

# Serial assessment of perfusion parameters in patients with GBM following anti-angiogenic therapy

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## Introduction

For patients with GBM, combining the current standard cytotoxic therapies (RT and Temozolomide) with anti-angiogenic therapy is hoped to inhibit tumor growth and prolong survival. Anti-angiogenic therapies have been shown to decrease tumor blood supply through suppression of tumor-induced angiogenesis, which is believed to be a major hallmark in the progression of these tumors [1]. T1 weighted dynamic contrast enhanced imaging (T1wDCE) [2] and arterial spin labeling (ASL) [3] are functional imaging techniques that can be used to assess changes in tumor vasculature in response to angiogenic inhibitors. The purpose of this study was to investigate how perfusion parameters derived from these two techniques change over time within tumor and healthy brain tissue regions of GBM patients following therapy.

## Methods

Ten patients (8 male, 2 female) with newly diagnosed GBM were examined in this study. All patients underwent surgical resection and were treated with radio-, chemo- and anti-angiogenic therapy. Patients were imaged prior to beginning therapy (post surgical resection) and scanned serially at 1, 2, 4 and 6 months after the start of therapy on a 3T GE EXCITE scanner with 8-channel phased array receive coil. Not all patients were able to receive both scans at every time point. Permeability (Kps) and fractional blood volume (fBV) maps were calculated from a T1-weighted dynamic 3D SPGR sequence acquired after the injection of 20 ml of Gd-DTPA with TR/TE=4.5/1.14ms, flip angle=20°, 26x26x8.4cm FOV, 256x256x28 matrix, 28 slices, and 12 time points (Taq=5:36min). Cerebral blood flow (CBF) maps were obtained from a pseudo-continuous Arterial Spin Labeling (ASL) scan that utilized a 3D FSE spiral sequence (TR/TE=11/3ms, 260x260x176mm FOV, 128x128x44 matrix, NEX=3) to acquire a labeled and control image which were subtracted to obtain a flow image. Anatomical T2-weighted FLAIR images, post-contrast T1-weighted SPGR images, and Choline-to-NAA index (CNI) maps derived from lactate-edited 3D MRSI, were acquired and used to define ROIs of T2-hyperintensity, contrast-enhancement, and abnormal (CNI>2) metabolic activity, respectively. The union of these ROIs yielded a composite map of abnormal brain tissue for each time point, from which a normal brain map that excluded this tumor region and ventricles was then generated. Composite regions were overlaid on to the normalized Kps, fBV, and CBF maps to create histograms of these parameters within the tumor and normal brain regions. Data were analyzed first by combining all voxels from all patients, and then for each patient individually and averaged across patients within each time point.

## Results and Discussion

**Combined Voxels for All Patients:** Within the normal brain region voxels combined from all patients, fBV and Kps values remained relatively constant over the 6 months of treatment (mean percent change from baseline to 6 months was <1% and <10% respectively). However, within the tumor region, both of these parameters showed significant (60% fBV and 32% Kps) reductions in mean values between pre-therapy and 6 months (p<.001, Wilcoxon rank sum test) as shown in Figure 1a for normalized Kps. Both the fBV and Kps data within the tumor region showed a trend toward the levels that existed in the normal brain region, showing similar Kps levels in the tumor and normal region at 6 months and similar fBV levels between these regions at 2 months. The combined voxels from all patients showed significantly lower CBF values in the tumor than the normal brain region for each of the time points after therapy (p<.001). Both the tumor and normal brain regions showed a significant (25% and 15%, respectively) decrease in CBF between the pre-therapy and 6 month scan (p<.001).

**Individual Patient Data:** As shown in Figure 1c, a reduction in the upper quartile values seems to have driven the significant decrease in fBV, Kps, and CBF values within the tumor region across the 6 months. To investigate this, the 90<sup>th</sup> percentile values for these parameters in the tumor region were tracked for individual patients. A 12% and a 28% reduction in the 90<sup>th</sup> percentile value for individual patients was seen for both the CBF and Kps parameters between the 1 month and 2 month scans (both with p=.07). Two patients were excluded from this part of the analysis since they had progressed on anatomic images and exhibited an increasing trend in vascular parameters between 1 and 2 months post-therapy. The reduction of fBV and Kps within the tumor region at 2 and 6 months from the pre-therapy levels can be seen in Figure 2. At 6 months, the elevated Kps appears to have resolved while most of the FLAIR hyperintensity remains (Figure 2, top).

