DSC-MRI Measures of Relative Cerebral Blood Volume (rCBV) as a Prognostic Marker for Progression-Free and Overall Survival in Recurrent Glioblastoma: Results from the ACRIN 6677/RTOG 0625 Multi-Center Trial

Kathleen M. Schmainda[1], Zheng Zhang[2], Jerrold Boxerman[3], Melissa Prah[1], Bradley Snyder[2], Devyani Bedekar[4], A Gregory Sorensen[5], Mark R Gilbert[6], and Daniel P Barboriak[7]

[1]Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin, United States, [2]Center for Statistical Sciences, Brown University, Rhode Island, United States, [3]Diagnostic Imaging, Rhode Island Hospital, Rhode Island, United States, [4]Medical College of Wisconsin, Milwaukee, Wisconsin, United States, [5]Massachusetts General Hospital, Massachusetts, United States, [6]Neuro-Oncology, University of Texas, Houston, Texas, United States, [7]Radiology, Duke University, Durham, North Carolina, United States

Target Audience: neuro-oncologists, neuroradiologists, neurologists, brain tumor researchers, pharmaceutical companies

Purpose: To report the results of multicenter, randomized, phase II trial of bevacizumab with irinotecan or temozolomide (ACRIN 6677 / RTOG 0625) for which a primary goal was to determine if RCBV, derived from DSC-MRI, is predictive of treatment response in patients with recurrent glioblastoma. As secondary goals, an automated method of determining enhancing tumor ROIs is evaluated and normalized versus standardized RCBV maps are compared.

Methods: Of 123 patients enrolled in the ACRIN 6677/RTOG 0625 study, 37 consented to advanced imaging with DSC-MRI, 23 of whom had DSC-MRI data sufficient for analysis including baseline and at least one post-baseline exam (13 patients underwent week 2 and 16 studies, 17 patients underwent a week 8 study). For these patients the contrast enhancing ROIs (regions of interest) were determined using an automatic method where a difference image was computed from standardized pre and post-contrast T1 weighted images and a threshold applied to automatically determine the ROI[1]. These ROIs were applied to both normalized (nRCBV) (to normal appearing white matter) and standardized (sRCBV)[2] RCBV maps, from which mean and median values were extracted. Progression status was determined clinically. Kaplan-Meier survival estimates and log-rank tests were used to determine if positive versus negative changes in nRCBV and sRCBV are predictive of PFS (progression free survival) and OS (overall survival).

Results: Of the 23 participants with DSC results, 12 are males with a median age of 54 (range 23-74). Shown in Figure 1 are the pre- and post-contrast MR images (T1, T1+C) and delta T1 map (dT1) from which an automated ROI is determined. This example illustrates the challenge with the determination of enhancing ROIs when there is bright signal on T1 and diminished contrast enhancement on T1+C post-bevacizumab, as well as the benefit of dT1 and automatic determination of the enhancing ROI. Also shown are the corresponding nRCBV and sRCBV maps for this patient. Percent changes at week 2 and 16 in both nRCBV and sRCBV are significantly different for the participants who are PFS at 6 month vs. the ones that are not (Table 1). Participants with positive changes of nRCBV and sRCBV at weeks 2 and 16 have much worse OS than the participants with negative changes, P= 0.0015(4 + , 9 -) and 0.0067(7 +, 6 -) for nRCBV and P= 0.0251(4 + , 9 -) and 0.0004(4 + , 9 -) for sRCBV, respectively. The similar pattern found for PFS, P= 0.0010 and 0.0155 for nRCBV and P= 0.0085 and 0.0015 for sRCBV, respectively. The week 2 and 16 Kaplan-Meier curves for OS for sRCBV are shown in Figure 2. The week 8 survival results showed a similar trend but failed to reach statistical significance.

Figure 1. Example Imaging Results

Table 1. Prediction of PFS at 6 Months
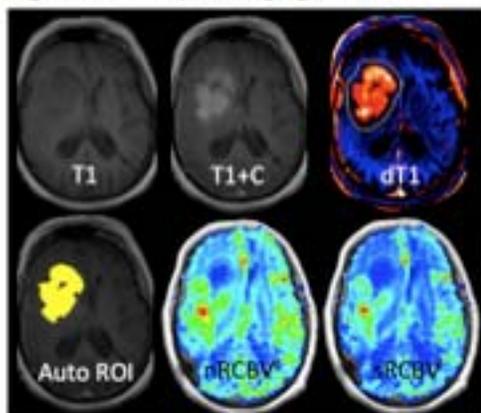
Scan Time Point		n.	Normalized RCBV (nRCBV)			Standardized RCBV (sRCBV)		
			Mean	Std	Wilcoxon rank sum test p-value	Mean	Std	Wilcoxon rank sum test p-value
Baseline	RCBV	23	1.505	0.679		4118.52	1527.31	
Week 2	RCBV	13	1.253	0.995		3033.16	2109.09	
	RCBV (% change)	13	-17.133	54.464		-16.06	54.08	
	PFS6	6	-57.205	31.718	p = 0.0047	-57.18	19.38	p = 0.0082
	Progression	7	17.214	45.960		19.18	48.96	
Week 8	RCBV	17	1.317	0.979		3618.24	2443.93	
	RCBV (% change)	17	-10.271	55.169		-12.51	52.40	
	PFS6	10	-32.860	48.889	p = 0.0878	-31.28	35.49	p = 0.1613
	Progression	7	22.000	49.657		14.31	63.31	
Week 16	RCBV	13	1.389	0.805		3585.14	1546.13	
	RCBV (% change)	13	10.082	60.075		-2.77	31.74	
	PFS6	10	-13.361	40.978	p = 0.0070	-14.15	24.14	p = 0.0140
	Progression	3	88.224	46.801		35.17	24.85	
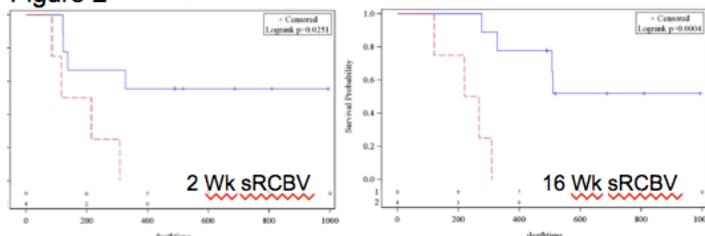
Discussion / Conclusions In this multi-center phase II trial (ACRIN 6677) we have demonstrated in 23 patients that the percent change from baseline in normalized or standardized rCBV, measured at 2 and 16 weeks post-bevacizumab, predicts both PFS and OS. If confirmed in a larger patient cohort as planned, these results should help facilitate early assessment of response to treatment on an individualized basis, and reduce unnecessary treatment, associated morbidities and expense in patients deemed unlikely to respond.

Figure 2

Acknowledgements: Imaging Biometrics LLC for their technical assistance with processing the data.

References: (1) Bedekar D et al., *Proc Int Soc Magn Reson Med* p2175 (2010). (2) Bedekar D et al., *Magn Reson Med.* 64(3):907-913 (2010). (3) Boxerman et al., *Neuro-Oncology* 15(7):945-54 (2013).