Citrate increases in gliomas in adult patients, as measured by 1H-MRS at 3T in vivo
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PURPOSE: Tumors reprogram their metabolism to meet the needs of rapid cell growth and survival in harsh environments. Changes in metabolism have been reported in gliomas, and the ability to monitor these changes noninvasively using MRS would have significant clinical utility in cancer. Citrate (Cit) is positioned at a crucial metabolic branch point, serving as an intermediate both for energy generation and for biosynthesis of lipids and related molecules [1]. Noninvasive analysis of citrate levels in tumors would therefore provide information about these pathways. Increased Cit was reported in pediatric gliomas [2], but to our best knowledge, detection of Cit in adult tumors has not been reported to date. The goal of this study is to evaluate abnormal Cit concentrations in gliomas in adult patients using 1H MRS in vivo.

METHODS: An MR study was carried out in 89 adult patients (ages > 25) with WHO grade 2 or 3 gliomas, determined based on histology and/or radiographic evaluation of the tumors. Written informed consent was obtained prior to the scans. Experiments were conducted in a Philips whole-body 3T scanner. A body coil was used for RF transmission and an 8-channel phased-array coil for reception. Following survey and T2-w-FLAIR imaging to identify tumor masses, single-voxel MRS data were obtained, with PRESS TE = 97 ms, from a voxel positioned within the tumor. Experimental parameters included TR = 2 s, sw = 2.5 KHz, and 2048 sampling points. The number of signal averages was 64 - 512, depending on the voxel size (4 - 8 mL). For MRS imaging, data were acquired from a 1.5 cm thick slab prescribed by the PRESS, with 1 voxel pos.

RESULTS: Figure 1 shows an in vivo spectrum from a patient with diffuse glioma. The spectrum shows the classic tumor pattern of increased choline and lactate, and decreased creatine and NAA. A large inverted signal was detected at 2.6 ppm. Spectral fitting was performed with two methods; one using a basis set with Cit and another using a basis set without Cit. While the LCModel fitting with Cit closely reproduced the experimental data and gave noise-level residuals at ~2.6 ppm, the analysis without Cit in the basis set did not reproduce the experimental data well in the Cit resonance region, resulting in large residuals at ~2.6 ppm. This incomplete spectral fitting affected estimation of aspartate which has resonances in the proximity of the Cit resonances, giving a ~2-fold higher estimate than that from the fitting with Cit. The NAA aspartate signals were also larger since NAA estimation was large and determined by the relatively large signal at 2.01 ppm. Figure 2 displays data from 6 patients with gliomas. An inverted signal was clearly discernible at 2.6 ppm in all of the spectra.

DISCUSSION & CONCLUSION: We have demonstrated elevation of Cit in the majority of gliomas in adult patients, using MRS in vivo. As Cit is unique to tumors, the specificity of Cit detection is a key advance in clinical MRS for gliomas. Interestingly, the incidence of the increased Cit in gliomas in our study (70%) is in good agreement with the reported incidence of IDH mutations (70 - 80%) [3]. Further study will be required to evaluate the potential correlation of abnormal Cit levels with IDH mutational status. Moreover, many of the patients of the present study had MR scans at multiple time points (1 - 10 scans over 1 - 3 years). Data analysis is underway to evaluate the potential clinical utility of Cit as a biomarker in the diagnosis and management of glioma patients as well as the workup of an undiagnosed mass.