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A potential role of MR spectroscopic imaging in the era of pseudoprogression and pseudoresponse in glioblastoma patient management

Hyunsuk Shim[1,2], **Chad A. Holder**[1], and **Jeffrey J. Olson**[2,3]

[1]Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, Georgia 30322, USA

[2]Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia 30322, USA

[3]Neurosurgery, Emory University School of Medicine, Atlanta, Georgia 30322, USA

Glioblastoma (GBM) is the most common primary brain tumor and is almost uniformly fatal, despite aggressive surgical and adjuvant therapies. Since median survival time is short, it is critical to determine therapeutic activity at an early stage. One major impediment to the development of new therapies for GBM is a lack of reliable biomarkers indicating treatment-response or lack thereof. Tissue biopsy following treatment can assess residual tumor viability; however, it may entail significant risk of morbidity or even mortality. GBMs are heterogeneous, comprising a combination of viable tumor of various grades, necrotic tissue, edema, and infiltration into normal brain. Additionally, glial scar and radiation changes can be mistaken for tumor recurrence. The current standard for assessing tumor progression relies on changes in size of the enhancing and/or nonenhancing components of the tumor on standard MRI. While this was usually adequate when patients were treated with radiation alone, the addition of temozolomide (TMZ) has significantly increased the incidence of “pseudoprogression”, while the use of anti-angiogenic agents (e.g. bevacizumab or cediranib) has increased the incidence of “pseudoresponse”, complicating the interpretation of standard MR images [1]. The increasing use of newer, molecularly-targeted drugs may further decrease the reliability of conventional MRI.

Thus, non-invasive methods of assessing GBM response to therapy are clearly needed. ^{1}H-magnetic resonance spectroscopic imaging (MRSI) offers a non-invasive means to differentiate tumors from post-treatment changes and to distinguish benign from malignant lesions based on specific metabolite levels without introducing exogenous variables [2, 3]. MRSI quantitates amino acids and other metabolites in tumor and normal brain, allowing characterization of metabolic processes *in vivo*. Spectra from GBMs differ from normal brain, with decreased levels of N-acetyl aspartate (NAA) and often increased levels of choline (Cho) and lactate (Lac) [4]. Another important compound is myo-Inositol (mI), the precursor of a number of secondary messengers, including inositol phosphate lipid derivatives [5]. In addition to decreased mI in cancer cells, cerebrospinal fluid of non-cancer patients with depression show low mI levels, and treating them with mI has been shown to

1365B Clifton Road, NE, Atlanta, GA 30322, Tel: 404-778-3091, Fax: 404-778-4472.

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significantly improve depressive symptoms [6, 7]. This is highly relevant, given the high frequency of depression in brain tumor patients [8]. In this patient population, depression is consistently associated with cognitive impairment, reduced physical function, and poor quality-of-life. Our previous preclinical studies have shown that brain tumors have reduced mI and NAA compared to normal brain, confirming speculation that this may be associated with mood alterations and depression among brain tumor patients [9]. Correlations between elevated mI and NAA levels and improved mood may provide the basis for interventions in the future that improve the quality-of-life of GBM patients.

