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BOLD asynchrony: An imaging biomarker of tumor burden in IDH-mutated gliomas

Behroze Adi Vachha and Raymond Y. Huang

Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, New York, USA (B.A.V.); Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA (R.Y.H.)

Corresponding Author: Raymond Y. Huang, MD, PhD, Department of Radiology, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02215, USA (ryhuang@bwh.harvard.edu).

The most recent World Health Organization (WHO) classification currently categorizes diffuse gliomas by molecular rather than histopathological features and depends primarily on the isocitrate dehydrogenase (IDH) enzyme mutation status.[1] IDH-mutant gliomas typically present at lower histologic grades (II and III) and have a better prognosis compared to their IDH wild-type counterpart gliomas.[2] Most IDH-mutant gliomas eventually transform to higher grades, suggesting the need for aggressive early treatment.[2] Therefore, current clinical practice advocates for maximal extent of safe tumor resection even in asymptomatic, incidentally discovered low-grade gliomas with the extent of tumor resection found to be associated with improved overall survival and progression-free interval in these patients.[3] Additionally, following surgical resection, those patients with IDH-mutant gliomas classified as high-risk benefit from adjuvant therapy with radiation and chemotherapy.[2]

Structural magnetic resonance imaging (MRI) is currently the standard of care to guide surgical resection, biopsy, or radiation therapy in gliomas. Unlike IDH wild-type gliomas, IDH-mutant gliomas usually do not show contrast enhancement, and tumor margins are demarcated by T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences are used to guide treatment including surgery and radiation planning.[4] However, signal abnormalities on FLAIR sequences are not specific; edema and gliosis can appear as similar signal intensities as infiltrative tumor, and normal appearing brain may have tumor infiltration that is not radiographically visible on structural MRI suggesting that tumor volume defined by FLAIR sequences on structural MRI may not accurately estimate actual disease.[4] To address these limitations of structural MRI, other imaging techniques are currently being evaluated to improve specificity in depicting tumor boundaries. Some of these techniques that are readily available in clinical practice such as ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and perfusion-weighted imaging (PWI) also have inherent shortcomings: IDH-mutant gliomas have low metabolic activity on FDG-PET and are indistinguishable from the adjacent normal brain on PWI, thereby limiting their utility in determining the full extent of tumor infiltration.[5] The need to explore additional imaging biomarkers of tumor burden and invasion is salient because a growing body of evidence indicates that resection of tumor beyond the boundaries visible on structural MRI (supratotal resection) confers prolonged progression-free survival, reduced rate of malignant transformation and a longer overall survival.[6]

Several recent studies have demonstrated that both high- and low-grade gliomas result in angiogenesis-induced vascular remodeling that can alter the normal coupling relationship between transient neural activity and cerebral blood flow (neurovascular uncoupling) with attenuation of blood oxygen level-dependent (BOLD) signal activation.[7] Taking advantage of this known phenomenon of vascular dysregulation in and around tumors, the study by Petridis et al reported in this issue of *Neuro-Oncology* utilized a novel imaging method to quantify asynchrony in resting-state BOLD functional MRI (fMRI) dynamics between IDH-mutant gliomas and normal healthy brain, which they term BOLD asynchrony (BA).[8] Previous work by the same group demonstrated that BA correlated with tumor burden in IDH wild-type gliomas[9] and that the degree of vascular dysregulation in IDH wild-type gliomas is greater than that of IDH-mutant tumors.[10] In this study, stereotactically localized biopsies were collected from ten treatment-naïve patients with IDH-mutant gliomas who also underwent preoperative standard-of-care MRI including PWI and resting-state fMRI. Signal intensity for BA and standard-of-care MRI was compared to histologic features of total cellularity, tumor density, cellular proliferation, and neuronal density. Results of this study demonstrated that BA had significantly more predictive power for all the histological features compared to standard-of-care MRI T1-weighted and FLAIR sequences and more predictive power for some histological features compared to apparent diffusion coefficient (ADC) and T2-weighted sequences. Specifically, the degree of BA was directly related to tumor density, total cellularity, and cellular proliferation and inversely related to neuronal density. Histological analysis of localized biopsies suggested that the vascular dysregulation was secondary to local

infiltration by glial cells. Of interest, BA maps demarcated regions of vascular dysregulation and predicted that greater than 99% of the tumor is within 1.84 cm of the margins identified on standard-of-care MRI. By comparison, PWI parameters did not reveal abnormalities adjacent to the tumor and were not predictive of any histologic features.

A few limitations of this study and of the novel imaging method must be discussed. BA is based on a statistical summary of voxel data, and therefore it has lower spatial resolution and can be prone to noise. Quantitative maps derived from BA data thus require registration with anatomical imaging to reduce the likelihood of false-positive interpretation. Therefore, resting-state BOLD imaging must be used in conjunction with standard-of-care structural imaging. The small study sample size with a mix of oligodendrogliomas and astrocytomas, and inherent glioma heterogeneity, limits conclusions about the differences in BA in these subtypes of IDH-mutant gliomas and warrants further investigation in larger sample sizes. Finally, despite the use of localized biopsies in this study, the mechanism underlying resting-state fMRI-based BA remains complex with the authors themselves raising the concern that BA may underestimate tumor burden at the boundaries of infiltration, suggesting the need for additional advanced imaging techniques to complement BA findings.

Despite these limitations, recent studies by Petridis et al and others represent an important evolving effort that aims to identify sensitive surrogate imaging biomarkers to assess the degree of tumor infiltration that could improve neurosurgical resection and radiation treatment planning while preserving healthy brain in patients with gliomas.

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