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Guidance for Sponsors
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The Challenge of Quantitative Measurements of Primary Brain Tumors in Clinical Trials

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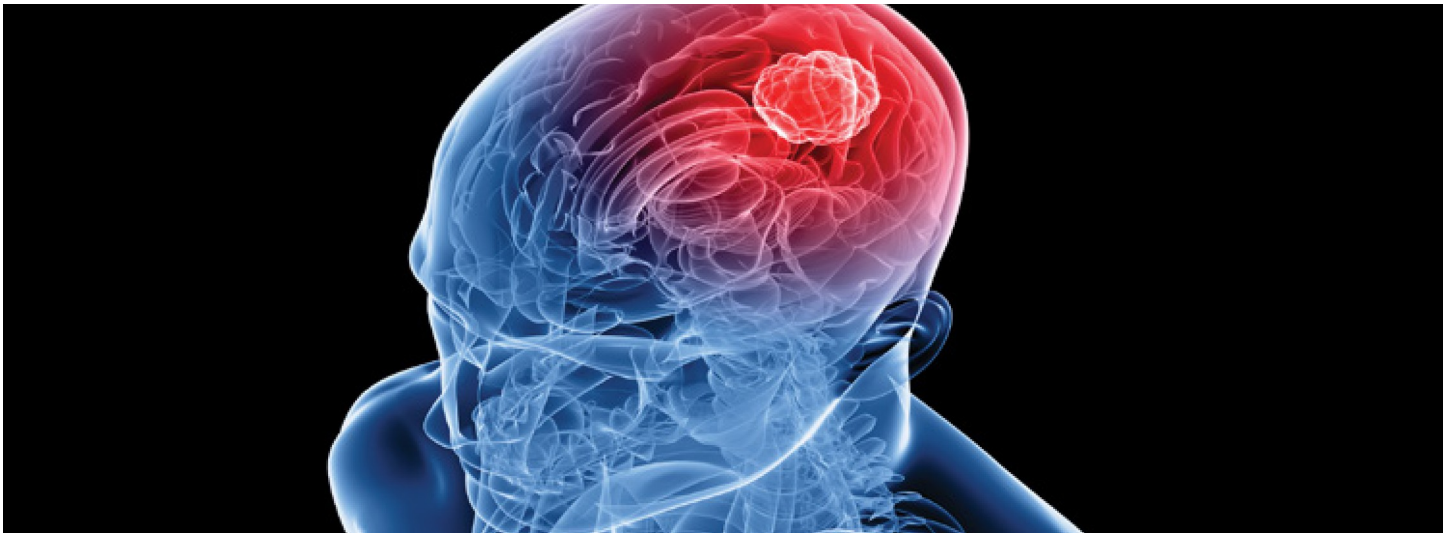

Glioblastoma remains the most common and most lethal malignant primary brain tumor, with a median survival of nine months. Measuring its response to treatment is uniquely difficult: gliomas infiltrate normal brain, contain necrosis by definition, and are mimicked by treatment effects that enhance and grow. RANO 2.0, published in 2023, unified response criteria for all gliomas, and a standardized brain tumor imaging protocol now underpins multicenter trials. The 2024 approval of vorasidenib, based on centrally reviewed radiographic progression, shows how much rests on getting imaging right. This issue explains the challenges and how sponsors can meet them.

The Clinical Challenge

An estimated 24,740 malignant tumors of the brain and spinal cord will be diagnosed in the United States in 2026, and 18,350 people will die of them.[1] Glioblastoma accounts for 51.5% of all malignant brain tumors. Its median survival after diagnosis is nine months, and five-year relative survival is 7.1%.[2] Since the 2021 WHO classification, glioblastoma has been defined as an IDH-wildtype tumor; IDH-mutant tumors are now classified separately as astrocytomas or oligodendrogliomas, with very different biology and prognosis.[3]

Many trials are evaluating treatments for gliomas, but reliable imaging endpoints remain elusive. Primary brain tumors infiltrate the surrounding brain extensively, so on imaging the transition from normal tissue to gross tumor is often imperceptible. Gliomas are irregular in shape, with infiltrative margins, and the planar measurements used elsewhere in oncology do not adequately capture the extent of initial, residual or recurrent disease.

Necrosis and Pseudoprogression

Necrosis complicates measurement further. It is a defining histologic feature of high-grade glioma, so any measured tumor volume inevitably includes nonviable tissue. Treatment adds its own necrosis. Radiation with concurrent temozolomide can produce new or increasing enhancement within the treatment field that mimics progression, particularly in the first twelve weeks after radiotherapy. Response criteria have long treated such early changes with caution because as many as half may represent pseudoprogression, although studies applying stricter definitions report lower rates.[4] Distinguishing active tumor from treatment effect remains the central problem in assessing glioma therapy.

