

# Parametric Response Map as an Imaging Biomarker to Distinguish Progression from Pseudoprogession in High Grade Gliomas

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**Introduction:** Accurate response assessment in GBM has significant clinical implications in patient management. We have developed a reliable method for distinguishing true progression from pseudoprogession by quantifying on a voxel-wise basis therapeutic-associated hemodynamic alterations in patients with high grade glioma [1].

## Methods and Materials:

### Patient

Patients (Total n=27: Stable Disease (SD)=13, Progressive Disease (PD)=8, Pseudoprogession (PP)=6) with Grade III/IV glioma were recruited for this trial. Patients underwent MRI 1-2 weeks before RT and at weeks 3-4 during RT. When MRI was performed at weeks 1-2 during RT, the patients had received a median dose of 12 Gy (range, 5-6). At Weeks 3-4, the median dose was 32 Gy (range, 26-40). MRI scans were acquired on a 1.5T GE clinical scanner (GE Medical Systems, Milwaukee, WI) or a 3T Philips clinical scanner (Philips Medical Systems, Andover, MA).

### Dynamic Contrast Susceptibility- Magnetic Resonance Imaging

Dynamic contrast-susceptibility (DCS) T<sub>2</sub>\*-weighted imaging with intravenous administration of a standard dose (0.1 mL/kg) bolus of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), and post contrast T<sub>1</sub>-weighted images were acquired by a gradient-echo echo-planar imaging pulse sequence (TR=2s, T<sub>2</sub>=60ms, field of view 220x220 mm<sup>2</sup>, matrix 128x128, flip angle 60°, and 14 interleaved slices with 6mm thickness and 0mm gap). The relative cerebral blood volume and flow (rCBV and rCBF) in the brain and tumor were computed as described by Ostergaard [2].

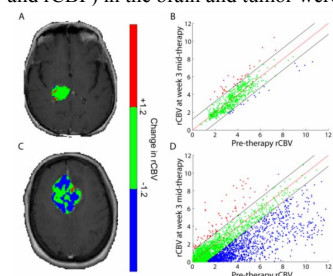


Figure 1: PRM<sub>rCBV</sub> color-coded overlay of a (A) pseudoprogession and (C) progression patient. Voxels were designated red with significant increase in rCBV, blue for a significant decrease in rCBV and green if they remained statistically unchanged. (B, D) Corresponding quantitative scatter plot analysis showing the distribution of rCBV at baseline compared to Wk3 cRT.

### Parametric Response Map (PRM)

All images were co-registered to Gd-enhanced T<sub>1</sub>-weighted images acquired before RT using an automated mutual information and simplex optimization module [3]. Following co-registration, brain tumors were manually contoured on the Gd-enhanced T<sub>1</sub>-weighted images by radiologists. The rCBV and rCBF values of each voxel within the tumor at week 3 were compared with respective pre-RT values. PRM<sub>rCBV</sub> and PRM<sub>rCBF</sub> was performed by thresholding the absolute difference of the respective modality in a voxel into three categories: significantly increasing (PRM<sub>X+</sub>; red); significantly decreasing (PRM<sub>X-</sub>; blue); and unchanged (PRM<sub>X0</sub>; green) parameter values (X). The thresholds were empirically determined to be the 95% confidence intervals calculated from normal contralateral brain tissue.

### Statistics

PRM and percentage change in the mean histogram for rCBV and rCBF at Wk 3 following cRT were determined for each clinical outcome group (SD, PD and PP). A one sample Kolmogorov-Smirnov test was performed to ensure the assumption of normality was not violated in the entire data, for example, the p value of the KS test for PRM<sub>rCBV</sub> for pseudoprogession was non-significant (p=0.664). Thus there is a lack of evidence to reject the assumption of normality.