In March, 2011, Emory initiated a trial to treat recurrent GBM patients with an epigenetic-modifying agent combined with standard-of-care TMZ. Epigenetic alterations are now recognized as a frequent occurrence in early phases of tumorigenesis [10]. Epigenetic alterations differ significantly from genetic modifications in that they may be reversed by "epigenetic drugs" such as histone deacetylase inhibitors (HDACi). Suberoylanilide hydroxamic acid (SAHA; vorinostat) is an orally-active, potent inhibitor of HDAC activity that crosses the blood-brain-barrier. Response to vorinostat therapy is associated with tumor redifferentiation/cytostasis rather than tumor size reduction, thus limiting the use of traditional imaging methods. To assess if MRSI predicts the redifferentiation effect of vorinostat, we optimized a two-dimensional MRSI protocol on a 3T scanner and applied it in this patient group. Forty-three percent of patients treated with vorinostat showed a significant restoration of normal brain tissue-like metabolism in tumors after only 7 days of treatment of vorinostat alone. Before treatment, GBMs all have decreased NAA (suggesting neuronal destruction and/or displacement), Cr, and mI as well as elevated Lac (suggesting increased anaerobic glycolysis in hypoxic regions). As an example, after 7 days of vorinostat in a patient, NAA, mI and Cr increased around the rim of the tumor by 0.18 (or 18%), 0.25, and 0.32, respectively, suggesting early cellular redifferentiation, and Cho and Lac decreased by 0.14 and 0.52, respectively. The Spectroscopic Restoration Index (SRI), the summation of the fractional changes in these five metabolites, was 1.40. Of note, in most GBMs, viable cells are around the rim (margin) of the tumor, with mostly necrosis centrally. Upon completion of the treatment (9 weeks of vorinostat+TMZ), NAA, mI, and Cr further increased and Lac decreased, to support continuing vorinostat efficacy as a redifferentiation-inducing agent. Contrast-enhanced MRI and perfusion scans at 9 weeks showing decreased size of the mass were concordant with the MRSI data. Another patient treated with vorinostat showed a different MRSI pattern. After 7 days of vorinostat treatment, no changes anticipated from a metabolic responder were observed. Even after 9 weeks of TMZ +vorinostat, MRSI did not show the trend of restoration of normal brain metabolites. MRI showed 25% increase in enhancing tumor volume, with no change in perfusion on the relative cerebral blood volume (rCBV) map. The data suggest that the tumors with early reversion towards normal brain metabolism go on to show good clinical response to vorinostat+TMZ treatment, based on standard-of-care MRI. These cases were in good agreement between MRI and MRSI.

However, as we enrolled more patients, we noticed a discrepancy in the responses between MRI and MRSI in two cases. One patient was enrolled in our trial two weeks following cessation of bevacizumab treatment, the period when tumor 'rebound' has been observed [11]. While the day 7 quantitative MRSI had favored a metabolic responder, with an SRI

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value of 1.14, MRI showed evidence of progression. In this patient, we could not determine if this metabolic responder was a true clinical responder, especially when 'clinical responder' was defined by standard-of-care MRI. Another patient case was also challenging, as the patient enrolled in the trial during the pseudoprogression period. This subject was enrolled in the trial after conventional MRI showed evidence of progression, and underwent 6 weeks of therapy with TMZ+vorinostat and an early MRI showed significant increase in contrast-enhancing mass, prompting patient withdrawal from the study; however, the day 7 MRSI had actually favored a metabolic responder, with an SRI value of 1.25. This discrepancy prompted a biopsy of the expanding enhancing lesion that showed that the majority of this lesion actually represented necrosis, with only small amounts of interspersed hypocellular tumor that appeared better differentiated than at original diagnosis. This case illustrates the inadequacies of standard, contrast-enhanced MRIs and supports the use of more sophisticated imaging modalities (such as MRSI) as an adjunct. Overall, these preliminary studies suggest that changes in metabolite levels measured by MRSI may potentially serve as reliable, early predictors of response to HDACi-containing combination therapy in GBMs, but further study in a larger number of subjects is required to demonstrate that the metabolic responders are indeed true clinical responders, using overall survival as an endpoint.

While the utility of MRSI in the diagnosis and evaluation of therapy response of brain tumors has been documented, it has not gained widespread clinical use due to poor resolution, long scan times, and difficulty integrating with other types of brain scans. Standardization of acquisition and analysis techniques across sites and different vendors is also important. At our institution, we implemented a state-of-the-art MRSI technology that can rapidly generate metabolite maps of the entire brain coupled with introduction of an imaging registration/analysis program that combines MRSI data with other imaging studies in a clinically useful fashion. An advanced MRSI technique combining 3D echo-planar spectroscopic imaging (EPSI) with parallel acquisition (GRAPPA) [12, 13], using a 32-channel head-coil that allows acquisition of whole brain metabolite maps with high spatial resolution MRS images has been implemented in a 12 minute scan time. The current version acquires whole brain 3D MRSI (4.4 mm × 4.4 mm × 5.6 mm nominal voxel size, 0.108 cc or 108 μl) with a short TE (17.6ms) on a 3T MR scanner. The acquisition method collects internal water signal as a denominator in order to obtain absolute metabolite concentrations in an interleaved manner, without increasing total scan time. The MRSI data are analyzed using Metabolic Imaging Data Analysis System (MIDAS) software [14] and then integrated with the FDA-cleared image-coregistration platform Velocity-AI [15]. This allows the display, annotation, volume-rendering, registration, and fusion of multiple medical image modalities, and is used to facilitate incorporation of MRSI metabolite ratio maps, using both rigid and deformable methods. By integrating these platforms, MRSI data can be presented in a format that can be co-registered with standard MR images, and automatically imported into the neuronavigation systems for biopsy/surgery or for treatment-planning systems for radiation therapy. This allows MRSI to be used for image-guided neurosurgery or treatment, in addition to the traditional MR images. As opposed to post-contrast MRI, which depicts regions of blood-brain-barrier breakdown which may have variable underlying etiology, MRSI highlights the tumor cells based on their altered metabolism, and may provide greater

