Prediction of progression free survival at 6 months in high grade gliomas using pre-chemoradiotherapy MRI

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Introduction: The purpose of this study was to investigate whether functional MR parameters measured post-surgery prior to chemoradiotherapy, could be used to 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: Multiparametric MR data was acquired from 33 patients with histologically proven gliomas following surgery but prior to chemoradiotherapy. Patients were scanned on a 3.0T GE 750 Discovery system using an eight channel phased array head coil. Standard morphological imaging was acquired along with DTI (32 directions), T_1 DCE (tdel=5sec) and T_2* DSC (tdel=2sec). Motion within and between sequences was minimised by applying a series of motion correcting registrations using FSL[1,2]. 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-Kety 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[3] models. Cerebral blood volume 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 all maps into a single 4D [x, y, z, parameter] volume[2]. Whole tumour volumes of interest (TUM) were manually contoured using morphological imaging (T_2 abnormality + T_1 post-contrast abnormality – necrosis/cyst – haemorrhage) as was the contrast enhancing portion of the lesion (CEL) (T_1 post-contrast abnormality – necrosis/cyst – haemorrhage). Mean and standard deviation (SD) 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 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. A critical event was classed either as tumour progression on conventional non-study MR imaging, a clear clinical deterioration as noted by a member of the care team or disease related death before 210 days. Censored data was defined as radiologically stable MR imaging and/or clinical performance at 210 days from surgery (6 months from scan) or the closest follow up appointment.

Results: Ten critical events occurred before 210 days after recruitment (approximately 180 days/6 months from the scan). Kaplan-Meier survival analysis was calculated for each parameter and VOI combination (Table 1). Out of 39 dichotomised mean TUM values, 8 were found to have a p-value less than 0.05. Following calculation of the false discovery rate (FDR) 26% of cases were likely to be false. Significant parameters ($p<0.05$) were longitudinal and radial diffusivity from the DTI and all PK parameters derived from the DCE. No DSC mean values significantly correlated with progression-free survival at this time point. Standard deviation values measured using the TUM VOI for each parameter revealed 5 significant results with a FDR of 17.2%. Significant survival differences were observed using the standard deviations of λ_L, K^{trans}, v_b and K_2. Mean values of CEL produced 5 parameter values with $p<0.05$, and a FDR, 25.5%. These were q from the DTI and v_b calculated from the DCE. Once again, no DSC parameters significantly correlated with progression-free survival. Finally, the standard deviation values measured using the CEL VOI for each parameter revealed 4 significant results with a FDR of 29%. Significant results arose from DTI and DCE data only. ADC, RA, R_1, $rCBV_{GVF}$ and $rCBV_{BOX}$ showed no significant differences in progression free survival any parameter and VOI combination.

Discussion: The results suggest that PK parameters derived from DCE MRI and diffusion tensor metrics following surgery prior to adjuvant therapy can predict progression-free survival. Elevated values of K^{trans}, v_e and v_b were all significantly associated with a shorter progression-free survival interval, with v_b producing the greatest number of significant results. The implementation of DCE prior to chemoradiotherapy is potentially beneficial in two ways. Firstly, contrast enhancement can more easily be identified amongst blood products to aid radiotherapy planning, and secondly, the PK parameters can be used to identify patients that would benefit from more frequent scans given the likelihood of early tumour progression. Patients with a mean λ_L higher than the median remained stable for significantly longer periods than patients with a lower λ_L ($p=0.003$). The higher diffusivity values may indicate an absence of tumour infiltration and subsequently reduced progression. Radial diffusivity (λ_R) measured using TUM_0 was also found to be a significant predictor for progression-free survival. Patients that had a lesion with high radial diffusivity fared better. The absence of significant results using mean TUM and CEL DSC derived parameters may be related to the recent surgery; with hemosiderin and other blood breakdown products likely to destroy the MR signal at all points along the DSC time course. Therefore, rCBV estimations of the residual disease, especially in CEL, have the potential to be incorrect at the time of the scan, given the interval from surgery (3-4 weeks); and that post-surgical effects can persist for several months within the brain.

Conclusions: The results from this cohort of patients, suggest that parameters derived from DTI and DCE MRI following surgery can predict progression-free survival. Increased K^{trans}, v_e and v_b values were all associated with more rapid disease progression. At this time point it would appear that it is not worth conducting DSC examinations based on the blood products present.

STAT	PARAM	POP	VOI TYPE (P=)	
			TUM	CEL
MEAN	FA	VOI	0.519	0.183
MEAN	FA	VOI_0	0.986	0.329
MEAN	FA	VOI_1	0.820	0.183
SD	FA	VOI	0.119	0.183
SD	FA	VOI_0	0.375	0.083
SD	FA	VOI_1	0.403	0.035
MEAN	q	VOI	0.488	0.024
MEAN	q	VOI_0	0.915	0.053
MEAN	q	VOI_1	0.566	0.012
SD	q	VOI	0.551	0.008
SD	q	VOI_0	0.183	0.053
SD	q	VOI_1	0.586	0.171
MEAN	λ_L	VOI	0.089	0.639
MEAN	λ_L	VOI_0	0.204	0.888
MEAN	λ_L	VOI_1	0.003	0.591
SD	λ_L	VOI	0.955	0.865
SD	λ_L	VOI_0	0.024	0.048
SD	λ_L	VOI_1	0.109	0.619
MEAN	λ_R	VOI	0.506	0.744
MEAN	λ_R	VOI_0	0.038	0.347
MEAN	λ_R	VOI_1	0.074	0.639
SD	λ_R	VOI	0.885	0.865
SD	λ_R	VOI_0	0.078	0.193
SD	λ_R	VOI_1	0.788	0.360
MEAN	K^{trans}	VOI	0.116	0.107
MEAN	K^{trans}	VOI_0	0.038	0.278
MEAN	K^{trans}	VOI_1	0.130	0.245
SD	K^{trans}	VOI	0.168	0.486
SD	K^{trans}	VOI_0	0.038	0.092
SD	K^{trans}	VOI_1	0.168	0.274
MEAN	v_e	VOI	0.146	0.889
MEAN	v_e	VOI_0	0.033	0.266
MEAN	v_e	VOI_1	0.047	0.791
SD	v_e	VOI	0.227	0.486
SD	v_e	VOI_0	0.163	0.586
SD	v_e	VOI_1	0.149	0.943
MEAN	v_b	VOI	0.028	0.023
MEAN	v_b	VOI_0	0.002	0.008
MEAN	v_b	VOI_1	0.028	0.008
SD	v_b	VOI	0.145	0.068
SD	v_b	VOI_0	0.003	0.008
SD	v_b	VOI_1	0.028	0.068
MEAN	K_2	VOI	0.452	0.216
MEAN	K_2	VOI_0	0.697	0.100
MEAN	K_2	VOI_1	0.906	0.637
SD	K_2	VOI	0.009	0.131
SD	K_2	VOI_0	0.201	0.100
SD	K_2	VOI_1	0.229	0.471

Table 1 – List of parameters which showed at least 1 significant difference in progression free survival interval. Significant p-values are highlighted in red.

VOI = whole volume. VOI_0 = GMM population 0. VOI_1 = GMM population 1.

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