In vivo spectroscopic imaging of 2-hydroxyglutarate in human brain tumors at 3.0 T

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INTRODUCTION Isocitrate dehyrogenase mutations (IDH1 and IDH2) give rise to a gain of function and are implicated in majority of low-grade gliomas [1-2]. The gain of function leads to production of 2-hydroxyglutarate (2HG) from α-ketoglutarate in the tricarboxylic acid cycle (TCA) cycle [3]. There is a great interest in *in vivo* measurement of 2HG as a diagnostic and prognostic biomarker reported in several *in vivo* studies [4-6]. 2HG has 5 coupled spins, giving multiplets at 4.02, 2.27 - 2.22 and 1.83 – 1.98 ppm. The largest signal is observed at 2.25 ppm, but this signal is extensively overlapped with glutamate (Glu) and glutamine (Gln) signals between 2.25 - 2.42 ppm [7-8]. Here we report for the first time ^{1}H spectroscopic imaging (SI) of elevated 2HG levels in brain gliomas. The PRESS echo time (TE) was numerically optimized to reduce the spectral overlap of Gln and Glu on 2HG. The SI method was validated in phantoms, normal healthy volunteers and applied for measurement of 2HG levels in patients with gliomas.

METHODS Numerical optimization of PRESS TE was carried out for improving the 2HG detectability over overlapping metabolite signals. From these simulations we obtained an echo time of 97 ms ($TE_1 = 32$ ms and $TE_2 = 65$ ms), where 2HG signal was well separated from Gln and Glu. The performance was validated on a phantom containing 2HG (8mM) and glycine (Gly) (10mM). *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 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 x 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. Volume of interest was selected to include FLAIR enhancing regions in tumor subjects. Regional saturation bands were used to minimize the signals from subcutaneous regions. Residual water signal was removed prior to metabolite estimation using the HL-SVD filter of the JMRUI [9]. Frequency-drift corrections were performed using in-house Matlab programs. LCModel software [10] was used for analyzing spectra with basis sets created using published chemical shift and coupling constants [7,8]. 2HG was estimated using creatine (Cr) from normal brain region at 8 mM. Written informed consent was obtained from subjects prior to the scans. 15 tumor patients were scanned, with multiple scans on several subjects over the course of treatment.

RESULTS AND DISCUSSION Fig. 1 displays SI spectra from the phantom containing Gly (10 mM) and 2HG (8 mM). The 2HG spectral pattern was consistent with the numerically simulated spectrum at TE = 97 ms shown in the inset (green). Figure 2 shows the SI grid overlaid on top of FLAIR images and spectra from an anaplastic astrocytoma patient. LCModel analysis of the spectra from normal brain region (like pixel 1) gave no measurable 2HG (a small signal at ~2.25 ppm is attributed to Gln and GABA). Spectra selected from the enhanced FLAIR regions showed a peak at 2.25 ppm which is attributed primarily to 2HG. The Cramer–Rao lower bounds (CRLB) of 2HG were as small as 3%. Figure 3 shows the metabolite maps of 2HG, choline (Cho), tNAA (N-acetylaspartate + N-acetylaspartylglutamate), Cr, Glu and Gln. Estimates with CRLB < 20% only were used for creating metabolite concentration maps. Regions with elevated 2HG levels correspond to FLAIR enhanced regions. In these regions, choline was high and tNAA was reduced. 2HG and Gln were well separated and estimated, as shown in the figure 2 and Gln concentration map of figure 3. Figure 4 shows the change in the 2HG levels over the course of treatment in a low grade oligodendroglioma patient. The patient underwent chemotherapy prior to the first scan and the interval between two post-chemotherapy scans was 4 months. 2HG levels were found to be decreased. Our SI method can be used to measure 2HG levels over the brain regions at 3T. We have shown that monitoring of the levels of 2HG over time will provide information on treatment efficacy.

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Fig 1: PRESS SI data from a phantom with Gly and 2HG. Inset shows simulated spectra at TE = 97 ms.

Fig 2: SI data from an anaplastic astrocytoma patient showing spectra (blue), LCModel fits (red) and residuals (brown) from selected pixels in tumor and normal brain regions.

Fig 3: 2HG, Cho, tNAA, Cr, Glu and Gln maps from a glioma patient Elevation of 2HG and Cho correspond to enhancing FLAIR regions. Gln was also elevated in the tumor region.

Fig 4: 2HG concentration maps at two time points post-chemotherapy in a low grade oligodendroglioma patient.