DIFFUSION WEIGHTED MRI OF THE BREAST: IS THERE A ROLE FOR APPARENT DIFFUSION COEFFICIENT VALUES IN THE PREDICTION OF RESPONSE AND IN THE EARLY ASSESSMENT OF RESPONSE TO NEOADJUVANT CHEMOTHERAPY?

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Introduction: MRI is routinely used to monitor tumour response neoadjuvant chemotherapy (NACT) for breast cancer. Conventional response assessment to NACT is by a repeat MRI at the end of treatment, but functional imaging techniques such as diffusion-weighted imaging (DWI) are showing promise for the earlier identification of disease response in oncology, and in some cases prediction of treatment response.

Aim: The goals of this study were 1) to look at the pre-treatment apparent diffusion coefficient (ADC) values and 2) early changes in the ADC and tumour size compared to overall radiological response in patients receiving NACT for breast cancer.

Methods: A retrospective computer based search identified 35 patients having NACT from October 2008 to Oct 2010. MRI with DWI was performed at 3 time points during treatment: pre, mid and post NACT. MR imaging was performed at 1.5 T system (Siemens, Erlangen, Germany) using a six-element breast matrix coil. DWI was acquired with a free breathe single-shot fat-suppressed (SPAIR) echo-planar sequence using gradient b-values of 0, 100 and 800 s/mm^2 in three directions (3-scan Trace mode). Standard T1W, T2W and T1W 3D fat sat dynamic and subtracted post gadolinium sequences were also acquired. The ADC was calculated by drawing regions of interest (ROIs) of 5-10 pixels over suitably homogeneously hypointense areas of the tumour, taking care to avoid heterogeneous areas of high SI. As far as possible, ROIs were placed in the same region of the tumour for the pre, mid and post treatment MRIs. Tumour size was measured as the maximum long axis dimension of the tumour. With respect to overall radiological response, the study population was divided into responders (>50% reduction in tumour size) and non responders (<50% reduction in tumour size). For each group, we looked at:

- The pre treatment ADC
- Early changes in ADC vs Early changes in tumour size

Parameters measured:

Results: Of the 35 patients identified for this study, there were 25 responders and 10 non responders. In our analysis we excluded 2 non responders and 5 responders because accurate ADC and/or size measurements could not be measured because they had complex solid-cystic or necrotic tumours (n=2), or the tumour appeared as non-mass like enhancement on MRI with no solid tumour to measure ADCs from (n=3), or because they had had a complete radiological response on the mid treatment MRI and no mid treatment ADC or size could be measured (n=2). Analysis of the remaining 28 patients is shown in Figs.1 and 2.

Fig. 1. Scatter plot chart showing pre treatment ADC values for responders and non responders. In general, lower pre treatment ADC values were seen in the responders over the non responders (p=0.003) with a threshold ADC of about 900 mm^2/s providing a good separation between the two groups.

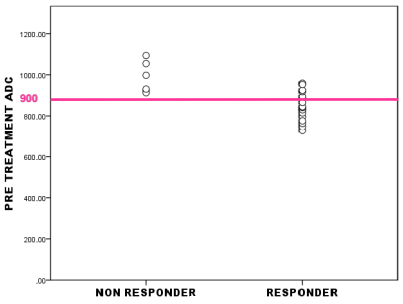
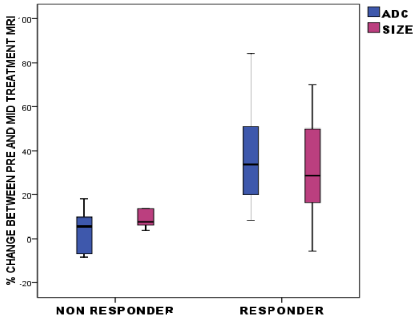


Fig. 2. Box and whisker plot showing early ADC changes versus early size changes for responders and non responders. There was a significant difference in early ADC changes (p=0.001). Although there was some difference in early size changes between the two groups, this was not statistically significant (p=0.093).



Limitations: Artefact caused by the MRI marker coil was one of the biggest limitations to accurately measuring the ADC. This became more problematic as tumours responded to treatment and became smaller in size. Tumour heterogeneity was another limitation. ROI selection, and thus ADC measurements, were more representative in homogeneous solid tumours, and less representative in heterogeneous micro or macroscopically partially necrotic tumours. Likewise, tumours which became fibrotic as they responded to treatment also posed limitations to measuring the ADC as this paradoxically lowered the ADC value. Using a mean ADC value was another limitation. Avoiding perfusion effects by excluding very low b-values, e.g. b0, from the ADC calculation may improve the accuracy of ADC by concentrating on true diffusion. Lastly, since ROIs were drawn on MR images from all three visits together, operators were not blinded to the overall radiological response.

Discussion: In keeping with earlier studies [1-3], these data show there is a correlation between early ADC changes and radiological response supporting the growing evidence that functional imaging changes occur early on in treatment for breast cancer (Fig.2). The data also indicates that early changes in ADC are a more reliable indicator of response over early changes in size (Fig. 3). We further evaluated this through subsequent receiver operating characteristic curve analysis, suggesting that early changes in ADC have a greater sensitivity and specificity in assessing response over early size changes. Lower pre treatment ADC were seen in responders over non responders (Fig. 1) suggesting that baseline ADC values may be able to identify those patients with a higher probability of responding to treatment, in keeping with another recent study [4]. In our data a threshold ADC value of 900×10^{-6} mm^2/s provided good separation between responders and non responders. These results support the idea that tumours with lower pre-treatment ADC values, reflecting higher cellularity, may have a better response to NACT by permitting greater drug access to the tumour cells, thereby increasing efficacy [4].

Future Work: Two studies have been published in 2006 and 2008 [1,2] which show changes in the ADC occur after only 1 or 2 cycles of NACT. They indicate the great potential in using ADC changes in assessing response earlier. Our aim would be to perform this study after 1 or 2 cycles of chemotherapy.

Conclusions:

ADC as a predictor of response: Pre treatment ADC values were significantly lower in responders in keeping with recent evidence for the use of ADC in predicting response to NACT in patients with breast cancer.

ADC as an early indicator or response: Changes in ADC associated with a response appear to be greater in the first half of treatment. In responders, these early changes in ADC occurred prior to early changes in tumour size. This supports the growing evidence for the use of ADC changes as an early indicator of response.

References: 1. Pickles MD et al. *Magnetic Resonance Imaging* 2006; 24: 843-847; 2. Sharma U et al. *NMR in Biomedicine* 2008; 22:104-113; 3. Yankeelov TE et al. *Magnetic Resonance Imaging* 2007; 25: 1-13; 4. Iacconi C et al. *European Radiology* 2010; 20:303-308.