3D MR Spectroscopic Imaging of 2-Hydroxyglutarate in patients with mutant IDH1 glioma

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Target Audience: Neuro-radiologists/oncologists/surgeons; cancer researchers; developers of pulse sequences for MRS imaging.

Purpose. The hallmark metabolic alteration in mutant IDH gliomas is the production of R-2-hydroxyglutarate (R-2HG) [1], and high levels of this metabolite may play a central role in propagating downstream the effects of gene mutations towards malignant transformation of cells [2]. Hence, 2HG may be an ideal biomarker for both diagnosing IDH mutations in tumors as well as monitoring response to treatments targeting these mutations. 2HG can be measured in-vivo by magnetic resonance spectroscopy [3-6] and there is a large interest in developing methodology that can perform reliable in patients. Here we present results obtained with a new 3D MR spectroscopic imaging (MRSI) that edits 2HG with high efficiency.

Methods. A robust and efficient 3D MRSI sequence for 2HG imaging was newly developed by integrating three highly optimized modules: i) J-difference spectral editing MEGA-LASER [5], ii) spiral spectroscopic imaging, and iii) real-time motion and shim correction. J-difference spectral editing can disambiguate the detection of brain metabolites such as GABA, Glx, and 2HG by removing overlapping signals. However, difference methods are susceptible to subtraction errors caused by subject movement and scanner instability. By acquiring in each TR a double-echo EPI volume navigator we can perform real-time correction of the head motion, update dynamically the shims and scanner frequency, and reacquire the TRs that are corrupted [7]. 3D brain coverage was obtained with a weighted stack of spirals. The acquisition parameters of the 3D MRSI sequence were: TR=1.6s, TE=68ms, FOV=200x200x200 mm^3, VOI=100x80x50 mm^3, 20mm isotropic voxels, acquisition matrix 10x10x10 zero-filled to 16x16x16, NA=20, acquisition time TA=9:55 min:s. The timing of the MEGA-LASER excitation was optimized by simulations and phantom measurements for the maximum edited signal. In particular, low power adiabatic pulses GOIA-W(16,4) [8] of 3.5ms duration and 20kHz bandwidth were used to provide uniform and sharp localization with negligible (2%) chemical shift displacement error. Spectra were fitted with LCModel software [9] and metabolic maps were obtained from the fitted signal. All experiments were performed on a whole-body 3T MR scanner (Tim Trio with VB17 software, Siemens, Erlangen), using body coil for transmit and a 32-channel head coil for receive. Measurements were performed in 10 patients with mutant IDH1 gliomas who were consented with an approved IRB protocol.

Results. Detectable levels of 2HG were measured in all patients that did not have gross total resection of tumor (eight out of ten). 3D metabolic maps were obtained for 2HG and several important metabolites for assessing brain tumors, such as total choline (Cho), N-acetyl-aspartate (NAA), glutamate and glutamine (Glx), and lactate (Lac). All metabolites were measured simultaneously within a single acquisition, 2HG and Glx maps were obtained from the difference spectra, while the other metabolites were obtained from the off-resonance spectra. Representative maps for these metabolites are shown in Figure 1. Difference (right) and off-resonance (left) fitted spectra from tumor (up) and healthy (down) brain regions are shown in Figure 2. 2HG signal can be clearly identified only in the tumor difference spectrum. The quality of 2HG editing is reflected in the map for goodness of fit Cramer-Rao lower bounds (CRLB).

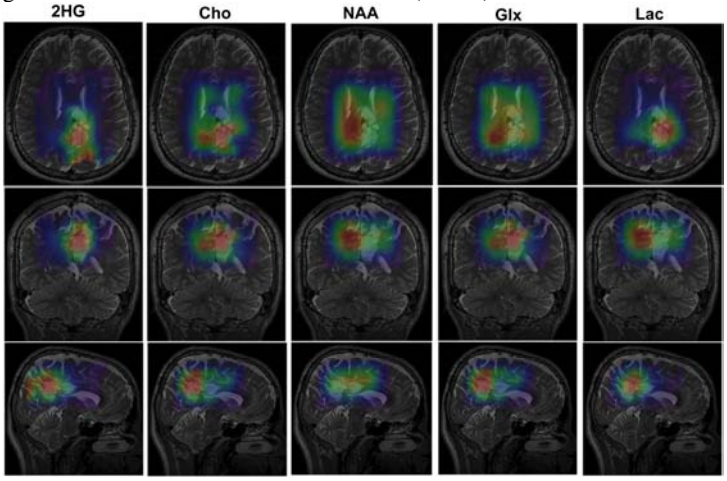

Figure 1. 3D metabolic maps obtained with the navigated MEGA-LASER spiral spectroscopic imaging. 3D 2HG map provides selectivity and specificity for the spatial extent of tumor in all directions.

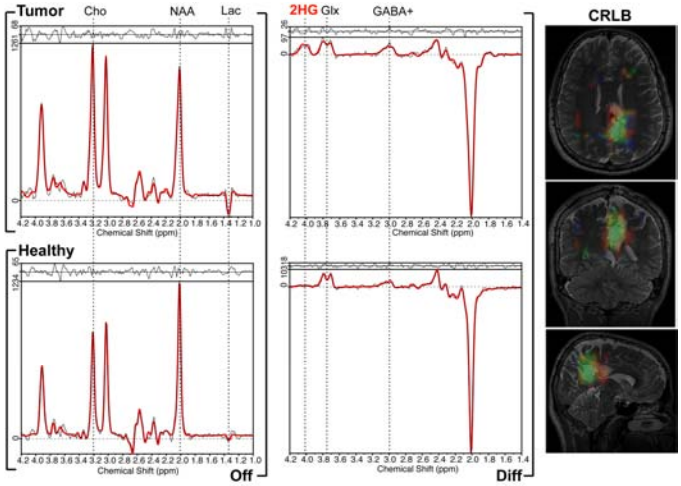

Figure 2. Tumor and healthy spectra, off-resonance (Off) and difference (Diff). 2HG signal is obviated in the difference spectrum of the tumor. CRLB map of 2HG fit shows voxels with CRLB<20%.

Discussions/Conclusion. 3D imaging of 2HG is clinically feasible in patients with IDH1 mutated gliomas and has not been shown previously. 3D mapping of 2HG and other metabolites is important to capture tumor heterogeneity and for longitudinal studies where changes in size and shape of tumors during treatment makes positioning of a single voxel or a single slice hard to match over time. 3D imaging can reduce variance in longitudinal MRS studies [10]. Further validation and development is underway for longitudinal quantification of 2HG levels during brain tumor treatment.

References: [1] Dang L et al, Nature 462:739-52 (2009); [2] Turcan S et al, Nature 483:479-83, (2012); [3] Pope WB et al, J Neurooncol. 107:197-205 (2012); [4] Choi C et al, Nature Med 18:624-29 (2012); [5] Andronesi OC et al, Science Transl Med 4:116ra4 (2012); [6] Choi C et al, Proc ISMRM 2013, #509; [7] Bogner W et al, Neuroimage, Epub; [8] Andronesi OC et al, JMR 203:283-93 (2010); [9] Provencher S, MRM 30:672-79 (1993); [10] Maudsley AA et al, NMR Biomed 23:251-56 (2010). **Acknowledgments:** 1K22CA178269-01 (NCI/NIH), and Harvard-MIT Bridge Project.