# CIMPLE maps derived from serial diffusion MR images in recurrent glioblastoma treated with bevacizumab

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***Introduction***

Microscopic invasion of tumor cells and undetected tumor proliferation is the primary reason for a dismal prognosis in glioblastoma (GBM) patients. Identification and quantification of spatially-localized brain regions undergoing high rates of cell migration and proliferation may be important for image guided therapies, testing efficacy and performance of new drug compounds, and ultimately improving patient survival. Recently, CIMPLE (cell invasion, motility, and proliferation level estimates) image maps constructed from serial diffusion MRI scans and an analytical solution to a glioma growth model equation were introduced as a potential biomarker to localize regions of high proliferation and tumor invasion.[1,2] CIMPLE maps represent a novel method of quantifying the level of aggressive malignant behavior in human gliomas. Previously, investigators have shown the CIMPLE characteristics of low-to-high grade gliomas and correlated these findings with MR spectroscopy.[1,2] In the current study, we demonstrate the utility of CIMPLE maps to predict progression free survival (PFS) and overall survival (OS) in recurrent glioblastoma patients treated with bevacizumab.

***Methods***

A total of 26 patients were selected retrospectively from our Neuro-Oncology database. Inclusion criteria included: 1) pathology confirmed GBM with recurrence based on MRI and clinical data, 2) radiation and temozolomide at initial diagnosis, and 3) a minimum of 3 follow-up MRI scans after treatment initiation not spanning more than 8 months, all with good quality diffusion MR data. It is important to note that pre-treatment ADC maps were not used in this analysis due to drastic changes in edema after bevacizumab. Instead, the first three ADC maps acquired after initiation of treatment were used for analysis. The average time period over which CIMPLE maps were constructed with respect to initiation of treatment was 124 days ± 6.2 days SEM. All patients were regularly treated every 2 weeks per cycle with bevacizumab (Avastin, Genentech; 5 or 10 mg/kg bw). Data acquisition and storage was performed in compliance with all applicable HIPAA regulations and the principles expressed in the Declaration of Helsinki.

Data was collected on a 1.5T MR system (GEMS, Waukesha, WI) using standard clinical pulse sequences. Diffusion weighted images (DWIs) were collected with TE/TR=100-120ms/8000ms; Δz/skip=5mm/1.5mm) using a twice-refocused spin-echo echoplanar preparation. ADC was calculated from $b$=0 and $b$=1000 s/mm$^2$ images. The mathematical solution to CIMPLE map estimates of proliferation and invasion has previously been introduced.[1,2] Briefly, the rate of change in cell density within a voxel of interest is equal to the net dispersion of cells into and out of that image voxel plus cells that have proliferated within the image voxel.[3,4] Using ADC as a surrogate for cell density,[5-7] image map estimates of cell proliferation and cell invasion can be created from three serial ADC maps.[1,2] All images for each patient were registered to a high-resolution (1.0 mm isotropic), T1-weighted brain atlas (MNI152) using a mutual information algorithm and a 12-degree of freedom transformation using FSL (FMRIB, Oxford, UK). Regions of interest (ROIs) were created for the entire T2 weighted signal abnormality on pre-treatment T2 weighted and/or FLAIR images.

***Results***

As illustrated in Fig. 1, CIMPLE map estimates of proliferation rate generated at the 3rd scan session post-treatment predicted spatial regions of future contrast enhancement in many patients. Overlap between CIMPLE map estimates of proliferation rate and new contrast enhancement occurred in 9 of the 26 patients examined (35%). CIMPLE maps did not detect any clusters of proliferative tissue larger than 0.2 mL and having a proliferation rate > 2 yr$^{-1}$ in 3 of the 26 patients (11.5%), but these patients had a PFS of more than 1 year and an OS of more than 2 years. This suggests patients exhibiting no detectable proliferative clusters at the beginning of treatment may have very slow growing tumors and thus longer PFS and OS. We observed a significant difference in PFS between patients having a mean proliferation rate greater than 3.73 yr$^{-1}$ (group average, median PFS=100.5 days) compared with patients having a mean proliferation rate less than 3.73 yr$^{-1}$ (*Fig.2;*median PFS=401 days*; Log-Rank, P=0.0248*). Additionally, patients with mean proliferation lower than the group average had a significant survival advantage (median OS = 711.5 days) compared to patients having a higher rate (median OS = 286 days; *Log-Rank, P=0.0049*). These results suggest patients having a larger mean proliferation rate are more at risk for early tumor recurrence and shorter survival. We found no differences in PFS or OS when comparing patients with a volume of proliferative tissue greater than or less than the group mean (PFS:*Log-Rank, P=0.3364*; OS:Log-*Rank, P=0.0573*) or patients having a cell migration rate larger than or smaller than the group mean (PFS:*Log-Rank, P=0.9086*; OS:*Log-Rank, P=0.6120*).

