Posttreatment Evaluation of Brain Gliomas

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KEYWORDS

• High-grade glioma • Glioblastoma • Treatment effects • Radiation necrosis • Pseudoprogression

KEY POINTS

- Clinical information is key to the correct interpretation of changes in imaging findings in treated gliomas.
- Subacute ischemia, blood–brain barrier breakdown related to recent surgery, pseudoprogression, and delayed radiation necrosis can cause increased or new foci of enhancement that do not reflect true progression of disease.
- Both antiangiogenic therapy and increases in steroid dosage can decrease tumor enhancement without affecting the underlying disease burden.
- Perfusion, spectroscopy, and PET can add specificity in differentiating treatment effects from true disease progression.

INTRODUCTION

Gliomas are the most common primary intracranial malignant neoplasm in adults. Among these, glioblastoma exhibits the greatest incidence, and simultaneously carries the highest grade and a dismal prognosis.[1,2] Lower grade glial neoplasms can range from nonaggressive lesions, amenable to curative treatment such as ganglioglioma, to infiltrative neoplasms with a high rate of transformation to higher grade disease. The World Health Organization classification segregates glial neoplasms into different grades based on resectability and proliferative potential.[3] The primary radiologic challenges are found in imaging gliomas of grade II or higher; the most commonly encountered such tumors include diffuse astrocytomas, oligodendrogliomas, anaplastic astrocytomas, and glioblastomas. These challenges are exacerbated in the posttreatment setting, particularly when imaging high-grade gliomas (World Health Organization grades III and IV lesions).

Complete surgical resection of diffuse gliomas is often compromised by the infiltrative nature of these tumors and the presence of tumor cells that lie beyond the tumor margin delineated by conventional imaging.[4–6] The current treatment paradigm for high-grade glial neoplasms begins with maximal safe resection of the enhancing portion of the tumor. If the entirety of the enhancing component can be resected safely, this is termed a gross total resection. This is followed by adjuvant therapy, the composition of which depends on the tumor's histology and cytogenetics. For glioblastoma, the current treatment paradigm status after primary resection is treatment with involved field radiation therapy and temozolomide, with recent possible consideration for the additional implementation of an alternating electric fields/tumor treating fields device.[7] Patients with primary treatment failure or recurrence may receive a variety of therapies; perhaps the most pertinent of these to the practicing radiologist is anti-vascular endothelial growth factor (VEGF) therapy, commonly undertaken with bevacizumab (an anti–VEGF-A antibody with the trade name Avastin). In this work, we explore a variety of current imaging approaches that attempt to

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distinguish posttreatment areas of true tumor progression from their common mimics.

TUMOR BIOLOGY

The typical high-grade glioma demonstrates 3 radiologic "zones." The first zone is defined by the enhancing core of the tumor, in which neoangiogenesis can result in a variety of aberrant vessel subtypes, ultimately leading to breakdown of the blood–brain barrier and leakage of radiologic contrast agent.[8,9] This *zone of neovascular proliferation* is important because it is both a cardinal feature of high-grade glioma as well as a potential target for antiangiogenic therapy, discussed in greater detail elsewhere in this article. The second zone is the perilesional area of T2/fluid attenuation inversion recovery (FLAIR) signal abnormality surrounding the core of the lesion, which comprises a mix of nonenhancing infiltrative tumor and vasogenic edema, sometimes referred to as *infiltrative edema*.[10,11] The third zone is the surrounding, normal-appearing brain parenchyma that harbors microscopic tumor at levels that are not currently detectable on conventional, routine 3T anatomic MR pulse sequences.[4,6] Although promising research is being undertaken currently to better define the extent of nonenhancing tumor burden using advanced imaging techniques such as quantitative magnetization transfer,[12] the full extent of the tumor is currently defined poorly in clinical practice. This is in part owing to the microscopic extensions of perilesional tumor that provide a mechanism for the apparent "skip lesions" identified when new sites of disease appear distant to previously perceived margins of the tumor, and help to explain the mechanism behind cases presenting with multifocal disease. Ultimately, it is the diffuse infiltrative nature of these lesions coupled with their relative resistance to chemoradiation that supports the observation that diffuse gliomas are largely, presently incurable.

In this context, tumor genetics is becoming increasingly relevant to the treatment of neoplasms. The recently released 2016 revision to the 4th edition of the World Health Organization (WHO) criteria for tumors of the Central Nervous System reflects an increasing emphasis on tumor genetics as they pertain to tumor behavior and therapeutic response.[13] A detailed discussion of tumor genetics is beyond the scope of this article, but the radiologist should be made aware of a few of the more relevant genetic markers for adult gliomas. The new WHO criteria place an emphasis on mutations of isocitrate dehygrogenase (IDH) and the codeletion of 1p and 19q loci as important determinants of tumor behavior.[14] IDH mutation, most commonly IDH-1, is positively correlated with survival versus the wild type gene product.[15–17] 1p 19q codeletion is also a mutant variant which demonstrates an improved survival; in addition, mutation of IDH-1 and codeletion of 1p 19q is now recognized as the genetic signature of an oligodendroglioma.[13,18] The gene, O6 methylguanine—DNA methyltransferase (MGMT), encodes an enzyme involved in DNA repair and has important therapeutic implications that can potentially impact radiological interpretation. Specifically, when the promoter of this gene is hypermethylated, its activity is downregulated and gliomas and other tumors are more susceptible to DNA damage from alkylating agents such as temozolomide.[2,14] Familiarity with these genetic marker subtypes and their effect on the behavior of high-grade gliomas is important for proper interpretation of imaging studies.

IMAGING TIME FRAME

Imaging is usually performed within the first 24 to 48 hours after maximal safe resection but should be undertaken within the first 72 hours to establish a new baseline while minimizing the confounding effects of postoperative changes.[19] The authors' institution currently performs follow-up imaging 4 weeks after the completion of chemoradiation to allow for the reduction of acute radiation- and chemotherapy-related changes before evaluation for a possible therapeutic response. However, it has been advocated that subsequent imaging may be delayed up to 12 weeks in nonenhancing tumors (eg, low-grade gliomas) to allow for complete resolution of postoperative edema and improved assessment of the true extend of tumor resection.[20]

CHALLENGES WITH IMAGING

In the untreated patient, the enhancing component of a tumor can represent a surrogate of high-grade disease with microvascular proliferation. However, once the patient has undergone treatment, a variety of therapeutic interventions can cloud this picture, causing increases or decreases in the amount of apparent contrast enhancement without a significant effect on the actual burden of high-grade disease. Because the amount of enhancing disease is a major criterion for therapeutic response in the currently implemented oncologic imaging criteria, the Response Assessment in Neuro-Oncology (RANO) criteria,[21] it is important to consider that changes in enhancement may not necessarily reflect changes in tumor burden.