

DSC-MRI Measures of rCBV Predict Response to Bevacizumab Treatment More Reliably than Standard MRI in Patients with Recurrent High-Grade Gliomas

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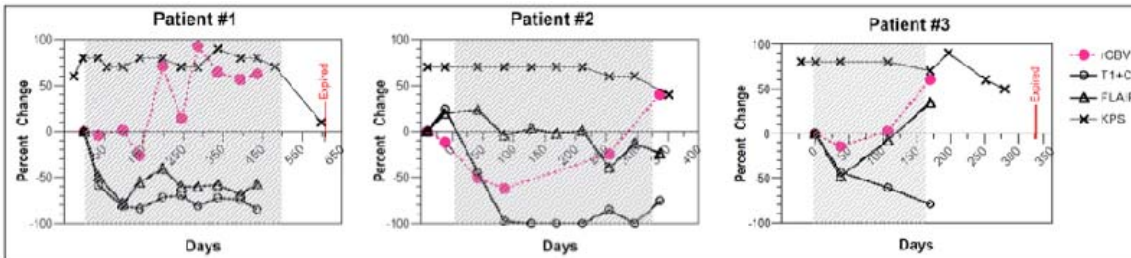
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Introduction: Promising results have been obtained with the anti-angiogenic agent, bevacizumab in combination with chemotherapy, for the treatment of brain tumor patients (1,2). In these studies, standard measures of tumor volume derived from contrast-enhancing T1-weighted images, or abnormal volumes on T2-weighted images, have been used to evaluate response. Yet, it is quickly becoming apparent that these measures of apparent 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 determine the response of recurrent, high-grade gliomas to bevacizumab & irinotecan therapy.

Methods: Six patients with recurrent high-grade gliomas, who were to receive a therapeutic regimen of bevacizumab (Avastin, Genentech, South San Francisco, CA) plus irinotecan, 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- and post-contrast 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. 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 before beginning treatment (except for one patient for whom imaging was performed shortly after starting treatment) 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) and registered across studies using the FSL-based linear registration technique (FLIRT: FMRIB Software Library, Oxford, UK). ROIs, and 3D volumes, of contrast-enhancing (T1+C) and FLAIR abnormalities were determined using a supervised, automatic, threshold-based algorithm. Mean rCBV was determined using the T1+C ROIs. The number of days from the start of treatment (designated as day 0) to maximum response (nadir) was determined, as well as the number of days prior to neurologic deterioration when the parameter of interest increased by at least 25%. Neurologic deterioration was defined as a sustained decrement of at least 20 points in the Karnofsky performance score (KPS) for at least 8 weeks and/or until the patient expired.

Results: Five of six patients showed a response to the bevacizumab & irinotecan treatment, with survival ranging from 299 to 1033+ days from the start of combined treatment. Representative results from the first three patients are shown in the Figure. Shown are rCBV (●), T1+C (○) and FLAIR-abnormal (□) volumes, along with Karnofsky performance scores (KPS) (X). The shaded areas indicate the period of bevacizumab & irinotecan treatment. The results for all patients are summarized in the Table below.



day of maximal response (nadir) was either earlier or similar to the nadir for T1+C or FLAIR volumes. Increases in rCBV preceded neurologic deterioration by 82 to 439 days, which was in general much earlier than any changes in either post-contrast or FLAIR abnormal volumes. In several cases (indicated by the dashes in the Table) there were no discernable increases in the T1+C or FLAIR abnormalities to indicate progression.

Patient	Day of Maximum Response (Nadir)			Days Prior to Deterioration (>25% Increase)			Survival
	rCBV	T1+C	FLAIR	rCBV	T1+C	FLAIR	
#1	140 days	140	98	311	-	-	605
#2	84	128	254	97	-	-	371 (+)&
#3	37	37	37	82	-	82	331
#4	n/a*	n/a	n/a	439	61	61	1033 (+)&
#5	47	47	47	64	64	64	299
#6	-	63	-	171	-	171	440

* In this one case imaging began after start of treatment, so nadir could not be determined. & The + indicates patient has not expired.

Discussion: This study of six recurrent brain tumor patients, treated with bevacizumab plus irinotecan, demonstrates that rCBV is a reliable indicator of response to treatment as well as being an earlier and more reliable predictor of disease progression compared to standard MRI measures of apparent tumor volume. These findings are currently being evaluated in a larger patient series to further confirm our hypothesis that rCBV is a more sensitive predictor of response and progression than standards MRI measures of apparent tumor volume and as such should become a standard part of the imaging protocols used to evaluate and optimize use of these new anti-angiogenic drugs.

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