MR-based Anatomic, Metabolic and Physiologic Imaging Information on spatial heterogeneity in newly diagnosed GBM

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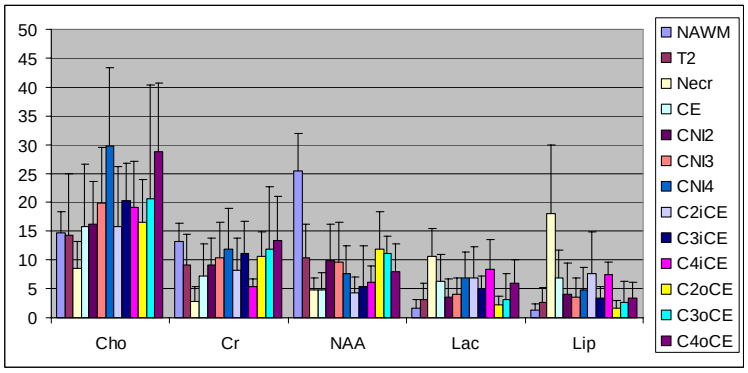
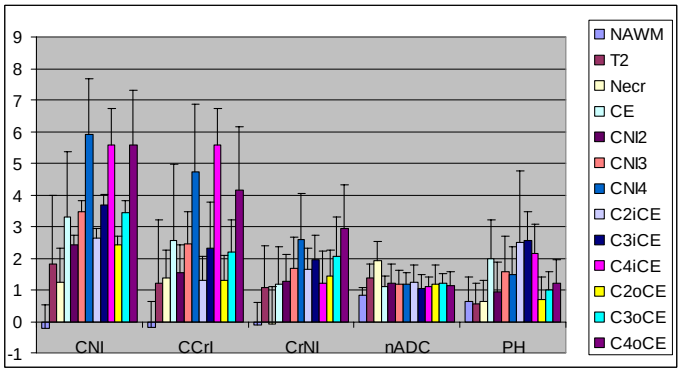
Introduction: Glioblastoma multiforme (GBM) is known to be the most malignant brain tumor in adults with a survival of less than one year despite aggressive multimodality therapy. The cause for the apparent resistance of these tumors to conventional treatments is multifold: the dissemination of malignant cells throughout brain parenchyma, the presence of a variably disrupted blood-brain barrier, and leaky capillaries that result in peritumoral edema are only to a limited extent assessable by conventional MRI. Enhancing the detection of this inherent heterogeneity of GBM might allow for optimized therapeutic interventions to overcome the current resistance of these tumors. We have performed a voxel-by-voxel analysis of data from MR-based multivoxel 3D Proton spectroscopy (MRSI), perfusion (PWI) and diffusion weighted imaging (DWI) to assess metabolic and physiologic properties of newly diagnosed GBM in comparison to its morphologic properties as derived from MRI.

Materials and Methods: Fourteen patients with newly diagnosed GBM were scanned on a 1.5 T GE Signa Echospeed scanner (GE Medical Systems, Milwaukee, WI) prior to any intervention. The MRI protocol included axial T2-weighted Fluid Attenuated Inversion Recovery (FLAIR), and post-Gd-DTPA T1-weighted Spoiled Gradient (SPGR) sequences. 3D MRSI with lactate editing was acquired using Point Resolved Spectroscopic (PRESS) volume localization with spectral spatial pulses and VSS outer volume suppression bands (TR/TE=1000/144 ms, 1 cc nominal spatial resolution). Spectral values were normalized relative to the noise levels at the right hand end of the spectra. MRSI data were quantified offline to estimate absolute peak heights of choline (Cho), creatine (Cr), N-acetyl aspartate (NAA), lactate (Lac) and lipid (Lip), and indices of Cho- to-NAA (CNI), Cho-to-Cr (CCrI) and, Cr-to-NAA (CrNI) were automatically calculated [1]. Axial diffusion imaging sequences with three gradient directions were acquired with TR/TE =5000/105 ms, and b-value=1000 s/mm2. Diffusion maps were calculated and normalized relative to the mean of the voxels in normal appearing white matter (NAWM) generating maps of nADC. The perfusion imaging consisted of the injection of a bolus of 0.1 mmol/kg series of 60 T2*-weighted gradient-echo, echo-planar images acquired during the first pass of the contrast agent bolus injection, with a TR/TE of 1000-1250/54 ms, 35o flip angle, FOV of 26x26 cm2, 128x128 acquisition matrix, and 3-6 mm slice thickness. Peak height (PH) values of the $\Delta R2^*$ curve of the post-bolus signal from the peak were calculated and normalized to the peak of a model curve function derived from normal appearing brain based on histogram analysis of the pre-contrast echo planar images. Perfusion and diffusion maps were resampled to the spectral resolution to allow for direct comparison. Manually defined, mutually exclusive, regions of interest (ROI) included macroscopic necrosis (Necr), contrast enhancement (CEL) and T2 hyperintensity (T2L) lesion, and NAWM. CNI contours of $\geq$ 2 (C2), 3 (C3) and 4 (C4) were generated from the CNI maps. Similarly contours of CrNI and CCrI of $\geq$ 2 were generated. In order to study the characteristics of spectroscopically abnormal regions overlapping or extending beyond the CEL, additional ROI's of CNI-inside/outside-CEL (i.e. C2iCE and C2oCE) were generated. A total of 3453 data voxels within the PRESS selected volume were studied; we included voxels that overlapped at least 60% with the respective ROI and excluded voxels containing >20% macroscopic necrosis. The Mann-Whitney rank sum test was applied to see whether any two regions of interest had significantly different metabolite or diffusion values.

