Analysis of metabolic levels in regions of abnormal perfusion in high-grade glioma patients

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Introduction: Magnetic resonance spectroscopic imaging (MRSI) and dynamic susceptibility-weighted perfusion MRI (PWI) are functional in vivo techniques capable of quantitatively differentiating between active tumor, necrosis, and edema. Numerous studies have implemented MRSI to extract information about brain tumor cellularity and cell membrane breakdown, cellular energetics, neuronal activity, hypoxia, and macroscopic necrosis through its ability to distinguish signals from choline, creatine, NAA, lactate, and lipid molecules.[1] Although MRSI is an excellent tool for elucidating metabolite levels in brain tissue, it does not provide a direct measurement of changes in tumor vasculature that result in increased vessel volume and/or blood-brain-barrier breakdown and subsequent leakage of contrast agent into brain tissue. PWI facilitates the tracking of a contrast agent bolus through the vasculature, resulting in a T2* relaxivity curve proportional to concentration. Voxel by voxel comparison of percent recovery and peak height values obtained from a non-parametric model can be easily employed to independently characterize regions of blood-brain-barrier (BBB) breakdown and increased vessel volume due to angiogenesis.[2] This study aims to combine 3D MRSI and PWI to investigate whether analysis of metabolite levels within regions of abnormal perfusion can assist in characterizing heterogeneous tumor tissue of high-grade gliomas.

Methods: Thirty-six patients with a diagnosis of grade III (15 patients) or IV (21 patients) gliomas were recruited for this study prior to receiving treatment. MRI exams were performed on a 1.5 T Signa Echospeed scanner (GE Medical Systems). The MRI protocol included post-contrast T1-weighted SPGR images and T2-weighted FLAIR or FSE images, which were used to define regions of T2 hyperintensity. 3D MRSI data were acquired using lactated-edited PRESS volume localization with BASING pulses and ellipsoidal k-space sampling (TR/TE=1s/144ms, 12x12x8 phase encode matrix, 1cc nominal spatial resolution). CHESS and VSS pulses were applied for water and outer volume suppression, respectively.[3] 3D MRSI data were quantified offline using software developed in our laboratory to estimate the levels of choline (Cho), creatine (Cr), and lactate (Lac).[1] Spectral values were normalized relative to the noise levels of the right hand end of the spectra. The perfusion imaging consisted of the injection of a bolus of 0.1 mmol/kg body weight of gadopentetate dimeglumine (Gd-DTPA) contrast agent at a rate of 5 mL/s. A series of 60 $T2^*$-weighted gradient-echo, echo-planar images were acquired during the first pass of the contrast agent bolus injection, with a TR/TE of 1000-1250/54 ms, 35° flip angle, FOV of 26×26 cm^2, 128×128 acquisition matrix, and 3-6 mm slice thickness. The metabolite and perfusion images were resampled to a 32×32 grid in-plane with a 16 x 16 cm^2 FOV to obtain a 5mm x 5mm voxel size so that the observed perfusion signal changes had sufficient signal to noise ratio to be analyzed reliably on a voxel by voxel basis and the degree of interpolation of the metabolite maps was minimized. Peak height and percent recovery of the post bolus signal from the peak were calculated from the $\Delta R2^*$ curve of the perfusion data for each voxel within the PRESS localized volume. Peak height values were 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.[2] Voxels with peak height values greater than twice the model curve were classified as having abnormal peak height, while those whose post-bolus concentration recovered less than 75% from the peak concentration were considered to have abnormal recovery. Metabolite levels of pure T2 hyperintensity, normal appearing white matter (NAWM), and for voxels experiencing abnormal peak height but not abnormal recovery (aPH), abnormal recovery but not abnormal peak height (aRec), and both abnormal peak height and recovery (aPH + aRec) were determined for grade III and grade IV patient cohorts. Statistical significance of group comparisons was determined through the use of a Wilcoxon ranked sum test.

Results and Discussion:

Volumes of abnormal perfusion regions: The mean volumes of aPH and aPH + aRec, expressed as a percent of the T2 lesion volume, were significantly larger in grade IV than grade III patients ($p<.05$), with respective values of 8.10% and 1.46% for grade III patients, and 17.92% and 6.13% in grade IV patients. An increasing trend was observed for aRec volume with grade, but the difference (6.95% vs 12.41%) was not significant. In both patient populations there was a decreasing trend in volume from aPH to aRec to aPH + aRec regions, signifying more angiogenesis than BBB breakdown for both tumor grades. This also suggests that angiogenesis and BBB breakdown may be two are separate processes that, for the most part, do not coexist in the same location.