Perfusion MRI

Dynamic susceptibility contrast (DSC) perfusion MRI has become a critical tool for that distinction. High-grade gliomas induce vascular proliferation, which raises relative cerebral blood volume; treatment necrosis enhances because of damaged,

leaky vessels but shows lower blood volume because normal vasculature is lost. In a meta-analysis of 19 studies, relative cerebral blood volume distinguished true progression from treatment-related change with a pooled area under the curve of 0.85.[5] Consensus recommendations published in 2020 standardized the DSC protocol for multicenter use.[6]

The Anti-Angiogenic Effect

Bevacizumab, an anti-VEGF antibody, illustrates how therapy can confound imaging. It received accelerated approval for progressive glioblastoma in 2009 on the basis of response rate, and full approval in 2017, although its confirmatory Phase 3 trial improved progression-free survival without improving overall survival.[7] By stabilizing vessel endothelium, it sharply reduces enhancement, edema and mass effect, in active tumor and treatment necrosis alike, a "pseudoresponse." It also normalizes the abnormal blood volume of tumor, so perfusion can no longer separate tumor from necrosis. Under anti-angiogenic therapy, subtle changes in T2 signal may be the only sign that nonenhancing tumor is progressing.

RANO 2.0

The Response Assessment in Neuro-Oncology (RANO) Working Group addressed these problems in 2023 with RANO 2.0, a single set of criteria for all adult gliomas.[8] In newly diagnosed disease, the post-radiotherapy MRI, rather than the postsurgical scan, serves as baseline. Within twelve weeks of radiotherapy, progression must be confirmed by a repeat MRI or by histopathology, and confirmation is highly recommended for any treatment likely to cause pseudoprogression. Nonenhancing disease is no longer evaluated in IDH-wildtype glioblastoma, except with anti-angiogenic agents, whereas trials in IDH-mutant tumors may assess both enhancing and nonenhancing components. Two-dimensional measurement remains the primary method, but volumetric measurement is an accepted option.[8]

The Case for Volumetry

Accurate assessment requires software that measures, separately, the volume of the nonenhancing component on T2-weighted and FLAIR images and the enhancing component on post-contrast T1-weighted images. The ideal tool would combine those volumes with the perfusion characteristics of each component, giving separate estimates of active tumor and treatment necrosis. Because high-grade gliomas almost always contain both, determining which process dominates is essential to patient management and to understanding response.

The standardized Brain Tumor Imaging Protocol, developed with FDA, NCI and academic experts, specifies matched 3D T1-weighted acquisitions before and after contrast that make such volumetry reliable across sites.[9] The need is most acute in slow-growing tumors. In the Phase 3 INDIGO trial, vorasidenib extended median progression-free survival in grade 2 IDH-mutant glioma from 11.1 to 27.7 months (hazard ratio 0.39), with progression determined by blinded independent central review under modified RANO criteria for low-grade glioma. FDA approved it in August 2024.[10]

Guidance for Sponsors

Imaging a glioma trial

- **Adopt the standard protocol.** Require the consensus Brain Tumor Imaging Protocol at every site.[9]
- **Apply RANO 2.0.** Use the post-radiotherapy baseline and confirm early progression.[8]
- **Include perfusion.** Add standardized DSC perfusion to help separate tumor from treatment effect.[6]
- **Measure volume.** Capture enhancing and nonenhancing volumes, especially in IDH-mutant disease.[8,10]
- **Read centrally.** Use blinded independent central review with neuroradiology adjudication.[11]

Summary

The growth characteristics of primary brain tumors make them among the hardest in oncology to measure. Unified RANO 2.0 criteria, a standardized imaging protocol, perfusion MRI and volumetric analysis now give sponsors the tools to define valid imaging endpoints. With the first new targeted glioma therapy approved in decades, rigorous and expert imaging assessment has never mattered more.

About the Author

Dr. James Dix, Medical Director of Neurology and Neurological Imaging at Intrinsic Imaging, wrote the original edition of this issue. A graduate of Georgia State University, he earned his medical degree at Emory University, completed his radiology residency at the University of Washington in Seattle and a two-year neuroradiology fellowship at the University of Virginia. He has authored multiple peer-reviewed articles in neuroradiology and neurosurgery, developed and published innovative techniques for percutaneous cement fixation of sacral and pelvic fractures, and lectures nationally on advanced imaging for radiologists and neurosurgeons. He is board-certified in radiology and holds a Certificate of Added Qualification in neuroradiology.

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About Intrinsic Imaging, LLC

Intrinsic Imaging is an ISO certified medical imaging CRO and imaging core lab providing comprehensive services in support of Phase I-IV clinical trials and Class I, II, III medical device trials. Intrinsic Imaging is also a world leader in conducting Artificial Intelligence studies. With its team of more than 650 board-certified and fellowship-trained physicians, Intrinsic Imaging's team has sub-specialization in all therapeutic areas, including Cardiovascular, Central Nervous System,Gastroenterology, Musculoskeletal, Oncology and Ophthalmology. Certified by the British Standards Institution (BSI), Intrinsic Imaging is the only company in the world to hold five ISO certifications specifically for providing imaging core lab services on clinical trials. For more information, please visit www.IntrinsicImaging.com.

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