Longitudinal Assessment of Avastin Therapy Using Biological Response Indicator Perfusion Maps: Predicting Response to Therapy

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Introduction

The study of brain tumor angiogenesis for the diagnosis of glioma has potential benefits in therapeutic management. With the recent clinical trials of vascular targeting agents, the necessity for development of angiogenesis biomarkers has become even more urgent. In this study we employed a noninvasive imaging technique, dynamic susceptibility contrast (DSC) MRI to estimate relative cerebral blood volume (rCBV), and with the aide of longitudinal registration, created biological response indicator (BRI) maps to track the vascular response to therapy in patients receiving Avastin. The BRI maps provide a visual summary of where the tumor vascularity is increasing, decreasing, or remaining the same. This study demonstrates the importance of longitudinal registration and the potential for BRI maps to provide a comprehensive and efficient way to monitor tumor response to treatment**.**

Methods

Patients: Five subjects with confirmed diagnosis of high grade gliomas, currently enrolled in an ongoing longitudinal clinical imaging study, were studied to test the efficacy of longitudinal registration and BRI maps for assessment of treatment response. All five subjects were receiving Avastin in concert with Irinotecan as a combination anti-angiogenic, chemotherapy treatment plan.

MRI: All MRI studies were performed on a 1.5T GE CV Scanner. A 0.10 mmole/kg dose of Gadodiamide (Omniscan; Nycomed Amersham, Princeton, NJ) was administered to diminish T1 effects that might result from agent extravasation. Perfusion weighted images were acquired using a lipid-suppressed, single-shot, blipped, GRE-EPI sequence with the following parameters: FOV=22cm, matrix=96x96, ST=5mm, skip=1.5mm, TE/TR=30ms/1100 ms, number of slices=13, flip angle=72°, number # of repetitions=180. For registration, 3D SPGR images were acquired (FOV=24x18cm, Matrix=256x192, flip angle=10°, TE/TR = 2.9/7.8ms, NEX/ST=2/1.3mm, 124 slices). Finally, conventional post-contrast T1-weighted images were acquired (SE, TE/TR/Matrix/NEX =10/450/256^2/2).

Image Analysis: Analysis of functional neuro-images (AFNI) tool was used for data analysis. All MR images were spatially coregistered using their first MR study SPGR images as the reference dataset. The rCBV maps were estimated using the trapezoidal numerical integration method over the entire concentration-time curve and T1 leakage correction method as previously described.[1] Voxel-wise estimates of rCBV were normalized to their average uninvolved white matter rCBV. To create BRI maps tumor CBV values from the first post-therapy MR study were plotted as function of the tumor CBV values from the initial MR study. Only tumor voxels present in both studies were included in this analysis. All of the tumor voxels were segmented into three categories: (1) Increased CBV, (2) No Change in CBV, or (3) Decreased CBV and the tumor volumes of each category were compared to the total tumor volume.

Statistical Analysis: Statistical analysis was performed using GraphPad Prism version 4.0a for Mac OS X (GraphPad Software, San Diego, CA). The thresholds for determining whether there was a significant change in the CBV of a voxel was determined empirically by evaluating rCBV values in normal contralateral brain of 6 patients. The standard deviation of normal rCBV was calculated and used as the threshold for the creation of the BRI maps.

Results and Discussion

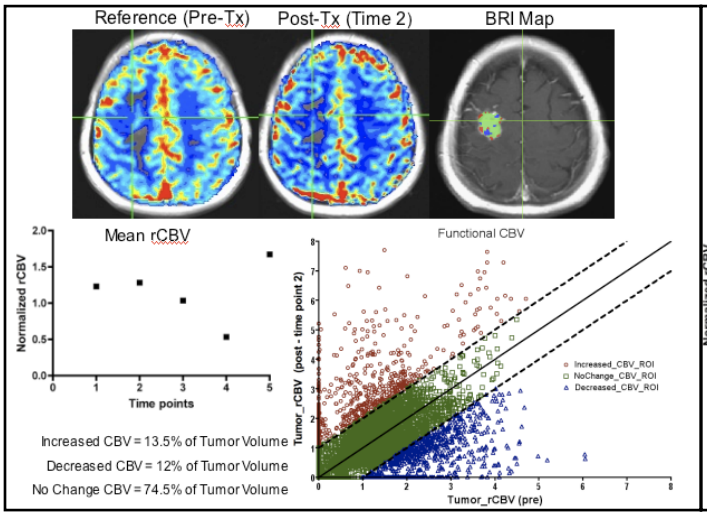

Figure 1: Representative Patient with Transitional Disease

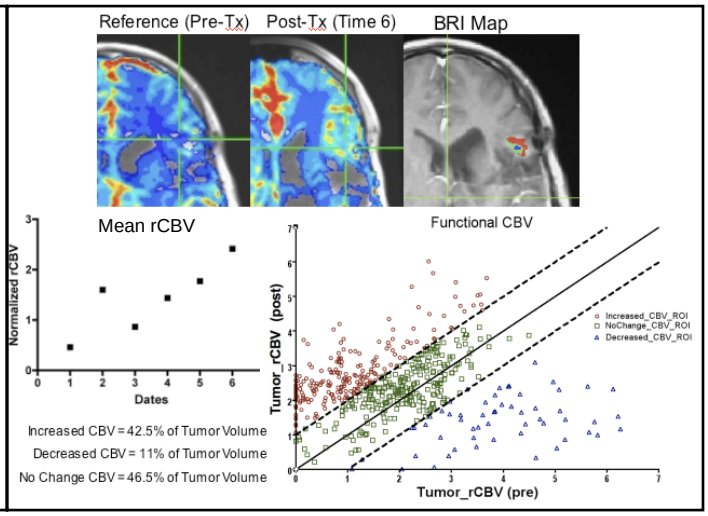

Figure 2: Representative Patient with Progressive Disease

Figure 1displays a patient with transitional disease. This patient has stable disease, as seen by the mean rCBV plot, from the pre-treatment date until time point 4. The BRI map, comparing time point 1 to time point 2, demonstrates that a majority (74.5%) of voxels have remained unchanged; however, looking at the scatter plot and the rCBV map there are areas of the tumor with increased blood volume after treatment. These high blood volume areas precede the return to a highly vascular tumor as seen at time point 5. The BRI map of time point five (data not shown) indicated an increase in CBV in 24% of the tumor. This change could not have been predicted looking at mean CBV alone. Figure 2 displays a patient with progressive disease. In this instance, the BRI map and scatter plot track with the mean rCBV plot. Clinically, this patient was stable, the perfusion imaging results in conjunction with other imaging results, aided in the decision to reevaluate the treatment protocol. Demonstrated by the above representative studies, as well as in the non-represented studies, longitudinal registration with BRI maps offer a comprehensive evaluation of patient treatment response as well as the potential to predict early changes not seen with conventional imaging techniques. Future studies, are planned to evaluate if BRI maps will consistently provide an earlier indicator of tumor progression.

References

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Acknowledgements

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