Results: All GBM exhibited CEL and T2L, macroscopic necrosis was present in 12/14 patients. A number of significant differences in metabolic and physiologic imaging characteristics were found with respect to the defined anatomic and anatomic/metabolic ROI's. All results are reported as mean values. Compared to NAWM, Cho values were similar in T2L and much smaller in Necr, whereas significantly higher in CEL but highest within C4iCE. Compared to NAWM, NAA signal intensities were significantly lower and of similar intensity in T2L and C2 and C3. NAA levels were smaller within the CEL compared to outside the CEL for all C2-4 regions. NAA levels were similar in C2-4iCE, indicating that the CNI inside the CEL was mainly driven by an increase in Cho, whereby NAA levels decreased with increasing CNI outside the CEL. Compared to NAWM, Cr was significantly lower in T2L, CEL, and Necr as well as within CNI2-4. Lac and Lip were found to progressively increase in T2L, CEL and Necr as well as with increasing CNI and they were always higher inside the CEL than outside the CEL within CNI regions. Lip levels increased outside the CEL with increasing CNI. nADC values were progressively increasing in CEL, T2L, and necrosis, and were significantly higher than NAWM in all of these regions. Perfusion PH values were similar in NAWM, T2L and C2oCE and were significantly increased in CEL and C2-4iCE and within C3-4oCE. CNI was increasing between Necr, T2L and CEL. With respect to the CNI contours overlapping or extending beyond the CEL, it was interesting to note that Cr increases with increasing CNI and was invariably higher in CNI regions beyond the CEL as compared to those overlapping with CEL. The same applied for CrNI even though NAA is higher in the regions beyond CEL. The opposite was seen with respect to CCrI, Lac, Lip and PH that were found lower beyond versus within CEL. One of the most notable findings of the study was that the C4iCE region had the highest Lip, second highest Lac and lowest Cr after Necr, and highest CCrI within all ROI's. Necrotic voxels had highest nADC, Lac, Lip, lowest Cr.





Discussion: Our findings confirm the assumption that the CEL in newly diagnosed GBM is highly heterogeneous. Perfusion PH was significantly increased in CEL and was highest in C2-3iCE indicating increased cell division and neovasculature. A subregion of the CEL that has CNI>4 (C4iCE) seemed to reflect micronecrosis and hypoxia, which likely would be an area particularly resistant to radiation therapy. The CNI regions extending beyond the CEL, on the other hand, exhibited clearly tumor suggestive metabolism with highest Cho, increased PH, increased Lac and, to a lesser extent Lip, demarcating the "leading edge" of the tumor. Regions of T2 hyperintensity had similar Cho, decreased Cr and NAA, slightly increased Lac/Lip, much increased nADC and similar PH values compared to NAWM indicating a mixture of edema and tumor cell infiltration. MR-based metabolic and physiologic imaging continues to hold promise as a means for enhanced biologic interpretation of the heterogeneity in GBM and should be used for optimized radiation and other targeted therapy.

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1. McKnight TR, et al. An automated technique for the quantitative assessment of 3D-MRSI data from patients with gliomas. J Magn Reson Imaging 13, 167-177, 2001