Longitudinal MRS imaging of 2-hydroxyglutarate in brain tumors in vivo

Sandeep Ganji[1], Zhongxu An[1], Dianne Mendelsohn[1], Marco Pinho[1], Edward Pan[1], Kevin Choe[1], Elizabeth Maher[1], and Changho Choi[1]
[1]*University of Texas Southwestern Medical Center, Dallas, TX, United States*

TARGET AUDIENCE Neuro-oncologists/surgeons and MR spectroscopists.

PURPOSE Isocitrate dehyrogenase mutations (IDH1 and IDH2) are most frequently mutated metabolic enzyme in gliomas and produces oncometabolite 2-hydroxyglutarate (2HG)[1,2,3]. Previous studies have reported reliable and reproducible single-voxel spectroscopy and spectroscopic imaging (SI) measurement of 2HG levels in gliomas[4,5,6,7]. Monitoring 2HG levels over time may provide clinically important information about diagnosis, prognosis, and response to therapy in IDH-mutated brain tumors[8]. We present first longitudinal assessment of 2HG levels in six clinically stable brain tumors, using SI data acquired over a period of 8 - 18 months.

METHODS *MR experimental design*: The MR scan protocol included T_2w-FLAIR imaging, and spectroscopic imaging using a previously reported PRESS TE = 97 ms (TE_1 = 32ms and TE_2 = 65 ms)[4]. Data were acquired on a Philips 3T whole-body scanner with 8-channel reception coil. SI data were acquired with a TR of 1.2 sec, a spectral width of 2000 Hz, 1024 complex points per FID with two signal averages. Water signal was suppressed using a four-pulse scheme. The PRESS RF carrier was set to 2.6 ppm. The PRESS 90˚ and 180˚ pulses had bandwidths of 4.2 kHz (9.8 ms) and 1.3 kHz (13.2 ms), respectively. The VOI was positioned to cover most of the tumor region and some normal appearing brain region for comparison. Typically a 200 × 160 mm^2 field of view (FOV) in the phase encoding directions was used for acquisition with an in-plane resolution of 10 × 10 mm^2, and slice thickness of 15 mm along head-foot direction. Regional saturation bands were used to minimize extraneous signals from subcutaneous regions. The scan time for each SI data acquisition was approximately 10 minutes. *Patient Population*: Six subjects with suspected brain tumors (no biopsy or surgery were performed during the study) and measurable 2HG signal were recruited for this study. Written informed consent was obtained from subjects prior to the scans. The number of datasets acquired per subject varied from 3 to 5. In total 22 datasets were collected for the study. Routine clinical follow up of the subjects showed no clinical and/or radiographic evidence of tumor growth or progression. *Post-processing*: The SI data were reconstructed with 2D Fourier transformation, after zero filling to obtain interpolated spatial resolution of 5 × 5 mm^2. Residual water signal in the metabolite data was removed using the HL-SVD filter of the JMRUI[9]. Frequency-drift and eddy current artifact corrections were performed using in-house Matlab programs. LCModel[10] software was used for spectral fitting and estimation of metabolite concentrations. Basis-sets for LCModel were created from density matric calculations[4] using published chemical shift and coupling constants[11,12]. The absolute quantification of the metabolites was performed using Cr signal in white matter dominant region at 6.4 mM[13]. Correction of chemical shift displacement effects was performed prior to creation of metabolite concentration maps. *Statistics:* Pixels within tumor region were selected to calculate mean and standard deviation of metabolite measures. Coefficient of variance (CoV) were computed for each metabolite.

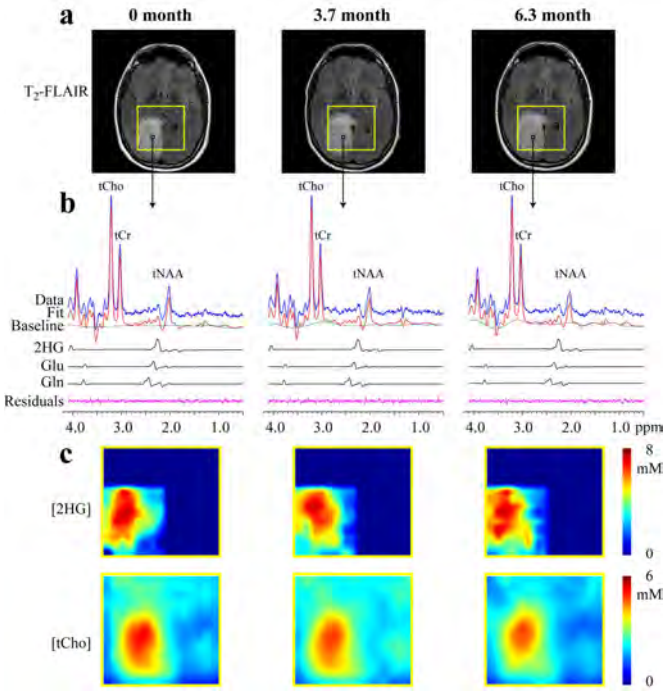

Fig. **1**: *In vivo* spectroscopic and T_2-FLAIR imaging data from a subject suspected of low grade glioma (last three time points of subject 1 in Fig **2**). (**b**) Spectra (blue), LCModel fit (red) and baseline (grey) along with metabolites signals for a chosen location are presented. (**c**) The 2HG and tCho concentration maps (shown in mM).

