Initial rCBV Predicts Response to Bevacizumab in Patients with High-Grade Gliomas

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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). Despite this promise many questions remain regarding the appropriate selection of patients most likely to respond to these new and expensive therapies both alone and in combination with chemotherapies. In this study we address the utility of rCBV (relative cerebral blood volume) image maps derived from DSC (dynamic susceptibility contrast) perfusion MRI, obtained prior to the initiation of therapy, to predict response to bevacizumab in combination with the chemotherapeutic irinotecan.

Methods: *Twelve patients* with new or recurrent high-grade gliomas, who were to receive a therapeutic regimen of bevacizumab (10mg/kg) (Avastin, Genentech, South San Francisco, CA) plus irinotecan (125 mg/kg), were enrolled in this study. All patients had previous resection(s) and adjuvant therapy including radiation and chemotherapy. All imaging studies were performed on a 1.5T MRI (GE Healthcare, Waukesha, WI). Standard pre-contrast and post-contrast anatomical MRIs were acquired: FLAIR (TE/TR=151ms/10s) and T1-weighted spin-echo imaging (TE/TR=20ms/450ms). Also, volumetric SPGR images were acquired to enable image registration across studies. To reduce T1 leakage effects, a loading dose of Gadodiamide (0.10 mmol/kg, Omniscan) was administered prior to the DSC study. Next, 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 Gadodiamide. Standard MRI and rCBV imaging was performed shortly before treatment initiation and periodically throughout and after treatment was completed.

Image and Data Analysis: Estimates of rCBV, corrected for leakage effects, were calculated, as previously described (3). All image series were standardized (4). ROIs, and therefore 3D volumes of contrast-enhancing and FLAIR abnormalities were determined using a supervised, automatic, threshold-based algorithm. The mean rCBV values were determined from the T1+C ROIs superimposed on the standardized rCBV maps. Overall survival (OS) was defined as the difference between the date of death or last follow-up and the date of initial diagnosis. Survival was also determined in reference to the date of the first bevacizumab treatment (bOS). The Kaplan-Meier method was used to determine if standardized rCBV values were predictive of survival.

Results: Of the twelve patients studied, six were alive at the time of data analysis. Using a standardized rCBV cut-off value of 5000, Kaplan Meier curves were generated for both overall survival (OS) and survival since the initiation of bevacizumab (bOS) as shown in Figure 1. A statistically significant difference in survival was found between patients for both OS ($p = 0.01$) and bOS ($p = 0.018$). For pre-bevacizumab rCBV < 5000, the median bOS was 601 days. For pre-bevacizumab rCBV > 5000, the median bOS was 183.5 days. Example post-contrast and standardized rCBV maps are shown for one patient in Figure 2 whose mean tumor (standardized) rCBV was greater than 5000, and whose OS and bOS were 59 and 31 days.

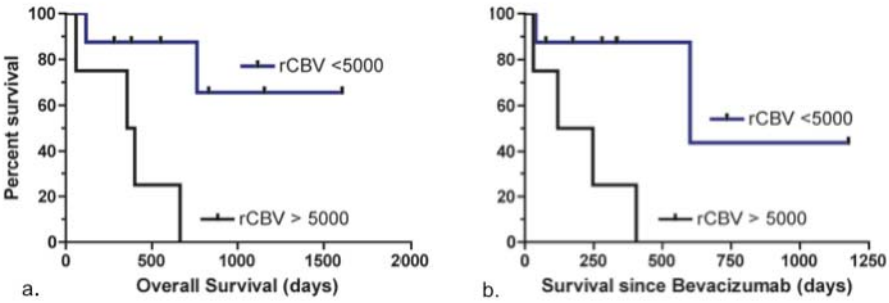

Figure 1. Pre-Avastin rCBV predicts (a) overall survival and (b) survival wrt start of treatment.

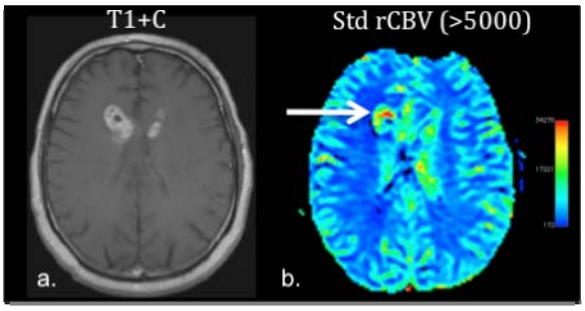

Figure 2. A 56 y/o patient with GBM. (a) Post-contrast T1w image and (b) standardized rCBV map.

Discussion / Conclusion In this initial study of twelve patients, with high-grade brain tumors treated with bevacizumab plus irinotecan, we have demonstrated that standardized rCBV, obtained prior to initiation of bevacizumab treatment, clearly predicts outcomes. If these results are borne out in a larger cohort of patients, as planned, this information should result in optimizing the clinical response and survival in patients on an individualized basis. It should also result in a decrease in unnecessary treatment, associated morbidities and expense if a given patient is shown to be an unlikely responder.

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