Choline levels: Increased levels of Cho were observed in all abnormal perfusion regions for grade III gliomas compared to both NAWM tissue and corresponding grade IV regions ($p<.001$). Grade IV gliomas showed elevated Cho in regions of combined aPH + aRec compared to normal ($p=.05$), possibly highlighting regions of grade IV tumors that are still rapidly dividing and need additional support from angiogenic vessels.

Lactate levels: Grade IV gliomas exhibited significantly elevated Lac compared to grade III gliomas in all abnormal perfusion regions. Although there was no significant difference in Lac levels among the three abnormal perfusion regions in grade III patients, lower levels of Lac were found in the aPH region compared to the other abnormal perfusion regions in grade IV gliomas ($p< .001$). In general, the presence of Lac did not appear to be localized to any particular region; the amount of Lac in all abnormal perfusion regions was consistent with levels found in the surrounding T2 hyperintensity. These findings intimate that the existence of Lac may be indicative of tissue that is a precursor of hypoxia where the angiogenic switch has not yet been activated. This is further supported by the fact that grade IV tumors that have progressed further showed more Lac in the aRec region.

Creatine levels: A reduction in Cre levels was detected for grade IV gliomas in all regions of abnormal perfusion when compared to both NAWM and corresponding grade III regions ($p<.001$), likely due to overall metabolite depression from evolving necrotic tissue. Grade IV patients exhibited the greatest decline in Cre levels within the aPH region, while grade III patients experienced a reduction in Cre levels from NAWM tissue only in the aRec region. The latter is consistent with previous findings of lower Cre values for grade III patients in regions of contrast enhancement[4] and supports Cre as a marker for hypoxia inducing angiogenic behavior.

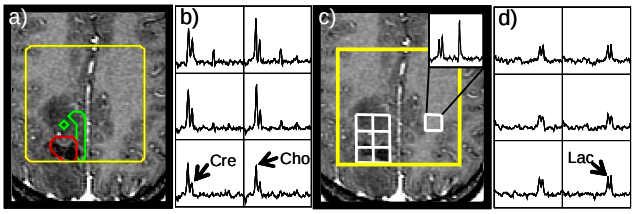

Figure 1: a) aRec (*red*) and aPH (*green*) regions, within the PRESS box (*yellow*), b) tumor spectra and d) lactate-edited spectra from same region shown in c), which also displays NAWM spectra for a grade III patient.

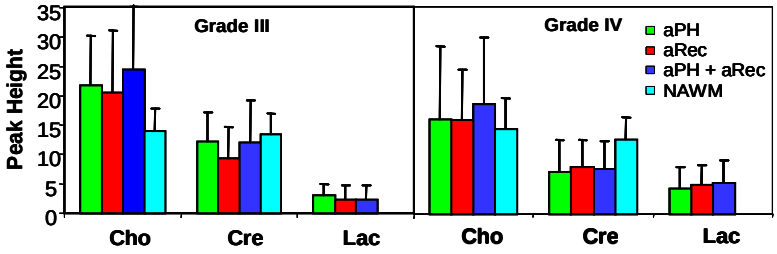

Figure 2: Depiction of mean metabolite levels in various abnormal perfusion regions and NAWM for grade III and grade IV gliomas.

Conclusions: Although lactate and creatine have both been implicated in brain tumor hypoxia, this study suggests that lactate may not be a spatially specific marker for localizing hypoxic regions. Knowledge of metabolite levels of creatine in conjunction with perfusion parameters could be a better way of predicting angiogenic regions within heterogeneous high-grade tumors. Noninvasively characterizing the most aggressive tumor region would be highly useful in both treatment planning and early detection of tumor progression.

[1] Nelson, S.J., *MRM*, 46: 228-239 (2001), [2] Lupo *et al. Proc. Intl Soc Magn Reson Med.* Kyoto, Japan. (2004), [3] Li X *et al, . Intl Soc Magn Reson Med.* Kyoto, Japan. (2004), [4] Ozturk E, *et al, . Intl Soc Magn Reson Med.* Kyoto, Japan. (2004).

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