Comparison of Perfusion MRI-Based Methods to Estimate Histologic Tumor Fraction and Predict Survival in Recurrent GBM

L. S. Hu[1,2], J. M. Eschbacher[3], A. C. Dueck[4], S. Liu[5], K. A. Smith[6], K. Kotagama[5], S. W. Coons[3], J. E. Heiserman[7], J. P. Karis[7], T. Jensen[8], W. Shapiro[9], J. Debbins[5], P. Nakaji[6], B. G. Feuerstein[9], and L. C. Baxter[5]

[1]Radiology, Mayo Clinic Arizona, Phoenix, AZ, United States, [2]Radiology, Barrow Neurological Institute, Phoenix, AZ, United States, [3]Neuropathology, Barrow Neurological Institute, [4]Biostatistics, Mayo Clinic Arizona, [5]Keller Center for Imaging Innovation, Barrow Neurological Institute, [6]Neurosurgery, Barrow Neurological Institute, [7]Neuroradiology, Barrow Neurological Institute, [8]Imaging Biometrics, LLC, [9]Neurology, Barrow Neurological Institute

PURPOSE: We studied three different Perfusion MRI (pMRI)-based methods of estimating tumor fraction and compared correlations with outcome. Specifically, we compared a new voxel-based relative cerebral blood volume (relCBV) thresholding method called pMRI Fractional Tumor Burden (pMRI-FTB) with previously published histogram-based Peak Height Position (PHP) and mean relCBV methods.

INTRODUCTION: Quantifying histologic fraction in recurrent GBM impacts management and prognosis.[1,2] Currently, Contrast-Enhanced MRI (CE-MRI) is the standard for non-invasive surveillance, but has severe limitations. First, brain parenchyma often develops therapy-induced injury, termed Posttreatment Radiation Effect (PTRE), which infers treatment success but exactly mimics GBM.[3,4] Second, CE-MRI lesions often contain histologically variable admixtures of GBM and PTRE, meaning that actual histologic tumor burden represents a fractional subcomponent of CE-MRI lesions.[1,5] Although binary classification of CE-MRI lesions (as all or no tumor) holds little prognostic value,[6] directly quantifying histologic tumor fraction (relative to PTRE) as a continuous variable correlates highly with survival.[1,2] Surgical biopsy is the current diagnostic standard, although pMRI measures of relCBV offer a potentially safer and cheaper alternative.[7-10] A previous study coregistered relCBV with small stereotactic biopsies (~ 0.2 cm^3) to establish highly accurate thresholds that distinguish GBM from PTRE voxels, but did not assess tumor fraction or survival.[7] In this study, we applied a similar threshold in a voxel-based manner, to quantify the proportion of enhancing CE-MRI lesion voxels with elevated relCBV predictive of GBM fractional subcomponents. We hypothesized that the proportion of GBM voxels, represented by the metric pMRI Fractional Tumor Burden (pMRI-FTB), would correlate highly with surgical tumor fraction and overall survival (OS). We compared histologic and prognostic correlations with previously established histogram and mean relCBV methods.

METHODS: With Institutional Review Board approval, we recruited recurrent GBM patients undergoing surgical re-resection of new CE-MRI enhancing lesions suspicious for tumor growth. Preoperative 3T imaging (General Electric, WI), included pMRI (gradient echo EPI; TR/TE/flip angle 2000 ms/20 ms/60°; FOV 24 x 24 cm; matrix 128x128; 5-mm sections; no gap; 0.1 mmol/kg i.v.,preload dose; 0.05mmol/kg Gd-DTPA i.v. injection at 3-5 cc/sec) and pre- and post-contrast stereotactic T1W spoiled gradient-refocused-echo MRI (TI/TR/TE 300/6.8/2.8 ms; matrix 320x224; FOV 26 cm; section thickness 2 mm).[7-11] We used an Osirix (v. 3.6.1) workstation with IB Neuro 1.1.430, and IB Suite 1.0.454 (Imaging Biometrics, LLC, WI) to calculate whole-brain relCBV maps coregistered to stereotactic data using: 1) one-to-one subtraction of voxel values between the coregistered pre- and post-contrast SPGR, 2) a volume of interest (VOI) drawn around all abnormal enhancing tissue, excluding the remaining brain, and 3) signal threshold adjustment to exclude non-enhancing brain and necrotic tissue within the VOI, to form a CE-MRI lesion mask. All mask voxels were categorized as PTRE (relCBV < 1.01) or tumor (relCBV ≥ 1.01), with pMRI-FTB representing the percentage of tumor voxels out of total mask voxels, (Figure 1). This threshold was determined in a subset of 9 GBM patients by correlating localized relCBV with multiple stereotactic biopsies classified as GBM or PTRE, as previously published (Figure 2).[7] Histogram analysis of peak height position (PHP) and mean relCBV were also calculated as previously published.[10-11] Histologic tumor fraction was quantified in all submitted surgical tissue.[2,6,9-11] For all patients, CE-MRI lesion pMRI-FTB, PHP, and mean relCBV were correlated with histologic fraction and overall survival (OS) from the time of surgical re-resection, using Pearson correlation and log-rank analysis, respectively.