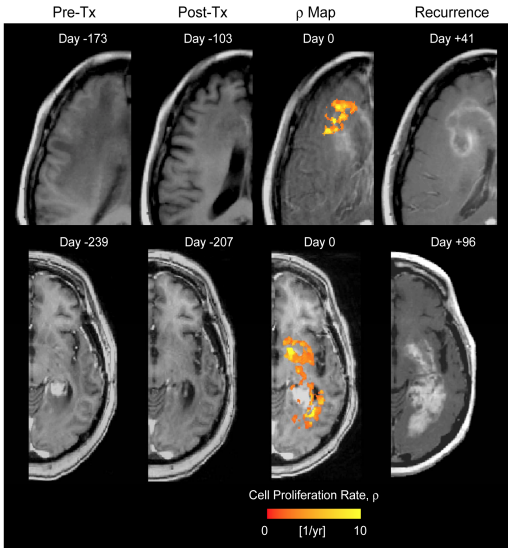


**Fig.1:** *Proliferation maps spatially predict contrast-enhancement. Left to right columns: Pre-treatment contrast-enhanced T1w image (T1+C), post-treatment T1+C, CIMPLE map estimates of proliferation rate, ρ, and T1+C at recurrence.*

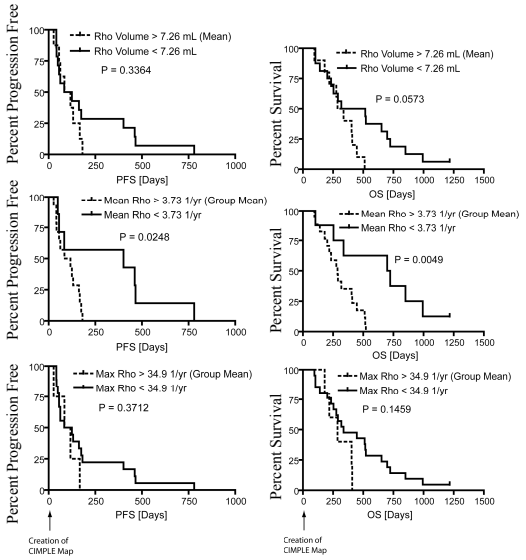


**Fig.2:** *Mean proliferation rate predicts progression-free (PFS) and overall survival (OS). Top Row: PFS and OS stratified by volume of proliferative tissue. Middle Row: PFS and OS stratified by mean proliferation rate. Bottom Row: PFS and OS stratified by maximum proliferation rate.*

***Discussion***

In the current study we demonstrate preliminary evidence suggesting regions of high proliferation rate on CIMPLE maps that appeared early during treatment may *spatially predict* regions of future contrast enhancement in approximately 35% of all patients. This finding is particularly important because it provides evidence that CIMPLE maps may be useful for prediction of the precise location of tumor recurrence sooner than conventional techniques. Preliminary results also found mean proliferation rate was a valuable biomarker for both PFS and OS in recurrent GBM patients treated with bevacizumab, suggesting the tonic, or general level of proliferation rate within the tumor may be the most important factor for determining a GBM patient's overall response to treatment, not necessarily the volume of tumor burden or the highest rate of proliferation within the tumor. Future studies in a larger cohort of patients are may be beneficial for testing these hypotheses.

***References*** [1]Ellingson BM, *MRM*, 2010. [2]Ellingson BM, *Proc Intl Soc Magn Reson Med*, 2009. [3]Swanson KR, Cell Prolif, 2000. [4]Swanson KR, J Neurol Sci, 2003. [5]Lyng H, *MRM*, 2000. [6]Chenevert TL, *J Natl Cancer Inst*, 2000. [7]Ellingson BM, *JMRI*, 2010.