Differences in response measures were assessed between groups using Analysis of Variance (ANOVA) adjusted for multiple comparisons (Bonferroni post-hoc test). These results were considered statistically significant at the two-sided 5% comparison-wise significance level, p< 0.0083. We performed a stepwise multinomial logistic regression with three outcomes: stable disease (SD), progression (PD) and pseudoprogession (PP). Four variables of interest (PRM<sub>rCBV+</sub>, PRM<sub>rCBF+</sub>, percent change in rCBV, and percent change in rCBF) were included in the stepwise procedure. Statistical significance was assessed at p<0.05.

**Results:** Median radiation dose was 72 Gy (range: 60-81). Of 27 patients, stable disease/partial response was noted in 13 and apparent progression in 14. Adjuvant temozolomide was continued in all patients. Pseudoprogession occurred in 6 patients. We analyzed standard imaging methods of analyzing hemodynamic alterations following chemo-radiation such as percentage change in whole tumor average of rCBV as a predictor of response. No difference was noted between patients in the SD and PD group. There was also no difference noted in patients with pseudoprogession compared to those with progression. Analyses using percent change in rCBF did not demonstrate any significant differences among the patient groups (data not shown).

We hypothesized that PRM, a voxel-wise method of image analysis, would better predict clinical outcomes in patients with high grade gliomas than standard imaging methods due to significant tumor heterogeneity. PRM<sub>rCBV</sub> color-coded overlay of the same patient with pseudoprogession (Fig 1A) is shown in contrast to a PD patient (Fig 1C). A corresponding quantitative scatter plots show the distribution of rCBV at baseline compared to Wk 3 cRT for the entire tumor volume region (Fig 1B, D). PRM analysis demonstrated a significant difference in PRM<sub>rCBV</sub> in the pseudoprogession compared to the progressive disease group (p=0.006). PRM<sub>rCBV</sub> showed a statistically significant difference between the stable and progressive disease group. (p=0.001) (Fig 2) A similar trend was observed in PRM<sub>rCBF</sub>, but was not found to be significant (p=0.107). We performed a multivariate analysis using a stepwise multinomial logistic regression. Based on Akaike's information criteria, only PRM<sub>rCBV</sub> remained in the model as a significant predictor of outcome, p-value = 0.002 (likelihood ratio test, chi-square = 12.405 on 2 degrees of freedom). In contrast, change in average percent rCBV or rCBF, MR tumor volume changes, age, extent of resection, and RTOG RPA classification did not distinguish progression from pseudoprogession.

**Discussion:** PRM<sub>rCBV</sub> at week 3 during chemoradiation is a potential early imaging biomarker of response that may be helpful in distinguishing pseudoprogession from true progression in patients with high grade glioma.

### References:

- Galban C.J., et al., Nature Medicine 2009. 15, 572-6.
- Ostergaard, L., et al., Magn Reson Med, 1996. 36, 715-25.
- Meyer, C.R., et al., Med Image Anal 1997. 1, 195-206.

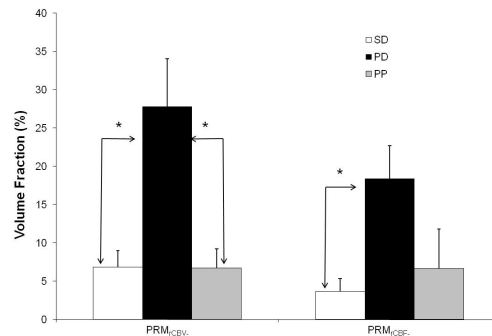


Figure 2: Presented is the volume fraction of tumor with a significant decrease in rCBV (PRM<sub>rCBV-</sub>) and rCBF (PRM<sub>rCBF-</sub>) assessed three weeks post-treatment initiation. A significant difference was noted in PRM<sub>rCBV-</sub> and PRM<sub>rCBF-</sub> between patients with stable (SD) and progressive (PD) disease. In this patient population (n=27), we also noted a significant difference in PRM<sub>rCBV-</sub> between the pseudo-progression (PP) and true progression patients. Data is presented as the mean ± the standard error of the mean. Statistical significance denoted by \*.