RESULTS Figure **1**(**b**,**c**) shows spectra and metabolite concentration maps from three scans (last three time points of Sub 1 in Fig **2**), in a subject with brain tumor. Spectra from a voxel within the tumor region showed similar spectral pattern at three time points, over 0.5 - 4.2 ppm region. A large signal observed at 2.25 ppm which is primarily attributable to 2HG, was estimated at 5.8 (CRLB 4%), 5.3 (4%), and 5.4 mM (6%) across the three time points, respectively. The Glu estimates were 2.5, 2.2, and 2.1 mM, respectively. The concentration maps of 2HG and tCho showed similar regional distribution over tumor mass across the times points (Fig. **1c**). The mean 2HG estimates over the tumor region (mean ± SD) were 5.6 ± 1.5, 5.3 ± 1.2 and 5.5 ± 1.4 mM, respectively. The mean 2HG levels were very similar during the study period for all the six subjects (Fig. **2a**). The 2HG levels varied across the tumor mass in a single scan (SD between 0.3 - 2.0 mM), however the mean 2HG levels were stable over time. The coefficient of variance of 2HG was 1.1% over six subjects and 22 scans. The CoV of tCho, Glu and Gln were 3.5%, 11.1% and 10.3%, respectively. The 2HG levels across time points for the six subjects were 5.3 ± 0.8, 3.3 ± 0.5, 3.8 ± 0.7, 4.4 ± 0.6, 1.7 ± 0.4, and 1.7 ± 0.2 mM, respectively. The mean 2HG levels over the tumor region remained between 0.2 - 0.8 mM across the time points.

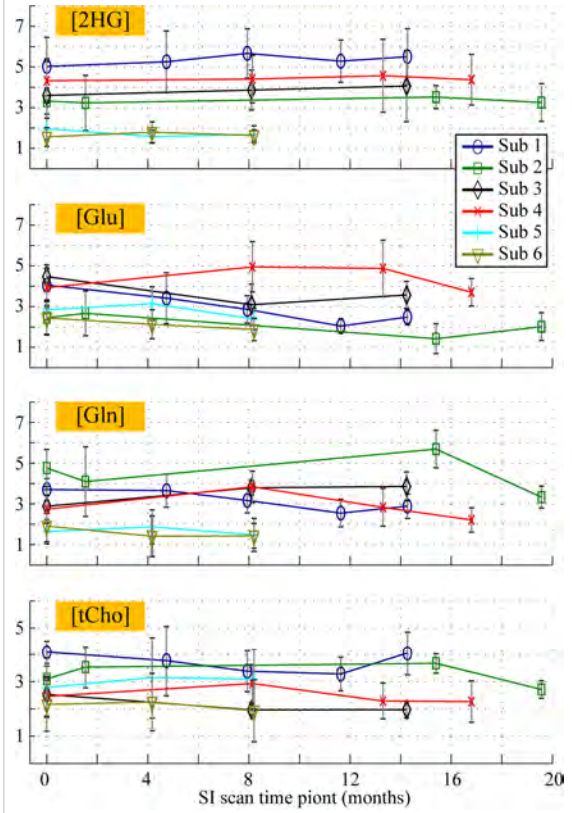

Fig. **2**: **Metabolite estimates in stable brain tumors over time**. The measurements were done in six brain tumors over a period of 8 - 18 months.

DISCUSSION AND CONCLUSION The present work reports the first longitudinal study of 2HG MR spectroscopic imaging in clinically stable brain tumors using optimized PRESS TE = 97 ms. The mean coefficient of variance of 2HG in the present study was 1% in 22 datasets, indicating high constancy of mean 2HG levels across the times points in clinically stable brain tumors. Longitudinal monitoring of 2HG in serial measurements in brain tumors may provide a novel noninvasive means of monitoring tumor progression and response to therapy.

REFERENCES **1**. Parsons DW *et al.* Science 321:1807-1812 (2008). **2**. Yan H *et al.* N Engl J Med. 360:765-773 (2009). **3**. Dang L *et al.* Nature. 462:739-744 (2009). **4**. Choi C *et al.* Nat Med 18:624-629 (2012). **5**. Pope WB *et al.* J Neurooncol 107:197-205 (2012). **6**. Andronesi OC *et al.* Sci Transl Med 4:116-114. **7**. Ganji S *et al.* Proceedings of the ISMRM 22nd Annual Meeting, Milan p:0006 (2014). **8**. Schiff D. *et al.* Neurol Clin Pract 3:326-333 (2013). **9**. Naressi A. *et al.* MAGMA 12:141–152 (2001). **10**. Provencher S.W. Magn Reson Med 30:672-679 (1993). **11**. Bal D. *et al.* A. Magn Res Chem 40:533-536 (2002). **12**. Govindaraju V. *et al.* NMR Biomedicine 13:129-153 (2000). **13**. Ganji S *et al.* NMR Biomed 27:1167-1175 (2014).

ACKNOWLEDGEMENTS This study was supported by NIH R01CA184584 and CPRIT RP130427.