## Conclusions

This study demonstrates differences in vasculature characteristics both between tumor and normal brain regions; and within the tumor region over the course of 6 months following treatment. Currently, studies that track changes of these perfusion parameters during treatment on a patient by patient basis in a larger GBM population are underway. Further analysis of the extreme values of these parameters during first two months post therapy will hopefully elucidate patterns of vasculature characteristics that can predict whether or not the treatment will be effective before progression ensues in these patients.

**References and Acknowledgements:** [1] Teicher B, et al., Ann Neurol. 2007;61:153-61. [2] Zaharchuk G. AJNR. 2007;28 1850-8[3]Liu T, et al, J Int Neuropsychol Soc. 2007;13: 517-25. This study was supported by UC Discovery grant ITL-BIO04-10148, NIH grants R01 CA127612-01A1 and P01 CA11816-01A2, and a Joelle Syverson American Brain Tumor Association Fellowship.

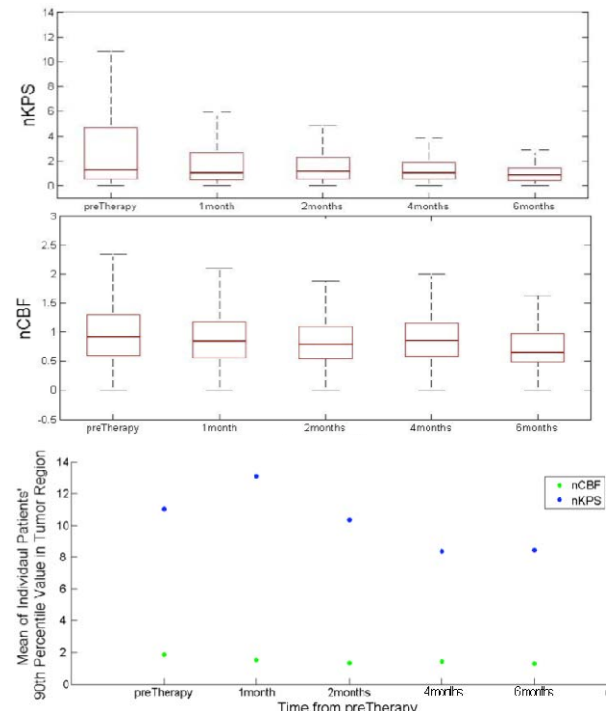


Figure 1. Combined Kps (a) and CBF (b) data for all patients within the tumor region. In (c), 90<sup>th</sup> percentile of individual patient data for Kps and CBF. Note pattern of change in preTherapy to 2 month levels.

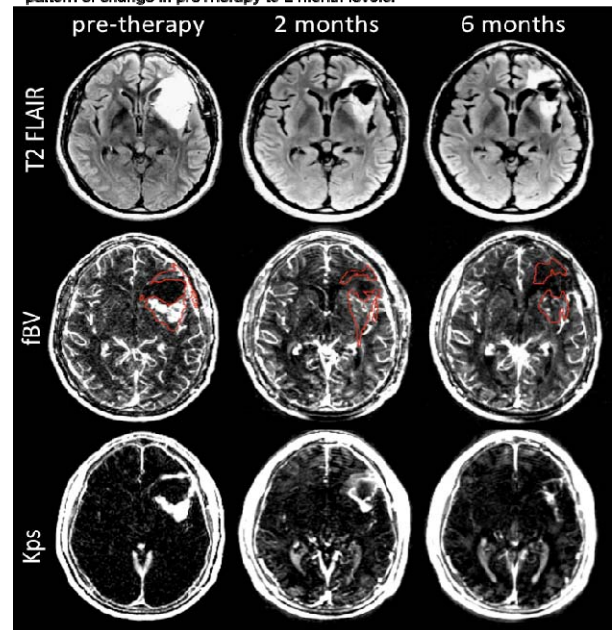


Figure 2. T2 FLAIR, fBV, and Kps Images with tumor region ROI in red. Note reduction of fBV and KPS at 2 months in tumor region.