Assessment of Treatment Response in IDH-mutant Gliomas by Quantification of 2-Hydroxyglutarate with in -vivo 3D Magnetic Resonance Spectroscopy

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Introduction

Mutations in isocitrate dehydrogenase (IDH) in a distinct subset of human gliomas characterized by younger age and improved prognosis cause a marked elevation of the metabolite 2-hydroxyglutarate (2HG) [1,2].
This excess production of 2HG represents an ideal biomarker for these gliomas and can be measured with in-vivo magnetic resonance spectroscopy [3,4].
We previously demonstrated that 2HG can be detected reliably in IDH-mutant gliomas with 3D spectral-edited MR spectroscopic imaging (MRSI) [5].
Here, we aimed to show that 3D metabolomic mapping of 2HG can be utilized to evaluate treatment response in IDH-mutant gliomas.

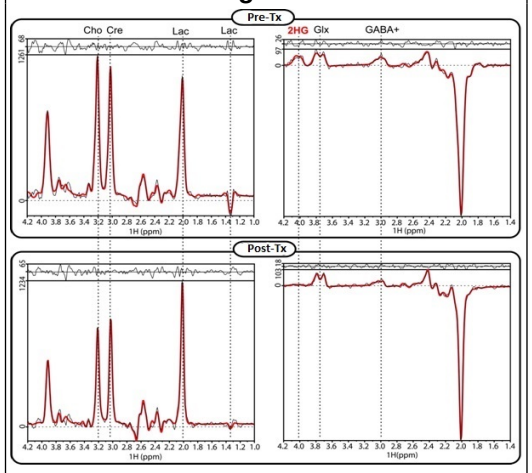
Methods

3D metabolomic maps were measured in 18 IDH-mutant glioma patients prior to adjuvant radiation or chemotherapy with a robust and efficient 3D MRSI sequence. All measurements were performed with a whole-body 3T MR scanner. Spectra were fitted with LCModel software. All patients with detectable levels of 2HG in the baseline scan were subjected to a post-treatment 3D MRSI to measure changes of 2HG-levels after adjuvant therapy.

Results

16 of 18 patients (88.9%) demonstrated detectable levels of 2HG on their baseline scan.

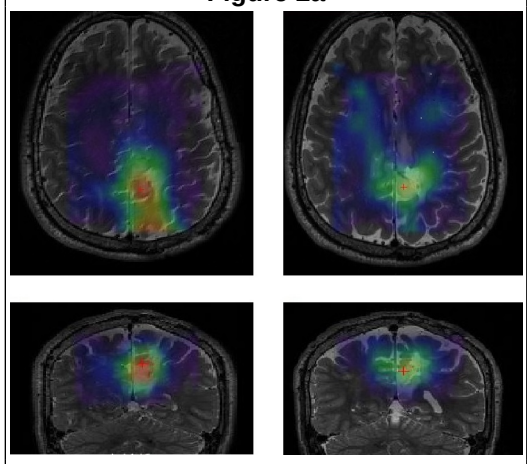
Figure 1



Conventional (left) and J-difference spectral edited (right) 3D MRSI spectra obtained pre- (top) and post-treatment (bottom): Significant reduction of 2HG.

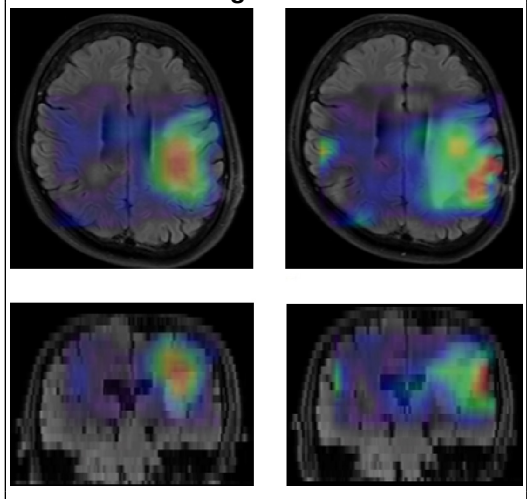
12 matched pre- and post- treatment 3D metabolomic maps indicated varying response to treatment: 5 patients demonstrated significant reduction of 2HG intensities after radiation therapy (Figure 2a), while the remaining patients demonstrated mixed response (partial reduction of 2HG) to adjuvant treatment (Figure 2b), or stable disease.

Figure 2a



Metabolomic maps of 2HG obtained by MR spectroscopic imaging pre- and post-treatment: Significant reduction of 2HG after radiation therapy.

Figure 2b



Metabolomic maps of 2HG obtained by MR spectroscopic imaging pre- and post-treatment: Mixed response (partial decrease of 2HG, partial increase of 2HG) after adjuvant chemoradiation.

Conclusion

Assessment of treatment response is feasible with in-vivo 3D MRSI of 2HG in IDH-mutant glioma patients.
Significant reduction of 2HG-levels in patients after completion of radiotherapy was found in a subgroup of patients in our cohort and is suggestive of positive response to treatment.
Further validation and longitudinal quantification of 2HG in IDH-mutant gliomas with 3D MRSI is needed to evaluate the ability of the presented approach to reliably determine treatment response. Nevertheless, this non-invasive method yields great potential for clinical applicability and could tremendously improve the management of IDH-mutant glioma patients.

References

[1] Parsons DW et al., Science 2008; 321:1807-12., [2] Yan H et al., N Engl J Med 2009;360(8):765-73., [3] Dang L et al., Nature 2009; 462:739-52., [4] Choi C et al., Nat Med 2012; 18:624-29., [5] Andronesi OC et al., STM 2012; 4:116ra114.