In vivo spectroscopic imaging of citrate in gliomas at 3.0 T

Sandep K Ganji1,2, Akshay Madan1, Zhongxua An1, Elizabeth A Maher1,4, and Changho Choi1,2
1Advanced Imaging Research Center, UT Southwestern Medical Center, Dallas, TX, United States, 2Radiology, UT Southwestern Medical Center, Dallas, TX, United States, 3Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, United States, 4Harold C. Simmons Cancer Center, UT Southwestern Medical Center, Dallas, TX, United States

TARGET AUDIENCE: Neuro-oncologists, MR spectroscopists.

PURPOSE: Citrate (Cit) is an important intermediate in the tricarboxylic acid (TCA) cycle, converted into lipid precursor cytosolic acetyl-coA and acts as a major negative allosteric regulator of glycolysis1,2. Cit is undetectable in healthy brain, but several studies indicated elevated levels of Cit in some pediatric brain tumors3-5. More recently Choi et al. reported first in vivo detection of Cit in adult brain gliomas at 3T using MR single voxel spectroscopy6. Taken together, these studies suggest that Cit may be an important biomarker in brain gliomas. Cit has 2 magnetically equivalent CH2 groups, giving multiplets at ~2.6 ppm. The largest signal is observed at ~2.6 ppm but its detection is challenging due to its close proximity to N-acetylaspertate (NAAasp) and aspartate (Asp) signals between 2.5 - 2.7 ppm. Here we report for the first time 1H spectroscopic imaging (SI) of elevated Cit in adult brain gliomas. The PRESS echo time (TE) was numerically optimized to reduce the spectral overlap of NAAasp and Asp with Cit signal. The SI method was validated in phantoms, and used for measurement of Cit levels in subjects with brain tumors.

METHODS: In this study, we used a non-invasive proton MRSI protocol to detect Cit in gliomas. PRESS 2D echo planar spectroscopy with 512 x 256 matrix, 4 averages, 0.43 x 0.43 x 0.43 mm3 voxel size, and 128 sub-echoes spaced by 27 ms were acquired on a Philips 3T whole-body scanner with 8-channel reception coil. Axial and sagittal T2-w-FLAIR images were acquired to localize the tumor region. In vivo data were acquired with TR of 1.2 sec, spectral width of 2000 Hz and 1024 complex points per FID. Water signal was suppressed using a four-pulse scheme. The PRESS RF pulse carrier was set to 3 ppm. PRF of 90° and 180° pulses had bandwidths of 4.2 kHz (9.8 ms) and 1.3 kHz (13.2 ms) respectively. Typically a 200 x 160 mm2 field of view (FOV) in the phase encoding directions was used for acquisition, with 15 mm thick slice along head-foot direction. In plane resolution was 10 x 10 mm2. Volume of interest was selected to cover FLAIR enhancing regions in tumor mass. Regional saturation bands were used to minimize the signals from subcutaneous region. Post-processing: Residual water signal was removed prior to metabolite estimation using the HL-SVD filter of the JMRUI software. Frequency-drift corrections were performed using in-house Matlab programs. LCMRmodel software was used for analysis. Basis sets were derived from density matrix simulations, using published chemical shift and coupling constants8-9. Metabolites were estimated using creatine (Cr) from normal brain region at 8 mM10. Seven subjects with brain tumors were recruited for this study. Written informed consent was obtained from subjects prior to the scans.

RESULTS AND DISCUSSION: Figure 1 (a) displays J coupling effects on the spectral pattern of Cit. The simulations indicated that the Cit multiplet at TE = 78 ms (TE1, ~ 58 ms; TE2 = 20 ms) exhibits a narrow peak around ~2.6 ppm, which helps to reduce the contamination from NAAasp and Asp signals. Figure 1 (b) displays SI spectra from the phantom containing Gly (10 mM) and Cit (10 mM). The Cit spectral pattern (green) was in excellent agreement with the theoretical calculated spectrum at TE = 78 ms. Figure 2 shows the spectra and concentrations maps of Cit and choline (tCho) from a subject with oligodendroglioma. Two spectra were selected, one each from tumor and normal appearing brain regions in the T2-w-FLAIR image. The Cit was estimated at 2.6 mM and 0 mM in tumor and normal brain spectrum, respectively. When Cit was excluded from the basis set, residual signals were clearly discernible at ~2.6 ppm in the tumor spectrum, indicating that the signal at 2.6 ppm was primarily attributed to Cit. This action also changed the estimates of NAAasp and Asp. However in the normal brain spectrum such residual signals were not observed when Cit was excluded from the basis set. Figure 3 shows the Cit, tCho and N-acetylaspertate+N-acetylaspartylglutamate (NAA) concentration maps in three glioma patients along with T2-w-FLAIR images. In the present study we detected elevated Cit levels in five out of seven subjects, with Cit concentration in the range of 1 – 3 mM. In conclusion, our SI method can be used to estimate Cit levels in subjects with brain tumors at 3T.