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GRAY ZONE EXPERT OPINIONS

Navigating Treacherous Waters

This patient's[1] imaging demonstrates significant nongadolinium enhancing tumor volume. Given her young age and performance status, there is temptation and rationale for treatment intensification to biologically relevant nonenhancing tumor in hopes impacting her disease course. Recent prospective radiation data and multi-institutional surgical data support escalating local therapy to nonenhancing glioblastoma.[2,3] Still, given the lack of larger trials such as BN001 demonstrating benefit to radiation dose-escalation for glioblastoma to date, I would treat with standard dosing while incorporating available imaging.

I would define the gross tumor volume (GTV) using both the positron emission tomography (PET) avidity and contrast enhancement, with a 1 cm anatomically constrained clinical target volume and a planning target volume receiving 60 Gy in 30 fractions. For a volume receiving 51 Gy in 30 fractions, I would anatomically expand beyond the GTV by 1.5 cm and manually include any T2 hyperintensity in the clinical target volume, with a planning target volume expansion. Although including T2 hyperintensity is not always mandatory for glioblastoma, in cases with clear nonenhancing tumor it is advisable.

Consider if the PET imaging was not available in this case. All suspicious T2 hyperintensity would be included in the high-dose GTV for this predominantly nonenhancing tumor. Advanced imaging allowed for targeted reduction of the high-dose-volume, potentially reducing risk of adverse events including necrosis. Although advanced imaging may someday guide dose intensification for glioblastoma in clinical practice if trials demonstrate benefit, this case demonstrates the potential for improved tumor delineation to facilitate reduction of margins and potentially safer treatment options.

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T1 Gadolinium-Enhanced Magnetic Resonance Imaging of Glioblastoma: What You See Is Not What You Get

This case[1] demonstrates a somewhat common scenario of high-grade glioma with large areas of T2-Fluid-Attenuated Inversion Recovery (FLAIR) hyperintensity but little T1-weighted gadolinium enhancement. FLAIR changes are nonspecific and may indicate nonenhancing malignancy, vasogenic edema, or other insults (eg, ischemia, demyelination, prior therapies, etc.). Treatment margins vary considerably. NRG Oncology glioblastoma protocols include FLAIR-positive regions plus a 2 cm margin, delivering 46 Gy in 23 fractions, followed by a boost to 60 Gy in 30 fractions based on T1-weighted gadolinium enhancement alone. Alternatively, 2023 European Society for Radiotherapy and Oncology and European Association of Neuro-Oncology guidelines specify that FLAIR inclusion is at the physician's discretion, with a recommended dose of 60 Gy in 30 fractions and variable or no margin. These guidelines also recommend amino acid positron emission tomography (PET) to assist in defining the areas of malignant FLAIR.

As another option to define high-risk subclinical glioma, we demonstrated that spectroscopic magnetic resonance imaging (sMRI) generates metabolite maps throughout the brain with PET-like resolution, without exogenous contrast, in a 15-minute 3T MRI scan. A 3-site pilot sMRI-guided

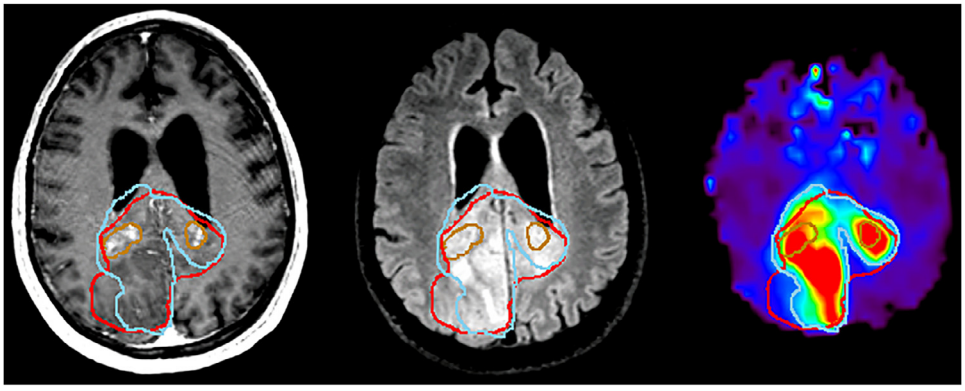

Fig. 1. Contrast enhanced T1-weighted MRI (left), FLAIR MRI (middle), and sMRI-derived Choline/N-acetylaspartate >2× map (right) of the brain used for radiation therapy planning after biopsy demonstrating glioblastoma. Delineated components include contrast enhancing lesions (brown), FLAIR signal abnormality (red), and sMRI-active region (cyan). *Abbreviations:* MRI = magnetic resonance imaging; sMRI = spectroscopic magnetic resonance imaging. Clinical target volume based on contrast enhanced T1-weighted MRI alone would not include the posterior areas of FLAIR hyperintensity that are positive for malignancy on sMRI.

dose-escalation trial for glioblastoma yielded promising results.[2] Figure 1 demonstrates sMRI in another patient with glioblastoma with limited contrast enhancement and extensive malignant FLAIR. As such, we routinely incorporate sMRI into upfront and recurrent glioblastoma workflows to define nonenhancing malignancy.

For the "Gray Zone" case patient, we would also request DNA sequencing and/or methylation assay to confirm the molecular features of glioblastoma and rule out hypoenhancing glioma variants, which are more common in pediatric and young adult populations and may have more favorable prognoses or targeted therapy options. For confirmed glioblastoma, we would deliver 60 Gy in 30 fractions to FLAIR hyperintensity plus a 1.5 cm clinical target volume margin. This FLAIR contour is similar to the PET contour, and our daily MRI-guided radiation therapy data demonstrate common 1 to 1.5 cm T2-weighted fluctuations during therapy.[3] We would consider 59.4 Gy in 33 fractions, or dose or field de-escalation, if molecular testing identifies a more favorable prognosis. Future trials could explore dose escalation to high-risk areas based on amino acid PET, sMRI, or other techniques. Clinical target volume reduction may also be possible with weekly adaptive radiation therapy that accounts for interfractional changes over the 6-week radiation therapy course.

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Defining the Biologically Active Tumor for Radiation Therapy

In the article entitled "Tip of the iceberg or the whole titanic: discrepant representation of glioblastoma on different imaging modalities," a case of a rapidly evolving glioblastoma in a 36-year-old woman with only a 1-week history of headache is presented.[1] Because of a syncopal episode, short interval serial magnetic resonance imaging shows relatively rapid progression of enhancing disease and the addition of ^{18}F-flucicovine positron emission tomography (PET) reveals discordant findings between the PET and magnetic resonance imaging. There is emerging compelling data that amino acid PET, including ^{8}F-flucicovine, can demonstrate areas of biologically active tumor before and after treatment and thereby can help define the more aggressive regions of glioma that may not be evident on magnetic resonance imaging.[2-4] The European Society for Therapeutic Radiotherapy and Oncology-European Association of Neuro-Oncology have published a guideline around the use of metabolic imaging in target volume definition for glioblastoma, specifically the use of amino acid PET in helping define the