Non-parametric and non-linear DSC-MRI post-processing methods predict underlying vascular histopathology in patients with treatment-naive GBM

Emma Essock-Burns[1,2], Joanna J. Phillips[3,4], Annette M. Molinaro[3], Janine M. Lupo[2], Soonmee Cha[2,3], Susan M. Chang[3], and Sarah J. Nelson[1,5]

[1]*Graduate Group in Bioengineering, UC Berkeley/UC San Francisco, San Francisco, CA, United States,* [2]*Department of Radiology and Biomedical Imaging, UC San Francisco, San Francisco, CA, United States,* [3]*Neurological Surgery, UC San Francisco, San Francisco, CA, United States,* [4]*Department of Pathology, UC San Francisco, San Francisco, CA, United States,* [5]*Bioengineering and Therapeutic Sciences, UC San Francisco, San Francisco, CA, United States*

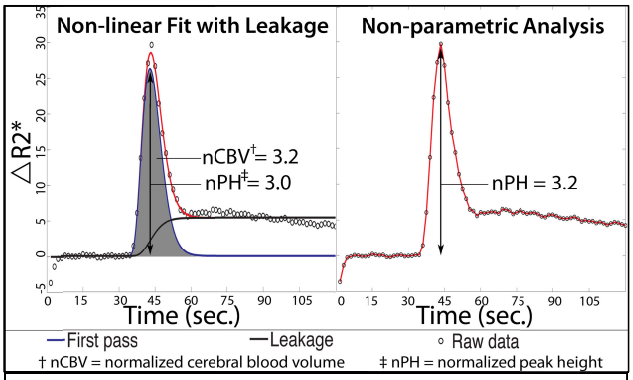

Figure 1. Hemodynamic curve from a biopsy with complex vasculature calculated using non-linear gamma-variate fit with leakage correction (left) and non-parametric analysis (right).

Introduction: Tissue heterogeneity of glioblastoma (GBM), a highly malignant and vascularized human brain tumor, has historically been a challenge for selecting biopsy samples for tumor grading that accurately represent the tumor biology. One hallmark of GBM is the presence of complex glomeruloid vasculature, characterized by microvascular hyperplasia, tortuous lamina, and breakdown of the blood brain barrier. Dynamic susceptibility contrast (DSC) MRI has been used to noninvasively assess microvasculature, yet there are known limitations near regions of contrast agent extravasation, common near glomeruloid vasculature. Multiple post-processing methods exist for addressing this limitation and have been shown to greatly influence the resultant estimates of cerebral blood volume (CBV) [1]. Non-linear gamma-variate fit with leakage correction is a common method for addressing this limitation in the research setting, yet necessitates curve-fitting which limits its use in the clinical practice. Non-parametric analysis is less computationally expensive, yet has not been extensively validated with histopathology. Histopathological validation of these strategy-dependent CBV estimates will help guide biopsy selection toward aggressive vascular features for diagnosis and characterize vascular burden for anti-angiogenic treatment planning. The goal of this study was to compare non-linear and non-parametric DSC post-processing methods to determine which CBV estimate most accurately reflects the underlying microvasculature in patients with treatment naive GBM.

Methods: 72 image-guided tissue samples were collected from 35 patients newly diagnosed with GBM. Preoperative 3T MR exams included T2* DSC gradient-echo echo-planar imaging (flip angle=35°, TE/TR=54–56/1250-1500ms, slice thickness=3-4 mm, matrix=128x128, 0.1mmol/kg Gd-DTPA) and anatomic imaging (pre- and post-contrast T1-weighted SPGR, T2-weighted FLAIR). A 5-mm diameter spherical region at the specimen target location was overlaid on the aligned DSC data at the native resolution. An average hemodynamic curve was calculated from within each specimen region and an average curve was calculated within the normal appearing white matter (NAWM) for normalization, using both the non-linear and non-parametric post-processing method [2-3] (see Figure 1). Vascular morphology of each specimen was graded on an ordinal scale (delicate, simple, complex) using Factor VIII immunohistochemical (IHC) staining by an experienced pathologist blinded to MRI findings. A random-effects ordinal regression model, adjusted for contrast-enhancement (CE) at the target location and repeated specimen samples per patient, was used to determine if the blood volume measure(s) from each post-processing method significantly predicted vascular morphology determined by IHC analysis.