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accuracy for localizing metabolically active tumor extent and margins. In addition, identification of a metabolite signature that shows significant tumor cell infiltration into normal brain in regions that do not appear abnormal on standard MRI scans would be of great value to neurosurgeons and radiation oncologists in optimizing brain tumor treatment.

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References

1. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010; 28(11):1963–1972. [PubMed: 20231676]
2. Kugel H, Heindel W, Ernestus RI, Bunke J, Du Mesnil R, Friedmann G. Human brain tumors: spectral patterns detected with localized H-1 MR spectroscopy. Radiology. 1992; 183(3):701–709. [PubMed: 1584924]
3. Ott D, Hennig J, Ernst T. Human brain tumors: assessment with in vivo proton MR spectroscopy. Radiology. 1993; 186(3):745–752. [PubMed: 8430183]
4. Horska A, Barker PB. Imaging of brain tumors: MR spectroscopy and metabolic imaging. Neuroimaging clinics of North America. 2010; 20(3):293–310. [PubMed: 20708548]
5. Lehninger, AL.; Nelson, DL.; M, CM. Lehninger Principles of Biochemistry. W. H. Freeman and Company; New York: 2005.
6. Barkai AI, Dunner DL, Gross HA, Mayo P, Fieve RR. Reduced myo-inositol levels in cerebrospinal fluid from patients with affective disorder. Biol Psychiatry. 1978; 13(1):65–72. [PubMed: 623854]
7. Levine J, Rapaport A, Lev L, et al. Inositol treatment raises CSF inositol levels. Brain research. 1993; 627(1):168–170. [PubMed: 8293297]
8. Rooney AG, Carson A, Grant R. Depression in cerebral glioma patients: a systematic review of observational studies. Journal of the National Cancer Institute. 2011; 103(1):61–76. [PubMed: 21106962]
9. Wei L, Hong S, Yoon Y, et al. Early prediction of response to vorinostat in an orthotopic glioma rat model. NMR Biomed. 2012
10. Sigalotti L, Fratta E, Coral S, et al. Epigenetic drugs as pleiotropic agents in cancer treatment: biomolecular aspects and clinical applications. J Cell Physiol. 2007; 212(2):330–344. [PubMed: 17458893]
11. Zuniga RM, Torcuator R, Jain R, et al. Rebound tumour progression after the cessation of bevacizumab therapy in patients with recurrent high-grade glioma. Journal of neurooncology. 2010; 99(2):237–242.
12. Maudsley AA, Domenig C, Govind V, et al. Mapping of brain metabolite distributions by volumetric proton MR spectroscopic imaging (MRSI). Magn Reson Med. 2009; 61(3):548–559. [PubMed: 19111009]
13. Zhu X, Ebel A, Ji JX, Schuff N. Spectral phase-corrected GRAPPA reconstruction of three-dimensional echo-planar spectroscopic imaging (3D-EPSI). Magn Reson Med. 2007; 57(5):815–820. [PubMed: 17457872]
14. Maudsley AA, Darkazanli A, Alger JR, et al. Comprehensive processing, display and analysis for in vivo MR spectroscopic imaging. NMR Biomed. 2006; 19(4):492–503. [PubMed: 16763967]
15. Schreibmann E, Pantalone P, Waller A, Fox T. A measure to evaluate deformable registration fields in clinical settings. Journal of applied clinical medical physics / American College of Medical Physics. 2012; 13(5):3829. [PubMed: 22955647]