Image-guided Tissue Validation of Combined Preload Dosing and Mathematical Modeling Correction of Perfusion MRI Measures

L. S. Hu[1,2], L. C. Baxter[3], D. S. Pinnaduwage[4], T. Jensen[5], A. C. Dueck[6], J. M. Eschbacher[7], J. E. Heiserman[8], J. P. Karis[8], J. Debbins[3], J. Placencia[9], S. Liu[3], B. G. Feuerstein[10], and K. M. Schmainda[11]

[1]Radiology, Mayo Clinic, Arizona, Scottsdale, AZ, United States, [2]Radiology, Neuroradiology Section, St. Joseph's Hospital - Barrow Neurological Institute, Phoenix, Arizona, United States, [3]Keller Center for Imaging Innovation, St. Joseph's Hospital - Barrow Neurological Institute, Phoenix, AZ, United States, [4]Radiation Oncology, University of California - San Francisco, San Francisco, CA, United States, [5]Imaging Biometrics, LLC, [6]Biostatistics, Mayo Clinic, Arizona, Scottsdale, AZ, United States, [7]Neuropathology, St. Joseph's Hospital - Barrow Neurological Institute, Phoenix, AZ, United States, [8]Radiology, Neuroradiology Section, St. Joseph's Hospital - Barrow Neurological Institute, Phoenix, AZ, United States, [9]Biomedical Engineering, Arizona State University, Tempe, AZ, United States, [10]Neuro-Oncology, St. Joseph's Hospital - Barrow Neurological Institute, Phoenix, AZ, United States, [11]Radiology, Medical College of Wisconsin, Milwaukee, WI, United States

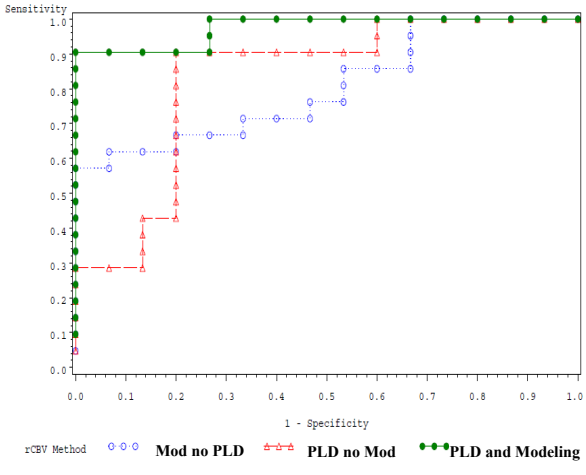
Purpose: We validate mathematical modeling correction of relative cerebral blood volume (rCBV) in regards to effectiveness of 1) minimizing T1W leakage and 2) correcting T2/T2*W residual effects, by correlating localized measures with image-guided tissue histopathology and microvascular density from stereotactic biopsies in post-treatment high-grade gliomas.

Introduction: Following initial standard multi-modality therapy for high-grade gliomas (HGG), clinicians must continually alter subsequent treatment to help extend survival and improve an otherwise dismal prognosis. Appropriate management depends critically on accurate detection of treatment response and tumor recurrence. Surgical biopsy currently provides definitive diagnosis of non-specific lesions detected on surveillance conventional MRI; however, Perfusion MRI (pMRI) measures of rCBV offer a non-invasive alternative to biopsy for accurate differentiation of tumor growth and non-tumoral post-treatment radiation effect (PTRE).[1] Preload dosing (PLD) and baseline-subtraction (BLS) pMRI protocols effectively minimize T1W leakage and correct T2/T2*W residual effects,[2] respectively, and prevent measurement inaccuracies that would otherwise degrade rCBV correlation with histopathology. [2,3] Disadvantages of BLS include 1) variability in correction accuracy due to possible intersubject and intralesion regional differences in recirculation; and 2) potential operator variability and reduced efficiency due to the BLS requirement of user-determined first-pass intervals. [3, 4] Alternatively, mathematical modeling of leakage effects on a per-voxel basis, with subsequent correction, may address the aforementioned BLS disadvantages by automatically generating regionally-specific leakage-corrected rCBV maps; [3-5] however, this approach has not yet been validated with stereotactic tissue analysis, and is therefore the goal of this study.

