EDITORIAL

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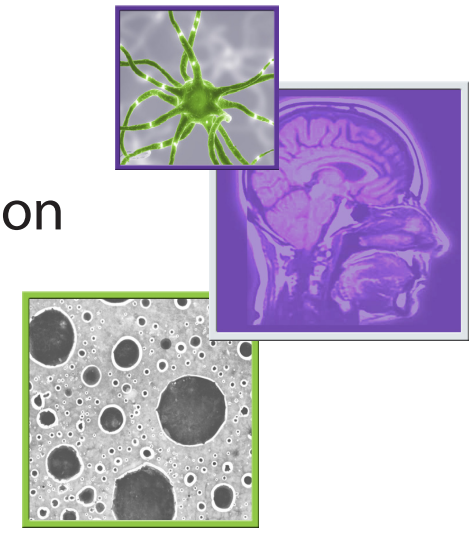
Magnetic resonance spectroscopic imaging in the era of pseudoprogression and pseudoresponse in glioblastoma patient management



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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 cause 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 is usually adequate when patients are treated with radiation alone, the addition of temozolomide (TMZ) has significantly increased the incidence of 'pseudoprogression', while the use of antiangiogenic agents (e.g., bevacizumab or cediranib) has increased the incidence of 'pseudoresponse', complicating the interpretation of standard magnetic resonance images [1]. The increasing use of newer, molecularly targeted drugs may further decrease the reliability of conventional MRI.

Thus, noninvasive methods of assessing GBM response to therapy are clearly needed. ^{1}H-magnetic resonance spectroscopic imaging (MRSI) offers a noninvasive 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

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increased levels of choline 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, the cerebrospinal fluid of noncancer patients with depression shows low mI levels, and treating these patients with mI has been shown to 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 with 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.

> "... 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."

In March 2011, Emory University (GA, USA) initiated a trial to treat recurrent GBM patients with an epigenetic-modifying agent combined with the 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 HDAC inhibitors. Suberoylanilide hydroxamic acid (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 whether MRSI predicts the redifferentiation effect of vorinostat, we optimized a 2D MRSI protocol on a 3 Tesla scanner and applied it in this patient group. Of patients treated with vorinostat 43% 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), creatine (Cr), and mI, as well as elevated Lac (suggesting increased anaerobic glycolysis in hypoxic regions). After 7 days of vorinostat in one patient, NAA, mI and Cr increased around the rim of the tumor by 18, 25 and 32%, respectively, suggesting early cellular redifferentiation, and choline and Lac decreased by 14 and 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 mainly necrosis centrally. Upon completion of the treatment (9 weeks of vorinostat plus TMZ), NAA, mI and Cr further increased and Lac decreased, which supports vorinostat's efficacy as a redifferentiation-inducing agent. Contrast-enhanced MRI and perfusion scans at 9 weeks showing a 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 plus vorinostat, MRSI did not show the trend of restoration of normal brain metabolites. MRI showed a 25% increase in enhancing tumor volume, with no change in perfusion on the relative cerebral blood volume map. The data suggest that the tumors with early reversion towards normal brain metabolism go on to show good clinical response to vorinostat plus TMZ treatment. These cases show 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 2 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 value of 1.14, MRI showed evidence of progression. In this patient, we could not determine whether this metabolic responder was a true clinical responder, especially when 'clinical responder' was defined by standard-of-care MRI. Another case was also challenging, as the patient was 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 plus vorinostat, and an early MRI showed a 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, which 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 MRI and supports the use of more sophisticated imaging modalities (e.g., 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 HDAC inhibitor-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 end point.

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 it with other types of brain scan. 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 and introduced 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 with parallel acquisition [12,13], using a 32-channel head coil that allows acquisition of whole-brain metabolite maps with high spatial resolution ^{1}H-magnetic resonance spectroscopic images has been implemented within a 12-min-scan time. The current version acquires whole-brain 3D MRSI (4.4 × 4.4 × 5.6 mm nominal voxel size, 0.108 cc or 108 µl) with a short echo time (17.6 ms) on a 3 Tesla magnetic resonance 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 the Metabolic Imaging Data Analysis System (MIDAS; IL, USA) software [14] and then integrated with the US FDA-cleared image coregistration platform Velocity-AI (Velocity, GA, USA) [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 coregistered with standard magnetic resonance 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 magnetic resonance images. As opposed to postcontrast 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 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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