Decreased tumour ADC correlates with response in viable high-grade glioma treated with Temozolomide

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Introduction: An increase in tumour apparent diffusion coefficient (ADC) obtained using diffusion-weighted magnetic resonance imaging (DWMRI) has been proposed as a potential method to monitor early response to therapy in patients with brain tumours [1,2]. Since this has potential clinical benefit, a study was designed to assess the association between tumour ADC and response in patients receiving Temozolomide for high-grade glioma.

Methods: 14 adult patients with histologically verified high-grade glioma received exclusive treatment prior to radiotherapy with the oral nitrosourea Temozolomide, administered at a dose of 200 mg per m^2 on five consecutive days. This treatment cycle was repeated 28 days later. Steroidal use was permitted. There had been no previous chemoradiation or surgery other than biopsy. MR imaging was performed prior to treatment and 7-19 days after finishing the second 5-day course. The MR imaging data was obtained using a Siemens Magneton Vision, 1.5T MRI scanner, equipped with a quadrature head coil. DW echo planar imaging was performed using 3 b-values; 0, 500 and 1000 s/mm^2. The gradients were applied in 3 orthogonal directions. The parameters for the sequence were TR = 4000, TE = 100, NEX = 1, field of view = 230 x 230 mm - 300 x 300 mm, acquisition matrix = 256 x 256, number of slices = 10 - 20, thickness of slices = 5-6 mm and slice separation = 6.0-7.1 mm. Conventional 2D T1-weighted spin echo imaging was performed after the adminstration of contrast agent (Magnevist™, Shering).

ADC values were calculated using in-house software developed on the IDL platform (IDL, RSI Boulder, USA). Perfusion-sensitive ADC maps were created using b-values of 0, 500 and 1000 s/mm^2 and perfusion-insensitive ADC maps created using b-values of 500 and 1000 s/mm^2. In both types of data the trace ADC was calculated (the average of the 3 directionally-dependent ADCs determined from the three orthogonal encoding gradients). An experienced observer outlined tumour and control ADC values on a single centrally positioned slice within the tumour. Surrounding oedema was avoided, as were obviously cystic or necrotic portions within the tumour. An example of the positioning of such regions of interest (ROIs) is shown in Fig.1. ROIs outlined on the perfusion-sensitive ADC map were then automatically transferred to the perfusion-insensitive ADC map. Tumour volumes were determined by a second experienced observer measuring the area of high signal on each contrast enhanced slice and multiplying by the distance between consecutive slices.

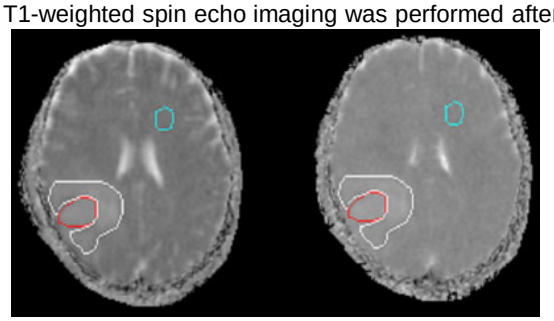

Fig. 1: Perfusion-sensitive map (left) and perfusion-insensitive map (right). Tumour (red), oedema (white) and a region of normal grey matter (blue).

All slices containing tumour were included in this analysis. Changes in tumour volume were expressed as a percentage normalised to the initial tumour volume.

Results: Of 14 patients entered, 3 had no MR imaging performed after the initial scan and technical difficulties rendered another patient's diffusion imaging data unusable. Of the remaining 10 patients it proved difficult to differentiate between tumour and surrounding oedema in 3. A summary of ADC values and their correlations with percentage tumour volume change for the remaining 7 patients are shown in table 1. The mean percentage reduction in tumour volume between the two MR scans was 20.4 ± 36.6%. Pre-treatment tumour volume is not associated with subsequent reduction in tumour volume (r=-0.10, p=0.83).

Table 1	**Perfusion-Sensitive ADC**			**Perfusion-Insensitive ADC**		
	Mean ± St. Dev	Correlation Coefficient	Two tailed P-value	Mean ± St. Dev	Correlation Coefficient	Two tailed P-value
Pre-treatment ADC x 10^{-6} mm^2/sec	1511 ± 379.2	-0.4	0.38	1354 ± 283.1	-0.31	0.5
Difference (final - pre-treatment) mean tumour ADC x 10^{-6} mm^2/sec	- 66.8 ± 149.5	0.96	0.0006	- 82.8 ± 101.6	0.84	0.02
Ratio (final/pre-treatment) mean tumour ADC x 10^{-6} mm^2/sec	0.96 ± 0.08	0.97	0.0003	0.94 ± 0.08	0.73	0.064
Difference (final - pre-treatment) mean control ADC x 10^{-6} mm^2/sec	37.6 ± 78.2	-0.05	0.90	30 ± 61.1	0.03	0.95

A significant correlation between the reduction of tumour volume and the reduction in mean perfusion-sensitive and mean perfusion-insensitive tumour ADC value is observed.

Discussion: The drop in tumour ADC values in patients that responded to treatment may arise predominantly from changes in tumour perfusion. Cystic and necrotic regions of the tumour are not included in the ADC data analysis and tumour volume has been assessed using post-contrast T1-weighted images (intrinsically linked to the vascularity of the tumour and the degree of blood-brain-barrier disruption). A reduction in the perfusion-insensitive ADC tumour value is also associated with response indicating that a reduction in tumour extracellular space may result as a high-grade glioma responds to this treatment with Temozolomide.

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References: 1. Chenevert TL, et al, J Natl. Cancer Inst. 2000; 92(24):2029-36 2. Mardor Y, et al, J Clin. Oncol. 2003; 21(6):1094-1100