CHARACTERIZING REGIONAL HETEROGENEITY OF GLIOBLASTOMA: REGIONS REPRESENTING METABOLIC AGGRESSION IN ENHANCING AND NON-ENHANCING COMPONENTS

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TARGET AUDIENCE

Clinicians treating patients with glioblastoma and scientists interested in imaging glioma invasion and intratumor heterogeneity.

PURPOSE

Glioblastoma (GBM) is the most common and aggressive of primary brain tumors in adults. These tumors demonstrate intratumor heterogeneity that results in unpredictable responses to treatment. Due to the risks involved in performing multiple biopsies on patients, non-invasive methods are needed for tumor analysis. This study aimed to identify known metabolic signatures of aggressive tumor, the choline to N-acetylapsartate (Cho/NAA) ratio, in different regions of GBM using thresholds for apparent diffusion coefficient (ADC) and relative cerebral blood volume (rCBV). The overall purpose was to determine whether regions of low ADC and high rCBV represented regions of elevated Cho/NAA ratios when compared to regions of higher ADC and lower rCBV, and whether they differed when located in the CE or fluid attenuated inversion recovery (FLAIR), referred to as the non-enhancing (NE) component of the tumor.

METHODS

42 Patients with confirmed GBM were imaged pre-operatively at 3T on a Siemens Trio using sequences for conventional T_1-weighted CE, T_2-weighted FLAIR, diffusion-weighted, perfusion-weighted and MR-spectroscopic chemical shift imaging (CSI). Global thresholds for normalized low ADC and high rCBV were developed and overlapping regions were selected as the primary regions of interest (primary ROI). Voxels within CE and NE components that did not meet the low ADC and high rCBV threshold were selected as control voxels of interest (control tumor VOIs). A voxel was placed in contralateral normal-appearing white matter (NAWM) for control purposes. Data were analyzed with IBM SPSS version 21 and significance was accepted at $P < 0.05$. Calculated Cho/NAA ratio values were categorized according to their location within the conventional tumor abnormality, either CE, NE or control VOI, or NAWM. Differences between the four groups were explored using ANOVA, with post hoc analysis using Tukey-Kramer HSD testing.

RESULTS

Primary ROIs located in CE regions had a mean value (1.08 ± 0.98) significantly greater than ratio mean of control VOI tumor regions (0.32 ± 0.08, $p < 0.001$) and NAWM (0.28 ± 0.13, $p < 0.001$). Primary ROIs situated within the NE component also had Cho/NAA ratio mean (0.80 ± 0.15) significantly greater than that of the control VOI ($p < 0.05$) and NAWM ($p < 0.01$). There was no significant difference in Cho/NAA ratio values between the CE and NE component of the tumors.

DISCUSSION

The increased levels of Cho/NAA ratio within the ROIs in this study, whether situated in regions of CE or NE, demonstrate that regions of combined low ADC and high rCBV may be representative of a more metabolically aggressive phenotype, in terms of either proliferation or degree of invasion[1], where an increase in Cho can be attributed to increased cellular density, and the decrease in NAA can be attributed to diminished neuronal integrity. Tumor regions not meeting the ADC and rCBV thresholds within the tumors (control tumor VOIs) had Cho/NAA values that were more similar to those of NAWM, possibly indicating that these regions, though they are located within conventional T_1- and T_2-weighted regions of abnormality, are not as metabolically aggressive as the primary ROIs of low ADC and high rCBV.

CONCLUSION

Further studies focusing on diffusion and perfusion properties of GBM, with the aid of spectroscopy, which gives additional information of the microenvironment in GBM, will promote further understanding of the tumor that goes beyond the enhancing component and into the invasive component that makes up the non-enhancing margin, which may be the driver behind treatment failure and tumor local recurrence. Results of this nature cannot be obtained in GBM analyses using conventional imaging alone, further supporting the rationale behind incorporating advanced imaging methods into assessment criteria of GBM.

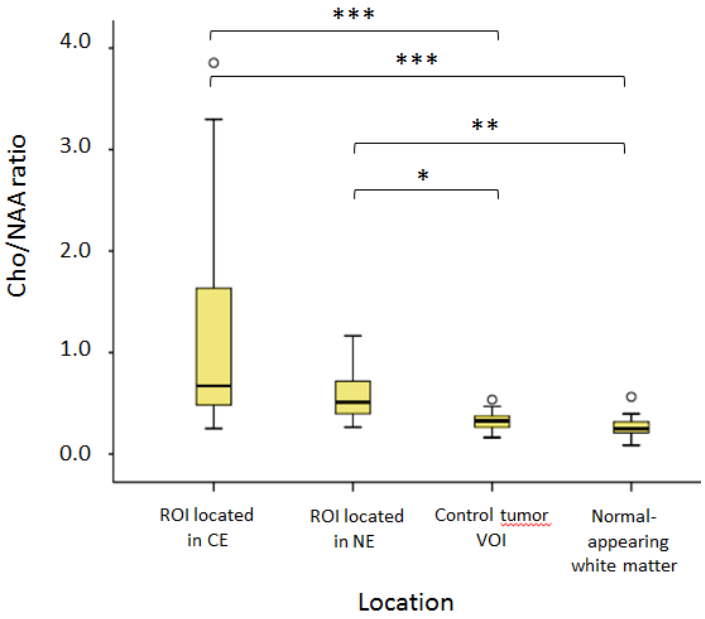

Figure 1: Differences in Cho/NAA ratios found in primary ROIs of combined low ADC and high rCBV, control VOIs and NAWM. Primary ROIs located within CE and NE had Cho/NAA ratios significantly larger than control tumor VOIs and NAWM. No significant difference was found between Cho/NAA ratios of CE and NE.

REFERENCES

1. Croteau D, Scarpace L, Hearshen D, et al. Correlation between magnetic resonance spectroscopy imaging and image-guided biopsies: semiquantitative and qualitative histopathological analyses of patients with untreated glioma. Neurosurgery 2001;49:823–9.