Comparisons of in vivo physiological imaging and histological characteristics for tissue samples from regions of gadolinium enhancing and non-enhancing tumor from patients with GBM

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INTRODUCTION: The cellular heterogeneity and infiltrative nature of Glioblastoma multiforme (GBM) creates challenges in delineating tumor margins during the initial surgical resection and in determining the optimal therapeutic interventions during subsequent stages of the disease. Understanding the relation between histological features of malignancy and in vivo physiological imaging biomarkers may improve treatment management for these patients. The goal of this study is to obtain image guided tissue samples from regions of suspected tumor in untreated GBM patients and compare ex vivo and in vivo parameters in order to characterize enhancing versus non enhancing tumor.

METHODS: A total of 119 image-guided tissue samples were obtained from 51 patients with newly diagnosed GBM, who received preoperative MR imaging (1.5T or 3T GE scanners). The scans included T1 weighted imaging, T2 with FLAIR and FSE weighted imaging, 6 directional axial Diffusion Weighted Imaging (DWI) with b=1000s/mm2; and Dynamic Susceptibility Contrast (DSC) imaging data with a 3ml/s injection of 0.1mmol/kg body weight Gd-DTPA. In some cases lactate-edited 3D MRSI was acquired with PRESS volume localization from the lesion and surrounding region of normal appearing brain. **Tissue Acquisition:** Tissue sample locations were selected in BrainLab navigation software based on surgically accessible areas with the following imaging criteria: low apparent diffusion coefficient <1200, elevated Choline/N-acetylaspartate index >2, or elevated DSC peak height >3. Images and coordinates of the tissue sample location were transferred offline for evaluation. Spherical regions of interest (diameter 5mm) were defined for each sample location and used to extract intensity information from anatomic images and maps of physiological parameters. Intensities were normalized to values in normal appearing white matter. They included T1 contrast enhancing intensity (nT1C), fast spin echo T2 hyperintensity (nFSE), FLAIR T2 hyperintensity (nFLAIR), apparent diffusion coefficient (nADC), fractional anisotropy (nFA), cerebral blood volume (nCBV), peak height (nPH), percentage of recovery to baseline (%REC), and recovery factor (RF). Tissue samples were processed using standard techniques and scored by a neuropathologist in terms of tumor cellularity, proliferation, cellular density, necrosis, hyperplasia, hypoxia, peri-axional infiltration and microvascular characterization (simple, complex, or delicate vessels). **Analysis:** Mixed effect models were applied to evaluate the following: 1) Compare MR imaging and histopathologic variables between contrast enhancing (CE) and non-enhancing (NE) regions, 2) MR imaging parameters versus histopathologic characterization within CE and NE regions, 3) associations between different in vivo MR imaging parameters within CE and NE regions.

RESULTS: Tissue sites within CE regions had increased levels of nT1C, nFSE, nCBV, nPH, and RF but lower levels of %REC than in NE regions (all P-values <.01). The distributions of nADC, nFA, and nFLAIR were not different between the two regions. CE regions had increased tumor cellularity/density, peri-axonal infiltration, and proliferation than NE regions (all P-values <.05). Complex vessels, hypoxia and necrosis were rare features in NE regions.
Univariate analysis within CE regions demonstrated that tumor cellularity, proliferation and hyperplasia were positively associated with nCBV and nPH (all P-values <=.01). In NE regions, tumor cellularity was inversely associated with nFSE (P= .03) and nADC (P= .02); proliferation was inversely associated with nFLAIR (P= .01) and nADC (P= .01); and peri-axonal infiltration was inversely related to nADC (P= .005) but positively correlated to nFA (P= .04).
In both regions proliferation was found to be positively associated with tumor cellularity, cellular density, peri-axonal infiltration, hyperplasia, and simple vessels (all P-values <.001). Expected relationships between imaging parameters derived from the same sequences were found in both regions. For DWI, nADC was inversely related to nFA, while for DSC imaging, rPH and rCBV were positively related and %REC and RF were inversely related (all P-values <=.05).
The CE and NE regions had different associations among MR parameters from different types of sequences (all P-values <=.05). In CE regions, nT1C was only associated with nCBV, while nFLAIR was only positively correlated with nFSE. The nFSE parameter was associated with diffusion (nADC & nFA) and perfusion parameters (nCBV & nPH). In NE regions, nADC and anatomic parameters nT1C, nFSE, and FLAIR were all associated with each other.

CONCLUSION: Characterizing associations between MR imaging parameters and histopathology feature by CE and NE regions is particularly important in evaluating residual tumor and planning therapy for patients who received surgical resection. Our study showed that DSC imaging parameters were associated with malignant histology in CE regions, while DWI parameters were associated with malignant histology in regions of NE tumor. This suggests that the definition of tumor burden should consider both of these physiological imaging parameters with respect to being in CE or NE lesions. Further studies will examine how to combine this information in order to generate more effective metrics for monitoring response to therapy than the current MacDonald or RANO criteria which are based solely on changes in the cross sectional diameters of anatomic imaging. ***Acknowledgments:*** Funded by NIH grant PO1CA118816-01A2