3D 1H MRSI, MRI, and Diffusion Tensor Imaging in Newly-Diagnosed Patients with Grade 3 Brain Tumors

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Introduction: Brain tumor incidence rate is increasing with 17500 new cases of primary brain tumors now being detected each year. MRSI has been successfully employed to extract information about brain tumor cellularity and cell membrane breakdown, cellular energetics, and neuronal activity through its ability to differentiate signals coming from choline (Cho), creatine (Cr) and N-acetyl aspartate (NAA) molecules. Diffusion weighted MRI has been used to examine disruptions in the integrity of white matter tracts and changes in water content or cell density. Previous studies have shown that MRSI is more reliable in defining the extent of tumor than conventional MRI imaging methods [1,2] for gliomas of all grades but were only able to identify relationships between mean levels of Cho, CNI, ADC, and ANI in patients with Grade 4 gliomas [1]. In this study we have focused on patients with newly diagnosed grade 3 gliomas in order to see whether voxel by voxel analysis of data from 3D MRSI and Diffusion Tensor Imaging (DTI) data can assist in characterizing tissue within the contrast enhancement (CE), T2 hyperintensity excluding CE (T2-CE), and areas of metabolically active tumor.

Materials And Methods: Thirteen patients (5 male, 8 female) who were diagnosed with Grade 3 gliomas, were scanned on a 1.5 T GE Signa Echospeed scanner (GE Medical Systems, Milwaukee, WI) prior to receiving treatment. The MRI protocol included axial T2-weighted Fast Spin Echo (FSE), and post-gadolinium (Gd) T1-weighted Spoiled Gradient (SPGR) sequences. Seven out of thirteen patients exhibited contrast enhancement on the SPGR images obtained after the injection of Gd. 3D MRSI data were acquired based on the SPGR images 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). DTI sequences with six gradient directions were acquired in the axial planes with TR/TE =5000/105 ms, and b-value=1000 s/mm^2. 3D MRSI data were quantified offline to estimate the levels of choline(Cho), creatine (Cr), N-acetyl aspartate (NAA), lactate/lipid (LL), and Choline to NAA index (CNI) [3,4]. DTI images were quantified using an in-house software to calculate the ADC and ANI maps. Diffusion maps were resampled to the spectral resolution and normalized relative to the mean of the voxels in normal appearing white matter (NAWM) to form maps of nADC and nANI. Spectral values were normalized relative to the noise levels of the right hand end of the spectra. Regions of contrast enhancement and T2 hyperintensity were manually defined based on the SPGR and FSE images to obtain the CE and T2-CE lesions, 2≤CNI<3 (CNI2), 3≤CNI<4 (CNI3), and CNI≥4 (CNI4) contours were generated from the CNI maps. A total of 2786 voxels of data within the PRESS localized volumes were considered, including 32 CE, 549 T2-CE, 186 CNI2, 107 CNI3, 178 CNI4, and 32 NAWM voxels. The Mann-Whitney rank sum test was applied to see whether any two regions of interest had significantly different metabolite or diffusion values. Spearman rank correlation coefficients for the spectral and diffusion values were calculated to detect correlations of pairs of parameters within the regions of interest.

Results: Several differences in the mean metabolite levels, CNI, and diffusion values were found between the regions of interest as shown in Figure 1. Although Cho levels were not significantly different between NAWM and CE, or NAWM and T2-CE, there was a significant increase in Cho in the CE region compared to T2-CE, as well as among increasing CNI levels. NAA was significantly lower among NAWM, T2-CE, and CE, and it was slowly decreasing between CNI levels. LL levels were similar in NAWM, T2-CE, and CNI2 regions, but significantly elevated for CE, CNI3 and CNI4. Compared to the NAWM, mean nADC value was 85% higher in T2-CE and 75% higher in CE, and the mean nANI value decreased 55% in CE, and 52% in T2-CE, but these values could not be distinguished between regions. nADC increased from CNI2 to CNI3 and CNI2 to CNI4, but it was not significantly different between CNI3 and CNI4. nANI decreased from CNI2 to CNI4, and CNI3 to CNI4, but it was not significantly different between CNI2 and CNI3. There was a significant increase in CNI values in all of the regions relative to NAWM. Table 1 shows the regions where there were significant correlations among diffusion and spectral parameters. There were no significant correlations among any of the diffusion and spectral values in the NAWM. There was a negative correlation of nADC and nANI in all of the tumor regions except for the CNI3. There were no correlations between nADC and LL in any of the regions. Cr was negatively correlated with nADC at all of the abnormal regions. NAA was negatively correlated with the nADC in the CNI regions but not the T2-CE or CE regions. Cho was negatively correlated with nADC in the T2-CE and CNI regions.

