

Parametric response maps from DCE-MRI predict response to chemoradiotherapy in high grade gliomas

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Purpose: The search by neuro-radiologists, oncologists and neuroscientists for effective methods of determining response to treatment in high grade gliomas has recently led to the development of functional parameter mapping¹. Maps based on volume changes of both ADC and rCBV have shown significant differences between treatment responders and non-responders². There are, however, many more parameters that can be generated from functional MRI approaches that could also be useful biomarkers of response. In this investigation we directly compare the ability of diffusion-tensor, dynamic contrast-enhanced and dynamic susceptibility contrast imaging to discriminate between responding and resistant tumours in the early phase of treatment.

Methods: Data were acquired from seventeen patients with biopsy proven gliomas who underwent chemo-radiotherapy following surgery. Baseline scans were conducted after surgical debulking but prior to any adjuvant treatment with subsequent imaging obtained within 2 weeks of completion of chemo-radiotherapy (CRT; Temozolamide 75mg/m²/day, 30x2gy fractions). Patients were scanned on a 3.0T GE 750 Discovery using an eight channel phased array head coil. Conventional imaging in the form of FLAIR and post contrast T₁ imaging was acquired along with 32 direction DTI, multi-flip angle T₁ volumes (MFA; 3, 5, 10, 20 and 40°), T₁ dynamics (DCE; tdel=5s, 60 phases) and T₂* dynamics (DSC; tdel=2s, 45 phases). Following motion and eddy current corrections using the FMRIB software library³, parameter maps were computed using in house software. Pharmacokinetic modelling was applied to the DCE data using a two compartment Tofts-Kety model with contrast concentration calculated using T₁ maps, while DSC data were processed using the Boxerman model⁴ with CBV maps subsequently normalised to normal appearing contralateral white matter. Parametric volumes were created by registering all maps into a single 4D volume. Post radiotherapy parametric volumes were registered to the pre-treatment maps prior to having them subtracted to create the parametric response maps (PRM). Separate regions of interest (ROIs) defined from the T₂ abnormality on FLAIR images and from the post contrast T₁ images of the pre-CRT exam were used to sample the PRMs on a voxel by voxel basis for all parameters. Thresholds for segmenting the volumes were calculated from the PRM in ~80ml of normal appearing grey and white matter in the contralateral hemisphere of 4 of the patients. The value used was 1.96 times the average of the four standard deviations for each parameter, i.e. the repeatability of each parameter. Percentage volume changes defined by ±1 threshold for the entire ROI for each parameter were calculated. Volume changes defined by each parameter were tested independently for their ability to discriminate between responding and recalcitrant lesions by performing a one-way ANOVA with treatment outcome as the main factor where outcome was based on clinical and radiological follow up at 6 months following initiation of CRT. Patients were classified into two outcome groups, deceased plus progressive disease (ADV) versus stable plus partial response (POS).

Results: Adverse events were observed in 5 patients at the 6 month interval following therapy. In these 5 cases the volume change within a 3D ROI defined by abnormal FLAIR signal and determined by increases in post contrast T₁ signal, K^{trans} and v_e were all significantly greater than in the 12 responding cases (Table 1). Similar changes were noted within a ROI defined from the post contrast T₁ signal. The thresholds for K^{trans} and v_e in both instances were 0.051min⁻¹ and 0.094 respectively. Figure 1 graphically illustrates the magnitude of the changes in v_e for one case from each group. For the other parameters, volume changes greater than threshold for v_b and rCBV approached significance but there were no obvious trends for ADC or FA.

Discussion: Unlike previous uses of PRMs^{1,2} it is important to note that our observations were made in tumours that had been subjected to surgical debulking. Thus there will have been considerable remodelling of brain tissue both within and surrounding the tumour cavity. Further we drew our 3D-ROI only on pre-CRT images. These factors may explain some of the inability of ADC and rCBV derived PRMs to differentiate between responding and non-responding tumours. However, it is also not unreasonable to suggest that these parameters would not be expected to identify responses to CRT in this, the recommended⁵, treatment scenario for gliomas since, unlike K^{trans} and v_e, their values may be non-zero in some brain tissue states (oedema, enhancement, necrosis).

Conclusions: Even with the small population and the relatively simple ROI used here it is evident that DCE derived response maps show potential in detecting early failure of CRT after surgery and may support the switch to a more potent alternative treatment. Further, the same parameters are highly suitable biomarkers for assessment of second-line treatments, for example, anti-vascular agents. Clearly there is room for improvement, especially in the choice of ROI selection where a T₂ abnormality plus T₁ contrast mask combined from the pre and post CRT data may have greater differentiating power.

References: 1. Galban CJ, Chenevert TL, Meyer CR et al (2008), Nature Medicine 15: 572-576. 2. Galban CJ, Chenevert TL, Meyer CR et al (2011), Clin. Cancer Res. 17: 4751-4760. 3. Jenkinson M, Beckman CF, Behrens TEJ et al (2012), NeuroImage 62: 782-790. 4. Boxerman JL, Schmainda KM and Weisskoff RM (2006), Am. J. Neuroradiol. 27: 859-867. 5. Stupp R, Tonn JC, Brada et al (2010), Annals Oncol. 21 Suppl 5: 190-193.

Parameter (Direction)	Vol. change (%) for ADV group	Vol. change (%) for POS group
T ₁ Contrast (>threshold)	31.3 ± 6.2	13.3 ± 4.0*
T ₁ Contrast (>threshold + <threshold)	57.2 ± 6.3	38.6 ± 4.0*
K ^{trans} (>threshold)	27.3 ± 6.0	3.2 ± 3.9***
K ^{trans} (>threshold + <threshold)	36.7 ± 7.7	11.8 ± 5.0*
v _e (>threshold)	29.1 ± 6.4	3.9 ± 4.1**
v _e (>threshold + <threshold)	42.0 ± 7.7	14.3 ± 5.0**

Table 1. Volume changes for parameters defining significant differences between responders and non-responders. *P<0.05, **P<0.02, ***P<0.01

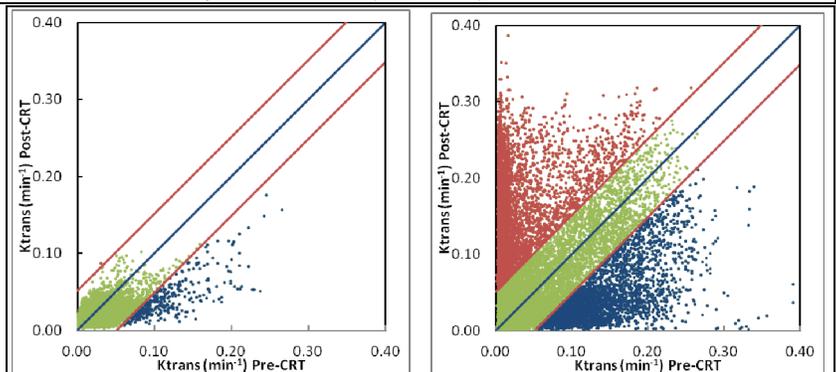


Figure 1. Scatter plots of post-CRT against pre-CRT K^{trans} for the complete 3D ROI in a treatment responding (left) and a non-responding case (right).