

# DSC-MRI Measures of Standardized rCBV Predict Response to Bevacizumab in High-Grade Brain Tumor Patients

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**Target Audience:** neuro-oncologists, neuro-radiologists, neuro-surgeons, brain tumor imaging scientists

**Introduction:** Promising results have been obtained with the anti-angiogenic agent bevacizumab in combination with chemotherapy, for the treatment of brain tumor patients (1,2). In these studies, standard measures of tumor volume derived from contrast-enhancing T1-weighted images, or abnormal volumes on T2-weighted images, have been used to evaluate and predict response. Yet, it is quickly becoming apparent that these measures of enhancing tumor volumes are no longer routinely reliable. Bevacizumab, which targets the vascular endothelial growth factor (VEGF), also has the effect of decreasing the permeability of the blood brain barrier and may result in decreases in apparent volume without an effect on the tumor biology. In this study we evaluate the role of using DSC-derived maps of relative cerebral blood volume (rCBV) to predict the overall survival (OS) of high-grade gliomas to bevacizumab therapy.

**Methods:** *Patients:* Thirty-six patients with high-grade gliomas, who underwent rCBV imaging within 60 days before and 20-60 days after starting treatment with bevacizumab (Avastin, Genentech, S San Francisco, CA), were enrolled in this study. All patients had previous resection(s) and adjuvant therapy including radiation and chemotherapy. All patients provided IRB-approved consent for advanced imaging. *Imaging:* Studies were performed on either 1.5T or 3T MRI systems. Standard pre- and post-contrast MRIs were acquired: FLAIR (TE/TR=151ms/10s) and T1-weighted spin-echo imaging (TE/TR=20ms/450ms). To reduce T1 leakage effects, a loading dose of contrast agent (0.05-0.1 mmol/kg) was administered prior to the DSC study. GRE-EPI images (TE/TR=30ms/1100ms, matrix=96x96, FOV=24cm) were acquired for 1 min before and 2 mins after a 0.1 mmol/kg bolus injection of contrast agent. *Image and Data Analysis:* The rCBV maps, corrected for leakage effects, were calculated and standardized (stdRCBV) as previously described (3, 4), and co-registered across studies. (Standardization precludes the need to select reference ROIs in normal brain, which are used to normalize rCBV maps for comparison.) Contrast-enhancing (T1+C) tumor regions of interest (ROIs) were determined using a supervised, automatic, threshold-based algorithm, for each visit separately. This approach automatically eliminated any bright signals due to blood products (5). Median stdRCBV was then calculated from within the T1+C ROIs. Overall survival was determined with reference to the start date of bevacizumab treatment. The Kaplan-Meier method was used to determine if stdRCBV, enhancing tumor volumes, obtained before or after treatment, or percent changes in these values were predictive of survival.

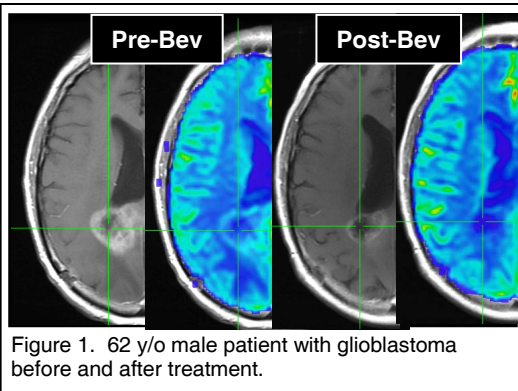


Figure 1. 62 y/o male patient with glioblastoma before and after treatment.

**Results:** Shown in Fig 1 are examples of T1+C images and corresponding stdRCBV maps obtained 2 days prior to and 32 days following treatment with bevacizumab. This patient showed a 46% decrease in stdRCBV with a post-bev survival of 175 days. Using ROC analysis, a stdRCBV threshold of 2900 was determined to distinguish an OS of  $\leq$  300 days, with a sensitivity and specificity of 81% and 60% and an AUC of 0.73. Using this threshold both the pre and post-bev stdRCBV predicted a significant difference in survival ( $p=0.0016$ ,  $p=0.0052$  respectively).

No significant difference in enhancing tumor volumes was found between these groups (Fig 2). Interestingly, the direction and degree of change in stdRCBV varied within each group, and was not predictive of OS (Fig 3). However, if either the pre-bev stdRCBV began low ( $<2900$ ) or the post-bev stdRCBV decreased to a value less than 2900, a clear difference in OS (101 days versus 329 days) could be predicted, which was highly statistically significant (Fig 4).

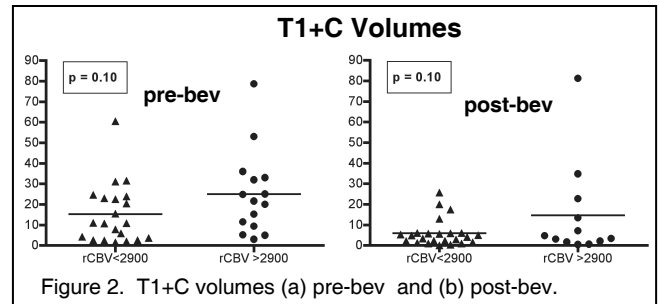


Figure 2. T1+C volumes (a) pre-bev and (b) post-bev.

**Discussion:** This study demonstrates that the stdRCBV and not enhancing tumor volume is predictive of response to bevacizumab. A stdRCBV value of less than 2900 either before or after treatment was most predictive of a longer survival. Future studies, which include a larger cohort of patients are planned to confirm this threshold value.

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**References:** (1) Vredenburgh JJ et al, *J Clin Oncol* 25:4722-4729 (2007) (2) Batchelor TT et al *Cancer Cell* 11:83-95 (2007) (3) Schmainda KM *Am J Neurorad* 25:1524-1532 (2004), (4) Bedekar D et al., *Mag. Reson. Med.* 64(3):907-13 (2010). (5) Bedekar D et al., *Proc. Intl. Soc. Mag. Reson. Med.* 18th Annual Meeting, Stockholm, Sweden (2010).

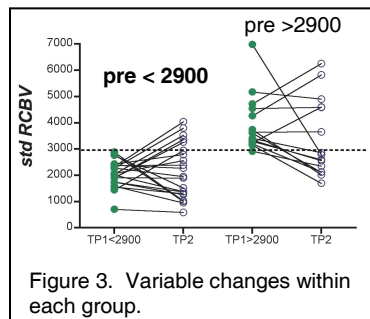


Figure 3. Variable changes within each group.

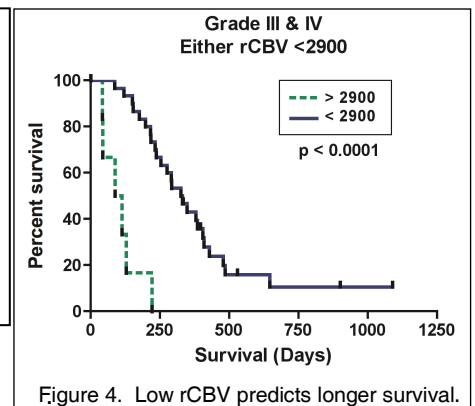


Figure 4. Low rCBV predicts longer survival.