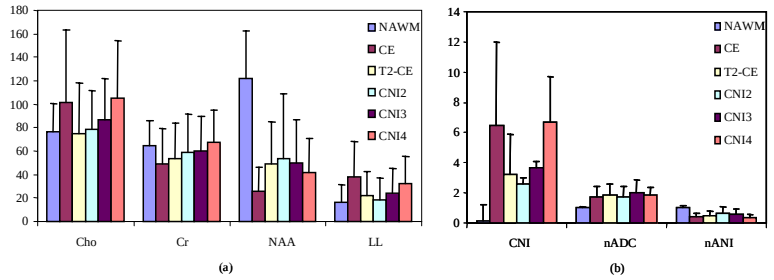

Figure 1. Mean spectral peak areas for Cho, Cr, NAA, LL, CNI, nADC and nANI

	Cho	Cr	NAA	LL	CNI	nANI
NAWM	-	-	-	-	-	-
T2-CE	nADC	nADC	-	-	nADC, nANI	nADC
CE	-	nADC	-	-	-	nADC
CNI2	nADC, nANI	nADC, nANI	nADC, nANI	-	-	nADC
CNI3	nADC, nANI	nADC, nANI	nADC, nANI	-	-	-
CNI4	nADC	nADC	nADC, nANI	nANI	-	nADC

Table 1. Significant correlations of spectral and diffusion parameters

Discussion: Grade 3 gliomas showed T2 hyperintensity in all lesions, with moderate CE in only 7/13 of them. When present, the CE region appeared to have a higher density of tumor cells based upon the relatively high Cho and low NAA. The fact that the CE had high LL and low Cr suggested that this region was also relatively hypoxic. The overall increase in nADC and decrease in nANI in tumor regions relative to NAWM suggested that they had increased water content and disruption of the normal tissue architecture. Regions with intermediate CNI values had fairly normal levels of Cho but increasing nADC, decreasing nANI and decreasing NAA. This suggested that they corresponded to regions where normal brain function was compromised but where tumor cell density was still only moderate. Regions with high CNI (>4) had relatively low nADC, high Cho, low NAA and low nANI than regions with intermediate CNI. This suggested that the voxels with high CNI corresponded to tumor with the greatest cell density. Note that increasing CNI reflects a reduction in normal function (decreased NAA) and an increase in cell density/membrane turnover (increased Cho). This means that the CNI is likely to be more sensitive than the use of Cho or NAA alone. Factors contributing to changes in nADC are more complex because there is an increase in the values in edema and infiltrative tumor due to higher tissue water content and a decrease in tumor due to higher cellularity. This suggests that MRSI and diffusion parameters contain information that may be valuable in distinguishing regions of the anatomic lesion that correspond to edema (increased water content with minimal disruption in normal tissue function, increased nADC but normal metabolism) and infiltrative tumor (disruption in normal tissue function, increased nADC and decreased NAA) from regions of tumor that have high cell density and are becoming hypoxic (high CNI and high LL). While changes in the levels of LL indicated that regions where the BBB has been disrupted are poorly oxygenated, there are also regions of non-enhancing tumor with similar metabolic characteristics. This suggests that the MRSI data are likely to be more valuable than contrast enhanced MRI in predicting sensitivity to radiation therapy.

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