Metabolic activity of the invasive microenvironment of glioblastomas determines time to progression: a multimodal MR study

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TARGET AUDIENCE:

Neuroradiologists and clinicians treating patients with brain tumors as well as imaging scientist interested in brain tumor invasive margin.

PURPOSE:

Despite improvements in surgical technique to enable complete resection of the contrast-enhancing component of glioblastomas, most patients' tumor will progress in the peritumoral region within a year of diagnosis. Tumor progression heralds deterioration in quality of life and eventual death. This progressive disease is due to occult invasive tumor that extends variable distances into the normal brain. Diffusion tensor MR has been shown to be a sensitive method of identifying this occult invasion and image-guided biopsies have confirmed the presence of invasive tumor in this DTI abnormality[1]. DTI-defined regions of invasion can predict the site of tumor progression. The microenvironment of this invasive region can be further characterized using dynamic susceptibility contrast imaging (DSCI) and multivoxel ^{1}H-spectroscopy. This study aims to understand how the tumor microenvironment influences progression and response to treatment.

METHODS:

50 patients with glioblastomas (mean age 58.1, range 31.4 – 71.6; 33 male) were recruited in this prospective study approved by the local ethics committee. Patients were imaged pre-operatively at 3T on a Siemens Trio scanner. Imaging involved conventional anatomical sequences, DTI (5 b values, 12 directions), DSCI (to produce maps of rCBV) and 2D multivoxel ^{1}H-spectroscopy with TE=35ms (MRS). DTI data was processed using the FDT diffusion toolbox in FSL 5.0.0 (FMRIB, Oxford, UK) and maps of p and q were produced using the previously published equations[2]. DTI and rCBV maps were co-registered to the T_2-weighted axial images used for MRS planning using the FSL FLIRT toolbox. Abnormal areas of the q (anisotropic diffusion, usually reduced only in gross tumor) and p (isotropic diffusion, elevated in both tumor and invasive margin) were delineated and the difference was taken as the invasive residual tumor (Figure 1). Measurements were made in these regions (starred in Figure 1) of rCBV and spectroscopic measures of N-acetyl aspartate (NAA), myoinositol (mI), total choline (Cho) and glutamate-glutamine (Glx) normalized to creatine, as well as the Cho/NAA ratio. All patients underwent 5-ALA fluorescence guided resection of the tumor with the aim of complete resection of the contrast-enhancing component (achieved in 78%) followed by chemoradiotherapy. The time to progression was recorded for all patients. An ROC curve was produced to assess the ability of rCBV and MRS measures to predict progression free survival (PFS) of greater than 1 year. Cut off values of the measures with the highest AUC were determined and these were used in a multivariate Cox regression model of progression that included age and the extent of resection.

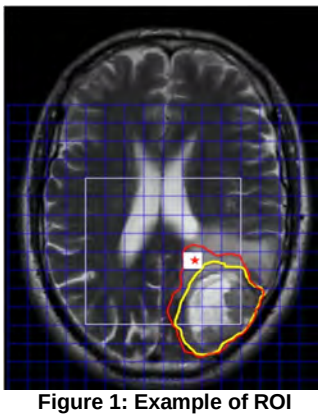

Figure 1: Example of ROI placement. The DTI-invasive margin is the area between the yellow line (*q*) and the red (*p*).

RESULTS:

30% of patients were progression free at one year. Table 1 outlines the AUC and showed that the Cho/NAA ratio provided the best predictor of one-year progression free survival with a cut off value of 0.6 providing 66.7% sensitivity and 74% specificity. Where Cho/NAA was <0.6 in the DTI-defined invasive region the median PFS was 230 days, in the 14 patients where it was >0.6 this improved to 497 days. In the multivariate Cox regression model this was associated with significantly prolonged PFS (P = 0.01; Kaplan Meier shown in Figure 2). There was no relationship between rCBV or other MRS measures and PFS.

Table 1: AUC from ROC curves

	AUC
Cho/NAA	0.73
NAA/Cr	0.69
Glx/Cr	0.65
Cho/Cr	0.58
rCBV	0.54
mI/Cr	0.48

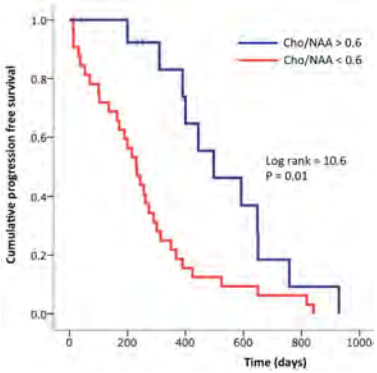

Figure 2: A Kaplan-Meier survival curve showing improved PFS where Cho/NAA > 0.6 (in blue) vs. Cho/NAA < 0.6 (in red)

DISCUSSION:

This data suggests that more metabolically active residual tumor in the invasive margin is a marker of a longer progression free interval. Cho/NAA has been proposed as a marker of glioma proliferation[3], and therefore the data presented here suggests that more metabolically active tumor is more likely to respond to cytotoxic therapy. Areas with low Cho/NAA would have less proliferative activity and would be less likely to respond to cytotoxic therapy. It may be that in this group cytotoxic therapy may be delayed in favor of other targeted therapies.

CONCLUSION:

Multimodal imaging methods that probe the pathology of the invasive margin are crucial in understanding individual variation in tumor progression and may aid further personalization of treatment in glioblastomas.

REFERENCES:

1. Price S, Jena R, Burnet N, et al. Improved delineation of glioma margins and regions of infiltration with the use of diffusion tensor imaging: An image-guided biopsy study. *American Journal of Neuroradiology.* 2006; 27(9):1969-1974.
2. Pena A, Green H, Carpenter T, Price S, Pickard J, Gillard J. Enhanced visualization and quantification of magnetic resonance diffusion tensor imaging using the p : q tensor decomposition. *British Journal of Radiology.* 2006; 79(938):101-109.
3. McKnight TR, Lamborn KR, Love TD, et al. Correlation of magnetic resonance spectroscopic and growth characteristics within Grades II and III gliomas. *J.Neurosurg.* 2007; 106(4):660-666.