Results: Predicting Vascular Morphology (delicate, simple, or complex): Adjusted for CE, non-linear: nCBV, non-linear: nPH, and non-parametric: nPH significantly predicted the tissue vascular morphology (non-linear: nCBV p<.05, nPH p<.03; non-parametric: nPH p<.05). Figure 2 illustrates how greater non-linear: nCBV, non-linear: nPH, and non-parametric: nPH are predictive of a greater degree of hyperplasia. Identifying Complex Vasculature: As expected, CE was a strong predictor of complex vasculature. Even adjusted for CE, these same CBV estimates were marginally significant predictors of complex vasculature (CBV measures: p<=.09, CE: p<.01). Identifying Abnormal Vasculature (simple or complex): Non-linear: nCBV, non-linear nPH, and non-parametric: nPH were each significant predictors of the presence of abnormal vasculature, while CE was not (non-linear: nCBV p=.03, nPH p<.03; non-parametric: nPH p<.02; CE: p=>.2). In general, a 1-unit increase in these blood volume measures was associated with approximately a 2.2-fold greater likelihood of presence of abnormal vasculature. Figure 3 illustrates an example of a patient with abnormal vasculature in both the CE and non-CE tissue, which is correctly identified with the CBV measures from both the non-linear and non-parametric method.

Conclusions: The blood volume measures from both the non-linear and non-parametric analysis of DSC data acquired with a 35° flip angle and single-dose of gadolinium significantly predicted the underlying vascular morphology determined by Factor VIII IHC analysis. Complex vasculature is far more likely to coincide with CE, but non-linear and non-parametric analysis may assist in guiding sampling toward complex vasculature when it is present within the heterogeneous CE-lesion. Abnormal (simple or complex) vasculature also existed beyond the CE-lesion and was accurately identified by both the non-linear and non-parametric analysis. This study provides histopathological support of the non-parametric and non-linear post-processing techniques as noninvasive methods for characterizing aggressive vasculature features within the heterogeneous GBM, which may assist in guiding biopsy location and identifying patients for targeted anti-angiogenic therapies.

References: [1] Paulson et al. (2008) Rad 249:2 [2] Weiskoff (1994) ISMRM p 279, [3] Essock-Burns et al. (2011) Neuro-oncol 13:1

Acknowledgements: NIH Grant R01 CA127612-01A1 and NIH Grant P01 CA11816-01A2.

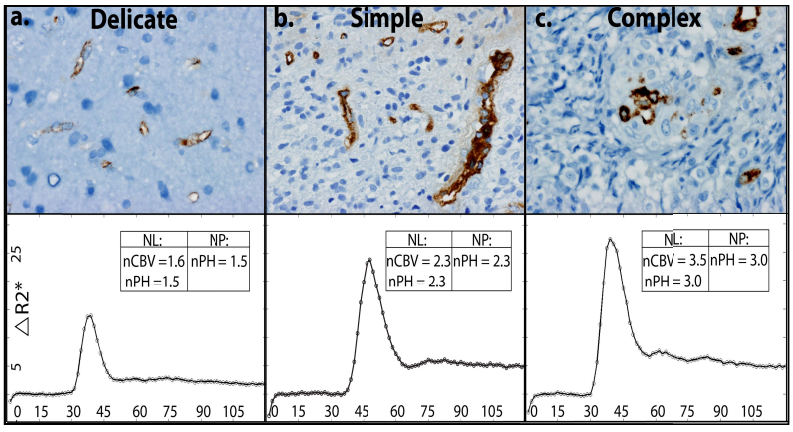

Figure 2. Factor VIII IHC staining (top) and corresponding ΔR2* curve (bottom) of 3 specimens with delicate, simple, and complex vasculature (a-c). Increased non-linear: nCBV, non-linear: nPH, and non-parametric: nPH are significant risk factors for increased microvascular hyperplasia.

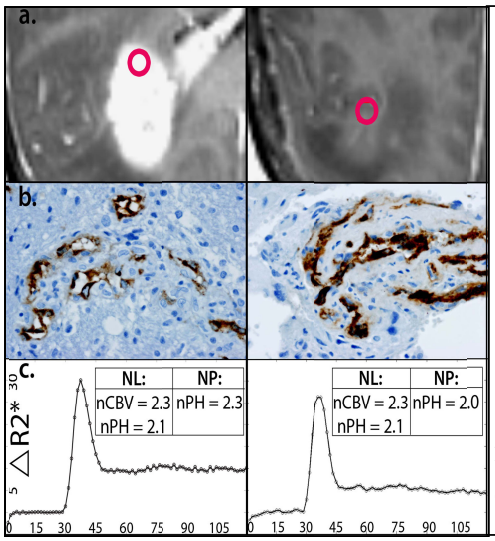

Figure 3. a. T1w-CE MRI of a patient with 2 biopsy targets (pink), from CE (left) and non-CE (right) tissue.

b. Factor VIII IHC staining shows abnormal vasculature in both specimens, which is identified by elevated non-linear and non-parametric CBV estimates in c.