Does diffusion weighted imaging have a role in predicting response to neoadjuvant chemotherapy?

M. D. Pickles[1], P. Gibbs[1], M. Lowry[1], and L. W. Turnbull[1]
[1]Centre for Magnetic Resonance Investigations, University of Hull, Hull, East Yorkshire, United Kingdom

Introduction. During neoadjuvant chemotherapy assessment of response is essential since not all patients respond to 1st line treatments. Traditionally this has been undertaken by evaluating tumour size measurements, however it is believed these alterations are a relatively late event. Currently alternative biomarker of response are been sought. DWI has been identified as a likely alternative since preclinical studies have demonstrated alterations in the apparent diffusion coefficient (ADC) prior to changes in tumour size measurements. This work evaluates DWI suitability for assessing response to neoadjuvant chemotherapy treatment in a cohort of breast cancer patients.

Methods. 21 patients were scanned prior to and post 1st, 2nd and final treatment cycles, a further 6 patients were imaged just at the pre treatment time-point. Patients were scanned either on a 3.0T or 1.5T scanner in combination with a dedicated breast coil. The use of two field strengths should not affect results since patients were exclusively scanned at one B_o and ADC values are independent of B_o. Diffusion weighted images of both breasts were acquired axially utilising a single shot dual spin echo EPI sequence with the following parameters: TR 4000ms, fractional TE 74ms (3.0T) or 98ms (1.5T), FOV/slice/gap 340x340mm/5mm/1mm, 10 averages, and *b*-values 0 and 700s/mm^2 applied in all three orthogonal directions, see Figure I. Short-term repeatability was assessed utilising the methodology proposed by Bland and Altman, since an understanding of repeatability is essential for longitudinal studies. Tumour volume and lesion longest diameter were obtained at each time-point. Patients who achieved ≥65% tumour volume reduction following treatment were classified as responders. Independent t-tests, paired sample t-tests, and one-way anova were employed to demonstrate the utility of DWI in predicting response and any relationship with histopathology grade and type.

Results. In the 27 patients scanned prior to treatment paired sample t-tests revealed a highly significant difference ($p < 0.0001$) between tumour (1.15±0.18 x10^{-3}mm^2/s) and normal breast parenchyma (1.63±0.24 x10^{-3}mm^2/s) ADC values. Similar to pre-clinical studies paired sample t-tests demonstrated a significant increase in ADC values following the 1st cycle (pre 1.20±0.19 x10^{-3}mm^2/s, 1st cycle 1.33±0.25 x10^{-3}mm^2/s, $p<0.001$) while a significant decrease in tumour volume (pre 22.00±20.15cm^3, 2nd cycle 12.89±11.51cm^3, $p=0.003$) and longest diameter (pre 40.73±13.50mm, 2nd cycle 32.13±13.33mm, $p=0.009$) was not noted until after the 2nd cycle. Following treatment 10 patients were classified as responders and 11 as non responders. Unlike tumour size measurements pre treatment ADC measurements revealed a borderline significant difference between response groups with responders demonstrating a lower ADC values. Changes during treatment did not reveal any significant differences between response groups for ADC measurements. However, significant differences were noted for both tumour volume and longest diameter between the pre and 2nd cycle time-points, see Table I. ADC values were significantly different between both histological grade (grade II 1.39±0.21 x10^{-3}mm^2/s, grade III 1.17±0.15 x10^{-3}mm^2/s, $p=0.01$) and type (NST 1.16±0.21x10^{-3}mm^2/s, ductal 1.28±0.12 x10^{-3}mm^2/s, lobular 1.64±0.06 x10^{-3}mm^2/s, $p=0.005$). Additionally ADC measurements revealed excellent short-term repeatability (±6.21%).

Conclusion. It appears, unlike tumour size measurements, pre treatment ADC values can give an indication of eventual response and tumour phenotype. It is also clear from these results that increasing ADC values at the 1st cycle time point demonstrate treatment induced cellular damage has occurred prior to tumour size indications of treatment response noted at the 2nd cycle time point. However, during treatment ADC values cannot differentiate between the response groups while tumour size measurements can at the 2nd cycle time point. The fact all tumours, regardless of eventual response classification, achieved tumour shrinkage explains diffusions poor response discrimination during treatment. For shrinkage to occur treatment induced cellular damage must have occurred, consequently ADC values will increase for all tumours regardless of eventual response classification. Consequently if DWI has a role in treatment prediction it appears the pre treatment time point offers the best prediction of eventual response.

Parameter	Response	Pre	Pre-1st	Pre-2nd
ADC	Responder	1.18±0.18 x10^{-3}mm^2/s†	11.64±15.72%	19.44±15.73%
	Non responder	1.34±0.21 x10^{-3}mm^2/s	10.30±6.36%	17.40±12.65%
Volume	Responder	25.83±23.51cm^3	-2.48±18.50%	-54.81±17.64%‡
	Non responder	18.50±16.91cm^3	6.02±9.06%	-22.02±25.78%
Diameter	Responder	40.41±14.15mm	1.52±8.62%	-32.12±26.24%‡
	Non responder	41.02±13.56mm	0.32±4.23%	-8.22±15.84%

Table I. Absolute pre treatment parameter values and percentage change in parameters between time points † $0.01<p<0.05$ ‡ $p<0.05$.

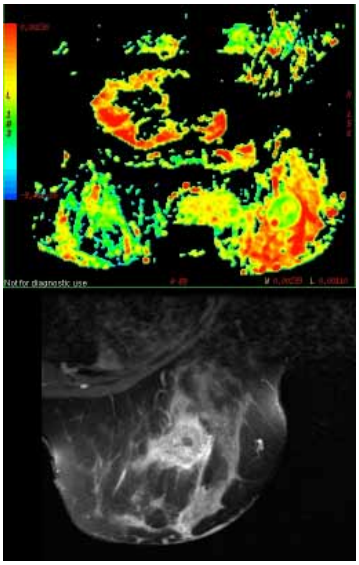

Figure I. ADC map with corresponding post contrast T1W fat saturated image of invasive breast tumour.