Correlation of Choline and Apparent Diffusion Coefficient in Glioma patients

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Introduction: Gliomas are spatially heterogeneous brain tumors; non-invasive methods for evaluating this heterogeneity are important in directing patient treatment. Previous studies have proposed both apparent diffusion coefficient (ADC) from diffusion weighted imaging and choline from magnetic resonance spectroscopic imaging (MRSI) as important prognostic factors and surrogate measures for cell density[1]. An inverse correlation between ADC and choline using a heterogeneous patient population with heterogeneous tumor regions[2] (i.e. edema, necrosis, cystic cavity and solid tumor) has also been reported. This study aims to verify the correlation between normalized ADC and choline levels in two distinct populations of patients with newly diagnosed glioma; namely patients with Grade II and Grade IV gliomas. We further sought to verify that the previously reported correlations held for tissue that was solely within sub-regions of T2 hyperintense region, contrast enhancement and necrotic regions.

Methods: A total of fifty newly diagnosed brain tumor glioma patients, consisting of twenty-four Grade II patients (15 male, 9 female, 22-71yrs; 15 astrocytomas, 9 oligodendrogliomas) and twenty-six Grade IV patients (19 male, 7 female, 30-82yrs) were scanned on a 1.5T GE Signa Echospeed scanner (GE Healthcare Technologies). The MRI protocol included post-gadolinium (Gd) T1-weighted image, axial T2-weighted images, 3D MRSI using PRESS volume localization (VSS outer volume suppression bands; TR/TE = 1100/144ms; nominal voxel size of 1 cc), and three directional axial diffusion imaging with (TR/TE= 1000/110-86ms), voxel size = 1.4x1.4x5mm, b=1000. 3D MRSI data were quantified offline using in house software to estimate the levels of choline (Cho)[3]. Diffusion images were quantified using in-house software to calculate the apparent diffusion coefficient (ADC). A semi-automated segmentation method was used to define the contrast enhancing lesion (CEL) and necrotic regions (NEC) from the post-gad T1-weighted image and T2 hyperintense region (T2All). A sub-region named T2L was also defined as T2All-CEL-NEC. Diffusion maps were resampled to the spectral resolution and normalized relative to the median normal appearing white matter (NAWM) to generate nADC maps. Choline was normalized to median choline within the NAWM. Patients were divided into two groups by grade. The analysis was performed at both a voxel by voxel basis as well as within anatomically defined tumor regions. The voxel level analysis included a Spearman rank correlation of the data from the plot of the nCho vs. nADC for voxels in the PRESS box within the defined sub-regions (Figure 1), repeated for each patient, and separated by grade. The correlation coefficients were used as individual samples in a Wilcoxon signed rank test to determine if the median correlation is zero within grade. A Wilcoxon rank sum test was used to test for equal medians between grades. The region level analysis compared the median nCho and median nADC for each of the abnormal regions (Grade IV: T2L, CEL, NEC, T2All, and Grade II: T2All, no CEL or NEC were observed in Grade II) for each patient (Figure 2). A Spearman rank correlation was performed for each grade for each abnormal region.

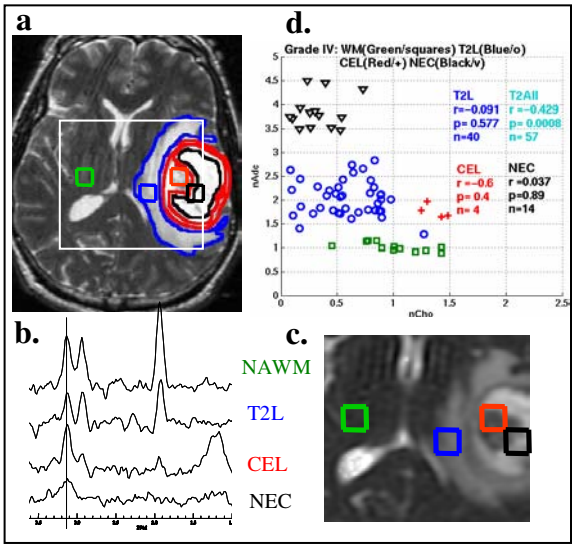

Figure 1. Data from a Grade IV patient. (a) Voxels within sub-regions defined [NAWM(green), T2L(blue), CEL(red) and NEC(black)]. (b) Cho determined from spectra . (c) ADC values determined in the same voxels as Cho. (d) Cho and ADC values normalized to NAWM. nCho vs. nADC plotted.