Methods: Following Institutional Review Board approval, we recruited previously treated (including chemo-radiation therapy) HGG patients undergoing surgical re-resection of enhancing lesions on surveillance MRI. Preoperatively, we acquired pMRI data (gradient-echo echo-planar imaging (EPI) with TR/TE/flip angle (FA), 2000 ms/20 ms/60°; FOV, 24 x 24 cm; matrix, 128x96; 5-mm sections; no gap; 0.05mmol/kg Gadodiamide hand injection at 3-5 cc/sec via large bore i.v. catheter at the 10th time point) and pre- and post-contrast stereotactic T1W spoiled gradient-refocused-echo inversion recovery-prepped MRI (TI/TR/TE, 300/6.8/2.8 ms; matrix, 320x224; FOV, 26 cm; section thickness, 2 mm). In each patient, two separate pMRI data sets (two-minute scans each) were acquired both 1) without preload dosing (PLD) and 2) following 0.1 mmol/kg PLD with a six-minute incubation time.[3] Intraoperatively, we recorded stereotactic locations of multiple biopsies and calculated coregistered localized rCBV measures similar to previous reports [1,2] on an Osirix (v. 3.6.1) workstation using IB Neuro 1.1.430 and IB Registration 1.0.454 (Imaging Biometrics, LLC, Wisconsin). This enabled rCBV calculation either without or with modeling based on a previously reported algorithm.[5] Based on different acquisition and post-processing variables, we created three distinct experimental methods to calculate rCBV: **A)** Modeling without PLD (to assess modeling correction of T1 leakage); **B)** PLD without modeling (to assess only the effects of PLD without T2/T2* residual correction); and **C)** Combined Modeling with PLD (to assess modeling correction of T2/T2* residual effects). We created Receive Operator Characteristic (ROC) curves for each experimental group to determine rCBV accuracy to distinguish tumor from PTRE. We calculated Areas under the curve (AUCs) for each group's ROC and statistically compared them using the Delong Clarke-Pearson method ($p < 0.05$). Sensitivity, specificity, and 95% confidence intervals (CIs) for distinguishing PTRE and tumor were generated from each ROC curve at a number of rCBV cutoff points to determine the optimal threshold value that maximized accuracy (defined as the average of sensitivity and specificity). We also calculated Pearson correlations between rCBV and tissue microvessel number for each group ($p<0.05$).[6] We calculated total microvessel number on CD-34 stained slides and normalized to the total slide specimen area (μm^2), using Axiovision Automeasure 3.4 software module (Zeiss, Germany). A biostatistician performed all analyses. A neuropathologist diagnosed specimens as tumor or PTRE.[1]

Results: We included 36 tissue specimens (from 11 subjects) and categorized each specimen as tumor (n=21) or PTRE (n=15). Microvascular analysis was available in 16 of these samples, which included both tumor (n=7) and PTRE (n=9) categories. We summarize AUC and Pearson correlations in the table below. Combined preload dose (PLD) and modeling (group C) provided the highest AUC (0.97), which was significantly higher than AUC in the absence of PLD (group A, p=0.01) or modeling (group B, p=0.04) (figure). Using combined PLD and modeling, the rCBV threshold of 1.07 maximized diagnosis of tumor and PTRE with 95.2% accuracy (95%CI = 73.9%–99.4%), 90.5% sensitivity, and 100% specificity. Combined PLD and modeling rCBV significantly correlated with microvessel number (r=0.524), whereas the other conditions did not.

Conclusion: Combined PLD and modeling correction maximizes rCBV correlation with tissue analysis, compared with either condition alone. Modeling provides similar T2/T2*W correction as previously reported BLS[2], but in a more automated and efficient manner, suggesting the potential utility of this combined method in clinical practice and multi-institutional trials.



Group	Preload dose (PLD)?	Modeling present?	Test AUC to diagnose tumor vs. PTRE	rCBV vs. microvasculature Pearson correlation (p-value)
A	no	yes	0.81	r = 0.30 (p = 0.26)
B	yes	no	0.83	r = 0.34 (p = 0.19)
C	**YES**	**YES**	**0.97**	**r = 0.52 (p = 0.03)**

References: 1) AJNR 30(3):552-8. 2) AJNR Sep 12. [Epub]. 3) Radiology 249(2):601-13. 4) JMRI 11(2):103-13. 5) AJNR 27(4):859-67. 6) J Neurosurg. 81(6):902-9.

Acknowlegements: Funding was provided by Arizona Biomedical Research Commission (LH, DP), Barrow Neurological Foundation (LH, DP, LB, SL), NIH/NCI RO1 CA082500 (KS), NIH/NCI R43 CA134031 (TJ, KS)