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

L. S. Hu1,2, J. M. Eschbacher1, A. C. Dueck1, S. Liu1, K. A. Smith8, K. Kotagama4, S. W. Coons3, J. E. Heiserman2, J. P. Karis1, T. Jensen4, W. Shapiro6, J. Debbins3, P. Nakaji5, B. G. Feuerstein5, and L. C. Baxter4

1Radiology, Mayo Clinic Arizona, Phoenix, AZ, United States; 2Radiology, Barrow Neurological Institute, Phoenix, AZ, United States; 3Neuropathology, Barrow Neurological Institute; 4Biostatistics, Mayo Clinic Arizona; 5Keller Center for Innovation and Imaging, Barrow Neurological Institute, 6Neurosurgery, Barrow Neurological Institute, 7Neuroradiology, Barrow Neurological Institute, 8Imaging Biometrics, LLC, 9Neurology, 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.1-3 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 actually 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 correlated relCBV with small stereotactic biopsies (∼0.2 cm3) 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 Neurology, Barrow Neurological Institute, 8.1.430, 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 localised 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.1,4,6,11,12 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.

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).

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.1,11 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) stratification of recurrent GBM based on tumor burden and prognosis to assist during clinical trial enrollment.


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