Results and Discussion:

Descriptive Statistics: The median ADC values for Grade IV within the sub-regions were 76.5±33.3(NAWM), 132.3±26.7(T2All), 129.8±26.1(T2L), 121.8±22.5(CEL), 191.7±52.8(NEC) x 10^{-3} mm^2/s. Grade II median ADC values within NAWM and T2All were 75.2±28.9 and 149.4±27.9 x 10^{-3} mm^2/s respectively. As previously shown, ADC values within the T2All were significantly different between Grade IV and Grade II ($p<0.04$ using a Wilcoxon signed rank test.). The nADC ranged from 0.8 to 4 and nCho ranged from 0.1 to 7 within the T2All of Grade IV lesions.

Voxel Level Analysis: In Grade IV, Wilcoxon signed rank of the nCho to nADC correlation coefficients from each patient for T2L, T2All and CEL showed significance with p(n) = 0.0422(26), 0.00003(26), 0.01860(11) respectively. This suggests that the median of the coefficients is not 0 and that there is a true correlation, which we can deduce is at least negative since 90% of the patients showed negative correlations. In contrast, NEC did not reach significance p(n) = 0.688(6). In the case of Grade II, T2All correlations were not significant ($p< 0.297(24)$). This was clear from the correlation coefficients since the ratio of negative to positive correlation coefficients was 13/15. This implies that at the voxel level there is no correlation within patients with Grade II glioma. The Grade II gliomas were divided into subgroups of astrocytomas and oligodendrogliomas and the analysis repeated for which the conclusions for each type showed no correlations. The Wilcoxon rank sum test verified $p<0.0036$ that the Grade II and Grade IV coefficients came from different samples demonstrating that the two tumors are different and that possibly the underlying physiological environment is causing this difference.

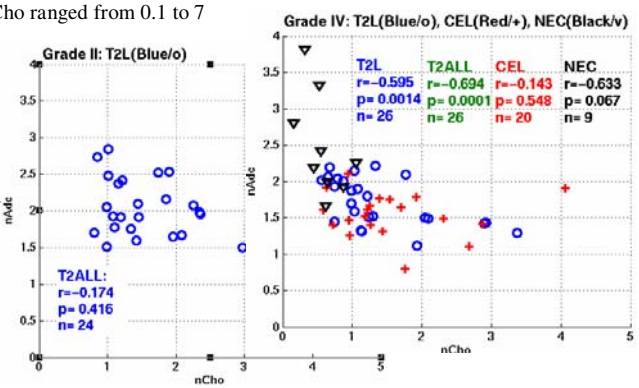

Figure 2. nCho vs. nADC per patient per sub-region.

Region Level Analysis: In the case of Grade IV patients, T2L and T2ALL were significantly correlated with p(n) = 0.00136(26), 0.0001(26) respectively, whereas CEL and NEC were not significant p(n) = 0.548(20), 0.067(9) respectively. Grade II patients did not show any significance p(n) = 0.41. The results from the regional level analysis agree with those from the voxel level analysis and emphasize the differences between the relationship of nADC and nCho values in Grade II and Grade IV gliomas for newly diagnosed patients.

Conclusions:

Previous studies have shown an inverse correlation of ADC to choline for heterogeneous grades and regions; this study suggests there is an inverse correlation specifically in Grade IV patients, but not in Grade II. Additionally, there is a strong correlation in the T2L region, but this correlation does not necessarily hold for the CEL and NEC regions. This suggests that there is independent information to be acquired from both diffusion and spectroscopic imaging. Furthermore, the range of values for ADC and choline within a Grade IV tumor are large and require image-guided biopsy to accurately correlate these values to cell density.

References:

[1] Gupta, R.K., *et al.*, *J. Neuro-Oncol.*, *50:* 215-226 (2000), [2] Gupta, R.., *et al.*, *MRM*, 41:2-7 (1999), [3] Nelson, S.J., *MRM*, 46: 228-239 (2001)

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