confirmed invasive breast cancer underwent MRI at 4 time points: pre-treatment (TP0), following the first cycle of NACT (TP1), following the second cycle of NACT (TP2) and prior to surgery (TP3). MRI investigations were performed on a 3T Achieva system whole-body MR scanner (Philips Medical Systems, The Netherlands) with a standard protocol including sagittal DW MRI (b-values = 0, 100, 400, 800 s/mm^2, spatial resolution =3 x 2 x2 mm^3). ADC values for each tumour were obtained by manually drawing regions of interest (ROIs) on the generated ADC maps from hypointense areas of tumour. If no diffusion abnormality was identified at Tp3, no ADC value was calculated. Patient response to NACT was determined by the Miller Payne grade (MPG) of the surgical specimen. Patients with MPG 2 or less were classified as non-responders. The mean and standard deviation of ADC values were calculated for each patient at the 4 timepoints. Box plots were drawn to examine the trend of ADC among responders and non-responders. Prior to initiation of NACT, 8 patients underwent tumour marker clip placement with a clip composed of a water-soluble polyethylene glycol-based hydrogel and a central marker of titanium. In order to determine the effect of this clip on tumour ADC values, a phantom was prepared consisting of a tumour-mimicking target with a hydrated clip embedded in it.

RESULTS: 10 patients were classified as pathological responders and 5 patients as non-responders. No significant difference of mean tumor ADC was identified at TP0 between responders (0.93 $\times 10^{-3}$mm^2/s) and non-responders (0.98 $\times 10^{-3}$mm^2/s). Compared with pre-therapy values, mean tumor ADC for responders was significantly increased at TP1 and TP2 (Figure 1A). No significant change in ADC values occurred in the non-responder group (Figure 1B). Statistical analysis of ADC values of responders at TP3 was unable to be performed as no diffusion abnormality was identified in 5 of the 10 patients. ADC values of a further 3 responders at TP3 could not be accurately determined as a result of artefact caused by the gel containing clip. Figure 2 shows representative ADC maps of a complete responder and a non-responder at TP0 and TP2. The ADC value of the gel containing clip in the phantom was 1.7 $\times 10^{-3}$mm^2/s and the ADC of the surrounding tumor was 1.4 $\times 10^{-3}$mm^2/s.

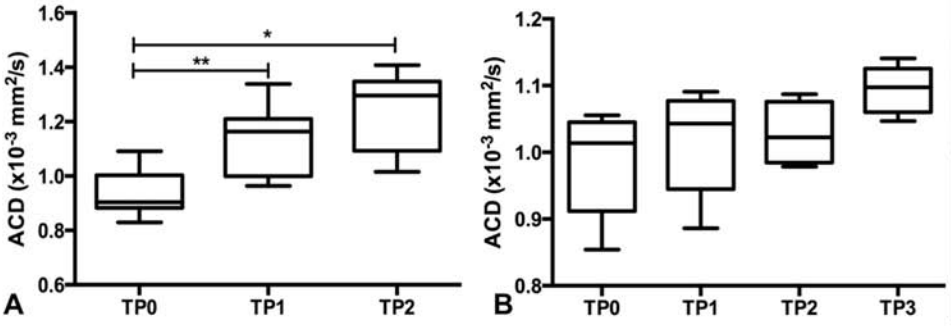

Figure 1: A. Box plot of ADC values of responders at TP0, TP1 and TP2. *p < 0.002 ** p < 0.004. Mean tumor ADC for responders was significantly increased at TP1 and TP2 compared to baseline values (TP0). **B.** Box plot of ADC values of non-responders at TP0, TP1, TP2 and TP3. No significant change occurred in the ADC values at the 4 timepoints.

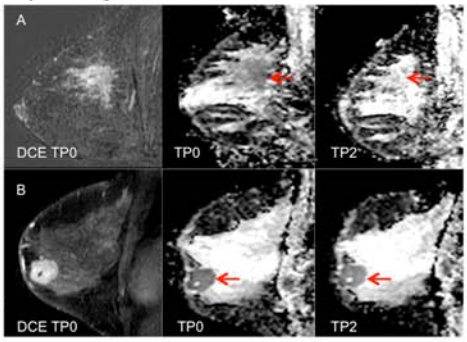

Figure 2: DCE images and ADC maps of a responder (A) and non responder (B) at TP0 and TP2. Tumour ADC increased by 40% between TP0 and TP2 in the responding patient but remained unchanged in the non-responder.

DISCUSSION: The results of the current study are in line with previous studies supporting ADC as a potential biomarker for treatment response[1-5]. For ADC values to gain acceptance as a response biomarker for incorporation into the clinical setting, further studies are required with larger numbers and attention to standardization of protocol design and reproducibility of technique. The high ADC value produced by the gel containing clip in the phantom, demonstrates a source of error when calculating ADC values in tumours containing these marker clips. It is important for clinicians to be aware of this error when drawing ROIs. Diffusion tensor (DT) imaging of the breast is an emerging concept with recent studies demonstrating differing degrees of anisotropy between breast lesions and normal breast tissue.[6-8] Fractional anisotropy (FA) is a parameter derived from DT MRI which describes the degree of anisotropic water diffusion in tissue. The fact that tumour composition changes following treatment, reflected by changes in the ADC values, provides an opportunity to evaluate FA values as a response biomarker. The scan protocol described above also included a DTI protocol and analysis is currently ongoing as to whether FA values correlate with changes in tumour size and ADC values.

CONCLUSION: Changes in ADC values early in the course of treatment predict response in patients receiving NACT for breast cancer. The gel containing clip, used for tumor marking prior to NACT, results in a potential source of error when calculating ADC tumor values and should be avoided when drawing tumor ROIs.

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