Prediction of progression free survival in high grade gliomas using pre-operative MR

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Introduction: The purpose of this study was to investigate whether pre-operative functional MR parameters reflecting cellularity, infiltration and perfusion could predict progression free survival at 6 months in high grade gliomas. With the addition of new information relating to the likelihood of disease progression, patient management such as scan frequency and treatment regime could be altered to reflect this new data. This work may be of interest to both clinicians and clinical scientists.

Methods: Multi-parametric MR data was acquired from 39 patients with histologically proven gliomas (Table 1). Patients were scanned with a 3.0T GE 750 Discovery system using an eight channel phased array head coil. Morphological imaging in the form of T_2 FLAIR and T_1 contrast imaging was acquired along with diffusion tensor imaging (32 directions), multi-flip angle T_1 volumes (3°,5°,10°,20°,40° flip angles), T_1 dynamics (tdel=5sec) and EPI T_2* dynamics (tdel=2sec). DCE-MRI preceded DSC-MRI to preload the tissue, reducing leakage effects that can cause misquantification. Motion within and between sequences was minimised by applying a series of motion correcting registrations using FSL[1]. All data was subsequently processed using in-house software. DTI parameters were: apparent diffusion coefficient (ADC), fractional anisotropy (FA), anisotropic component of diffusion (q), relative anisotropy (RA), longitudinal (λ_L), and radial diffusivity (λ_R). Pharmacokinetic modelling using a two compartment Tofts-Key model and a population AIF was applied to the DCE-MRI data transformed to contrast concentration using T_1 values calculated from the multi-flip angle data (R_1). DSC-MRI was processed using gamma variate and Boxerman[2] models. Cerebral blood volume (CBV_{GVF}, CBV_{BOX}) maps were then normalised to global white matter ($rCBV_{GVF}$, $rCBV_{BOX}$). T_1 and T_2* dominant leakage rate (K_2) was also measured. Parametric volumes were created by registering the FLAIR, T_1 post contrast, ADC, FA, q, RA, λ_L, λ_R, R_1, K_{trans}, v_e, v_b, $rCBV_{GVF}$, $rCBV_{BOX}$, and K_2 maps into a single 4D [x, y, z, parameter] volume[3]. Whole tumour volumes of interest were manually contoured using morphological imaging (T_2 abnormality + T_1 post contrast abnormality – necrosis/cyst – haemorrhage) (Fig. 1). Mean values were sampled for each parameter in all lesions. Gaussian mixture modelling (limited to 2 populations) was also applied to the VOI of each parameter, generating a further two means for each parametric volume. These two additional values were sorted in ascending order and labelled Population 0 and 1 respectively. Patients were dichotomised using the median value for each parameter over all patients. Kaplan-Meier survival analysis at 210 days from pre-operative MR was calculated for all 39 dichotomised groups (3 VOIs [Combined, Pop 0, Pop 1] x 13 parameters). Log rank tests were used to test for significant differences between the stable and progressive populations.

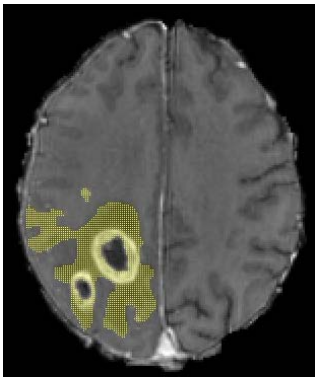


Figure 1 – Single slice from whole abnormality VOI (yellow pixels) in GBM patient. Note the exclusion of necrosis.

Table 1 – Grade versus 6 month status.

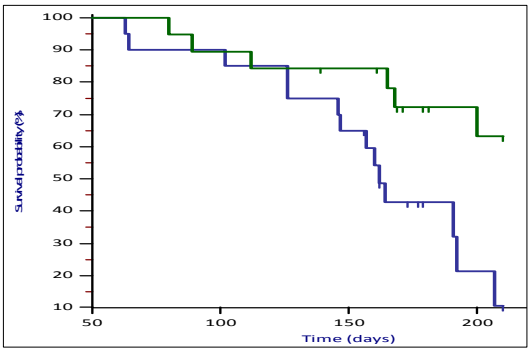
		Status		Total
		Stable	Progressive	
Grade	3	7	3	10
	4	12	17	29
Total		19	20	39

Results: Eight of the 39 mean values were significant discriminators of progression free survival at 6 months using P<0.05. The most significant results for each parameter are reported in table 2 (Fig. 2). FA, RA, λ_L, R_1, $rCBV_{GVF}$ and $rCBV_{BOX}$ were not significant predictors of disease progression.

Table 2 – Most significant results for each parameter using Kaplan-Meier survival analysis at 210 days using dichotomised mean parametric values.

	VOI	Median Cut-off	N	Events	95% Confidence Interval (days)		Sig.
					Lower Bound	Upper Bound	
ADC	Pop 0	< 1.0275	19	12	133	177	0.021
		>= 1.0275	20	8	172	204	
q	Pop 1	< 0.45325	19	5	165	208	0.003
		>= 0.45325	20	15	142	177	
λ_R	Pop 0	< 0.89895	19	12	133	177	0.021
		>= 0.89895	20	8	172	204	
K_{trans}	Pop 1	< 0.12325	19	7	170	203	0.033
		>= 0.12325	20	13	137	180	
V_e	Combined	<0.13015	20	7	168	203	0.031
		>= 0.13015	19	13	138	181	
V_b	Pop 0	< 0.02995	20	8	167	203	0.041
		>= 0.02995	19	12	139	182	
K_2	Pop 0	< -1.6923	20	14	140	180	0.009
		>= -1.6923	19	6	166	205	

Figure 2 – Kaplin-Meier survival chart for 6 months progression free survival dichotomised using a value of -1.6923 for Population 0 of K_2. P=0.009.



Discussion: Functional parameters derived from pre-operative MR can predict progression free survival at 6 months. The use of T_1 and T_2* dynamic imaging to derive parameters such as K_{trans}, v_e and K_2 should be considered for pre-operative MR assessment in these patients. From the data, it appears that tumours with high levels of vessel leakage progress more rapidly than less well perfused lesions. Lowest mean populations of ADC and radial diffusivity which reflect cellularity should be further examined. q relates to fiber tract integrity and is also a significant predictor of disease free progression but is unexpectedly higher in patients who progressed earlier. This possibly reflects the increased volume of oedema associated with more aggressive gliomas and the amount of intact white matter tracts included in the VOI. The use of Gaussian mixture modelling appears to improve the ability of MR to predict disease progression. For 6/7 parameters, subpopulations of parameters were more significant predictors of disease progression than whole tumour volumes of interest (combined). This process is fully automated requiring no hot-spot techniques and accounts for the entire volume of abnormality. These results underscore the non-Gaussian nature of these parameter distributions, and that statistical descriptors such as mean and standard deviation should be used with caution for whole tumour measurements. Functional pre-operative MR could be used to influence how radical surgical resection should be, as well as the scan interval and chemotherapeutic regimes for patients with high levels of vessel permeability.

Conclusions: Pre-operative MR parameters can predict progression free survival at 6 months in high grade gliomas. DTI, DSC and DCE all have added value.

References: 1. Jenkinson *et al*. Medical Image Analysis. (2001) **5**: 143-156. **2**. Boxerman *et al*. Am J Neuroradiol. (2006) **27**: 859-67. **3.** Kenning *et al.* Proc. 21st ISMRM. (2013). 0975.