MR spectroscopy as an early indicator of response to anti-angiogenic therapy in patients with recurrent glioblastoma: ACRIN 6677 / RTOG 0625

Eva-Maria Ratai[1], Zheng Zhang[2], Bradley Snyder[2], Melanie Yeh[2], Darryl L'Heureux[3], Jamie Downs[3], Jerrold Boxerman[4], Yair Safriel[5], Gregory Sorensen[1], Daniel Barboriak[6], and Mark Gilbert[7]

[1]Department of Radiology, A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, United States, [2]Center for Statistical Sciences, Brown University, United States, [3]American College of Radiology Imaging Network, United States, [4]Diagnostic Imaging, Warren Albert Medical School of Brown University, United States, [5]Radiology Associates of Clearwater, United States, [6]Department of Radiology, Duke University Medical Center, United States, [7]Department of Neuro-Oncology, University of Texas MD Anderson Cancer Center, United States

Introduction: The prognosis for patients with recurrent glioblastoma multiforme (GBM) remains poor, despite a range of chemotherapy treatment regimens. Recently, significant interest has been generated in targeting angiogenesis, a prominent feature of malignant gliomas. Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) and has been approved by the FDA in 2009 as monotherapy for recurrent GBM. In the multi-center clinical trial RTOG 0625/ACRIN 6677, bevacizumab was used in combination with cytotoxic agents, either temozolomide or irinotecan to treat patients with recurrent GBM. While structural MRI remains the standard for assessment of recurrence of glioblastoma, MRI provides little physiological information. Therefore, a sub-study was performed using advanced MR imaging to gain insight into the possible tumor biology. Specifically, 1H MR spectroscopy (MRS) provides biochemical information about the proliferative activity of the tumor. In GBMs, choline (Cho) is significantly elevated due to increased cellular turnover and the accelerated membrane synthesis that occur in rapidly dividing cancer cells. Levels of N-Acetylaspartate (NAA) serve as a marker for neuronal health and viability which are compromised in tumor progression. The purpose of this study was to assess the potential role of MRS as an early indicator of response to the anti-angiogenic treatment.

Methods: One hundred twenty three patients with recurrent GBM were enrolled in ACRIN 6677; 20 received MRS of which 13 patients (9 men, 4 women, mean age 54.8 ± 12.9 years old) had analyzable datasets containing a baseline scan. Patients were scanned prior to bevacizumab treatment, at 2 and 8 weeks post treatment and at every 2 months until the endpoint of the study (96 weeks). 2D MRSI was performed at three different sites using either 1.5T or 3T scanners. Acquisition parameters included TR/TE = 1700 to 2000/144 ms, 16 x 16 phase encoding steps, slice thickness of 10 to 15 mm and a FOV of 160 to 240 mm^2. The spectra were grouped in three regions of interest (ROI) on the baseline and all subsequent time points: (i) enhancing tumor, defined by the corresponding T1-weighted post-contrast images; (ii) non-enhancing peritumoral tissue around tumor voxel (periphery), and (iii) normal tissue on the contralateral side of tumor. Concentration of NAA/Creatine (Cr) and Cho/Cr were quantified using LC Model. All data was normalized to the pre-treatment scan. Karnofsky performance status, a measure of functional impairment, was assessed post stratification and prior to randomization and treatment. Repeated measures analysis of variance (RM-ANOVA) was utilized to analyze MRSI changes from baseline. A receiver operating characteristic (ROC) statistical analysis (area under the ROC curve, AUC) was conducted to determine the predictive value of the changes in MRS measurements to 12-month survival. Furthermore, changes in metabolic ratios at specific time points were correlated with changes in Karnofsky performance status using Spearman Rank analyses.

Results: Treatment of bevacizumab in combination with cytotoxic agents results in transient decreases in Cho/Cr in the tumor ROI at 2 weeks ($p = 0.0155$), possibly due to a decrease in number of rapidly dividing tumor cells. No other significant changes in Cho/Cr or NAA/Cr in the tumor or periphery were observed. The major goal of this study was to determine if early changes in Cho/Cr and NAA/Cr are predictive of the patient outcome of 12-month survival. Six of the 13 patients were alive at 12 months. Table 1 summarizes the AUC results.