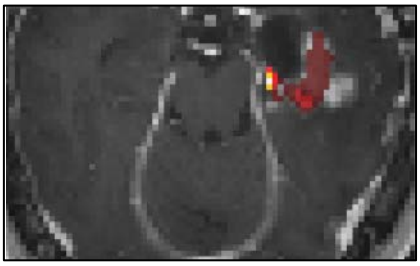

Figure 1: Representative pMRI-FTB map overlay on a CE-MRI lesion showing color voxels as those with relCBV above threshold, predictive of GBM fractional subcomponents.

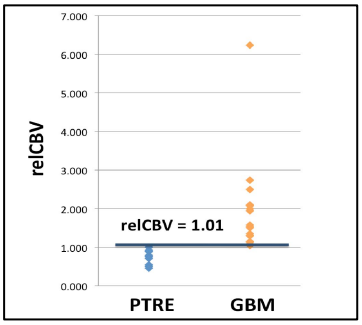

Figure 2: Twenty-six biopsy specimens and relCBV values showed no overlap between PTRE and GBM with a 1.01 threshold.

RESULTS: Of 20 recurrent GBM patients, median clinical follow-up time was 543 days, with 11 subjects deceased at analysis. Histologic tumor fraction showed the strongest correlation with pMRI-FTB (r=0.82, p<0.0001) compared with histogram PHP (r=0.68, p<0.001) and mean relCBV (r=0.52, p<0.02). Overall Survival (OS) correlated only with pMRI-FTB (p<0.006), with the Kaplan-Meier curves shown in Figure 3. OS did not reach statistical significance with mean relCBV (p=0.62) or PHP (p=0.20).

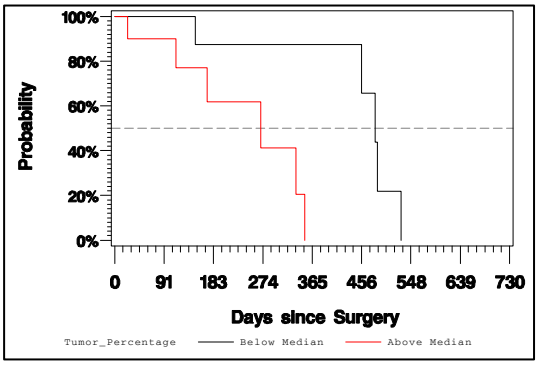

Figure 3: Kaplan Meier curves showed significant differences in OS between patients with pMRI-FTB above (red) versus below (black) median values.

DISCUSSION: Use of pMRI-FTB in this pilot to characterize recurrent GBM differed from previously reported pMRI-based methods by 1) using a validated relCBV threshold based on stereotactic biopsy; 2) quantifying histologic fraction as a continuous variable; and 3) correlating multiple pMRI-based parameters with clinical outcome.[7-11] Our data suggest that pMRI-FTB more strongly correlated with histologic fraction and OS, compared with other pMRI methods to date, and offers a potentially feasible adjunct to surgical biopsy. Future applications of this technique include A) serial tracking of tumor burden to assess treatment response; B) localization of tumor growth to assess patterns of treatment failure and to guide stereotactic biopsy; and C) substratification of recurrent GBM based on tumor burden and prognosis to assist during clinical trial enrollment.

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This work was funded in part by the Arizona Biomedical Research Commission (LSH) and Barrow Neurologic Foundation (LCB).