In vivo spectroscopic imaging of citrate in gliomas at 3.0 T

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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 glycolysis[1,2]. Cit is undetectable in healthy brain, but several studies indicated elevated levels of Cit in some pediatric brain tumors[3,4]. More recently Choi *et al.* reported first *in vivo* detection of Cit in adult brain gliomas at 3T using MR single voxel spectroscopy[5]. 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[6]. The largest signal is observed at ~2.6 ppm, but its detection is challenging due to its close proximity to N-acetylaspartate (NAAasp) and aspartate (Asp) signals between 2.5 - 2.7 ppm. Here we report for the first time ^{1}H 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 *TE optimization*: Quantum-mechanical simulations were carried out to optimize the TE of the PRESS to improve Cit detectability over overlapping metabolite signals of NAAasp and Asp. The performance of the optimized TE was validated on a phantom containing Cit (10 mM) and glycine (Gly) (10 mM). *MR experimental design*: All experiments were carried out on a Philips 3T whole-body scanner with 8-channel reception coil. Axial and sagittal T_2w-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. PRESS 90˚ and 180˚ pulses had bandwidth of 4.2 kHz (9.8 ms) and 1.3 kHz (13.2 ms) respectively. Typically a 200 × 160 mm^2 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 × 10 mm^2. 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[6]. Frequency-drift corrections were performed using in-house Matlab programs. LCModel[7] software was used for analyzing spectra with basis sets created from density matrix simulations using published chemical shift and coupling constants[8,9]. Metabolites were estimated using creatine (Cr) from normal brain region at 8 mM[10]. 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 (TE$_1$, = 58 ms; TE$_2$ = 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 T_2w-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-acetylaspartate+N-acetylaspartylglutamate (tNAA) concentration maps in three glioma patients along with T_2W-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.

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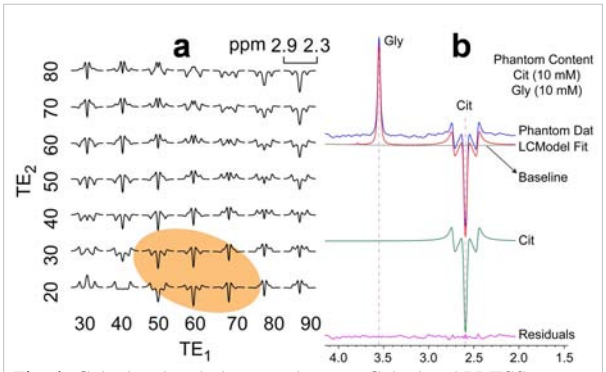

Fig. **1**: Calculated and phantom data. (**a**) Calculated PRESS spectra of Cit at 3T, are displayed vs. subecho times TE$_1$ and TE$_2$. The spectral range is 2.3 - 2.9 ppm. Spectra, calculated without T2 relaxation effects, were broadened to phantom linewidth of 5 Hz. (**b**) *In vitro* spectra at PRESS (TE$_1$, TE$_2$) = (58, 20) ms, obtained from a phantom with Cit (10 mM) and Gly (10 mM). Vertical dotted lined are drawn at 2.59 ppm.

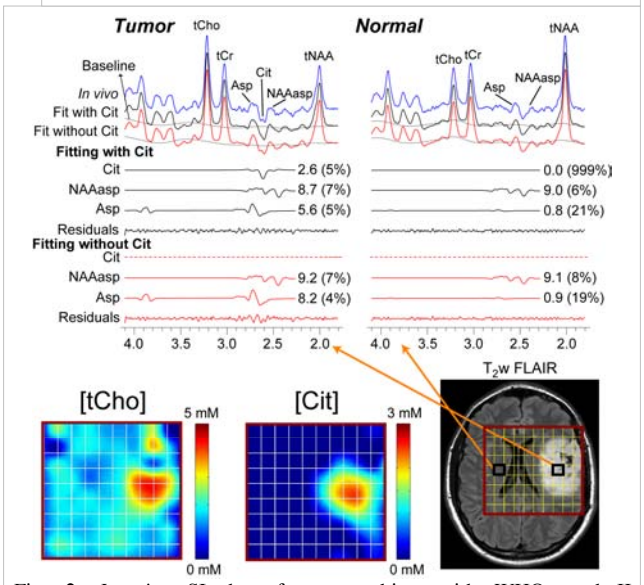

Fig. **2**: *In vivo* SI data from a subject with WHO grade-II oligodendroglioma. (**a**) Calculated PRESS spectra of Cit at 3T, are displayed vs. subecho times TE$_1$ and TE$_2$. The spectral range is 2.3 - 2.9 ppm. Spectra, calculated without T2 relaxation effects, were broadened to phantom linewidth of 5 Hz. (**b**) *In vitro* spectra at PRESS (TE$_1$, TE$_2$) = (58, 20) ms, obtained from a phantom with Cit (10 mM) and Gly (10 mM). Vertical dotted lined are drawn at 2.59 ppm.

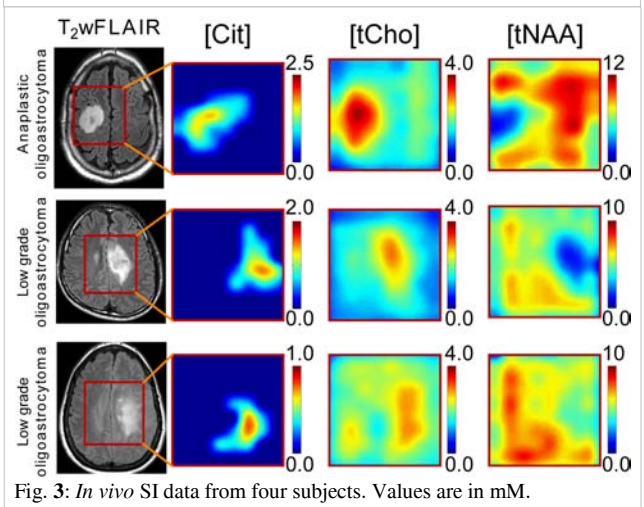

Fig. **3**: *In vivo* SI data from four subjects. Values are in mM.