Table 1: ROC analysis

%-Change	ROI	AUC @ 2wks post treatment	AUC 8wks post treatment (CI)	AUC 16wks post treatment (CI)
Cho/Cr	*Tumor*	0.38 (0, 0.79)	**0.80 (0.47, 1)**	0.73 (0.19, 1)
NAA/Cr	*Tumor*	0.71 (0.33,1)	0.55 (0.12, 0.98)	0.60 (0,1)
Cho/Cr	*Periphery*	0.70 (0.34, 1)	0.50 (0.13, 0.87)	**0.89 (0.63, 1)**
NAA/Cr	*Periphery*	0.57 (0.16, 0.97)	**0.81 (0.52, 1)**	**1 (1,1)**

AUC: Area under the curve; CI: Confidence Interval
Underlined AUC are significant, bold AUC show trends

Figure 1: %-Change Cho/Cr Tumor

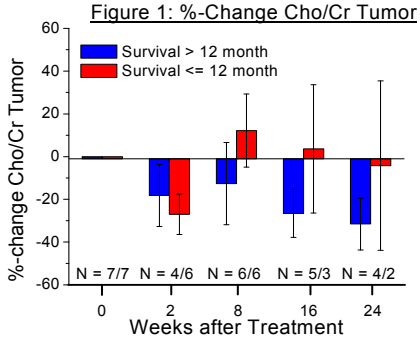


Figure 2: %-Change NAA/Cr Periphery

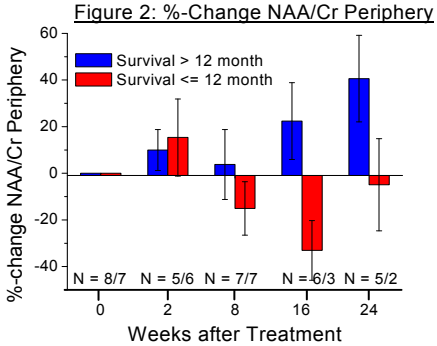
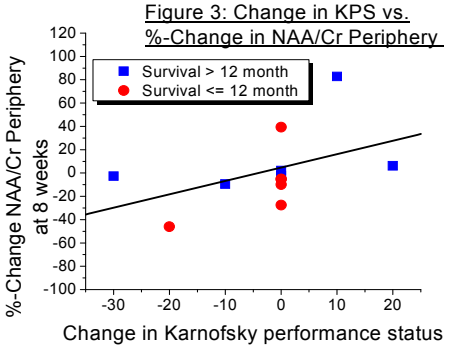


Figure 3: Change in KPS vs. %-Change in NAA/Cr Periphery



Interestingly, at 2 weeks post treatment, ROC curve analysis revealed no significant differences between patients that did survive or did not survive; data shows a decrease in Cho/Cr and an increase in NAA/Cr in all patients regardless of survival outcome. From the 8 week scan, patients that had survived 12 months could be distinguished from those who did not survive: AUC for Cho/Cr changes in the tumor at 8 weeks revealed a trend towards lower Cho/Cr in patients who were alive at 12 months, suggesting that Cho/Cr changes are associated with treatment response. In addition, decrease in Cho/Cr in the periphery at 16 weeks was also associated with patient survival. NAA/Cr changes in the tumor were not predictive of survival. However, changes in NAA/Cr in the periphery after 8 weeks were suggestive of survival. In addition, Spearman Rank analysis revealed a correlation between change in NAA/Cr and change in Karnofsky performance status at 8 weeks ($p = 0.049$, $R\rho = 0.58$).

Discussion: Our preliminary MRSI data suggest that treatment of bevacizumab in combination with cytotoxic agents resulted in transient decreases in Cho/Cr at 2 weeks in all patients regardless of survival. Decreases in Cho/Cr and increases in NAA/Cr (at periphery only) at 8 and 16 weeks post anti-VEGF therapy are associated with 12-month survival. However, these findings need to be confirmed in larger study. Previously, our group reported that increases in NAA/Cho levels in tumor at 8 weeks after administration of cediranib, another anti-angiogenic treatment, showed a high prediction to 6-month overall survival (Kim et al.: *Cancer Res. 2011).* A significant correlation between NAA recovery in the periphery and improving Karnofsky status was observed. This raises the possibility that clinical deficits in these patients are at least in part related to tumor replacement within and/or sustained injury to the tumor periphery. In conclusion, changes in Cho and NAA may potentially be useful as an imaging biomarker in assessing response to anti-angiogenic treatment. Thus, standardized MRSI should be considered for incorporation into future clinical multi-center trials to study treatment response in neoplasms.

Acknowledgements: ACRIN receives funding from the National Cancer Institute through the grants U01 CA079778 and U01 CA080098.