Posttreatment Evaluation of Central Nervous System Gliomas

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KEYWORDS

• Glioma • Glioblastoma • MacDonald criteria • Response assessment • Radiation necrosis
• Pseudoresponse • MR imaging • Imaging biomarkers

KEY POINTS

- Use of the MacDonald criteria has been the most widely used method to assess therapeutic response in high-grade gliomas and involves examining changes in contrast-enhancing area, typically on conventional contrast-enhanced magnetic resonance (MR) imaging.
- Several limitations of the MacDonald criteria have been identified since their introduction in 1990. The most critical limitation rests on its reliance on contrast enhancement as a criterion of therapeutic response. Although contrast enhancement is a sensitive marker of blood-brain barrier disruption, it is not a specific finding of active tumor, and can be the result of many other processes including treatment-related effect, ischemia, seizure, inflammation, and postoperative changes.
- With the recent recognition of the entities of pseudoprogression and pseudoresponse associated with chemoradiation with temozolomide and antiangiogenic agents, respectively, the neuro-oncology community has been forced to reevaluate traditional imaging criteria of treatment response.
- The latest Response Assessment in Neuro-Oncology Working Group recommendations to address limitations in the MacDonald criteria are reviewed. In addition, the most recent advances in quantitative biomarker development using advanced imaging modalities are highlighted. However, until these techniques are thoroughly validated, conventional contrast-enhanced MR imaging follow-up should remain the standard of care.

INTRODUCTION

Gliomas represent the most common adult primary brain malignancy with an annual incidence of about 4 to 5 per 100,000.[1] The prognosis for glioblastoma in particular remains dismal. Postoperative radiation therapy has been an integral part of the treatment of high-grade gliomas (HGGs) since the 1970s.[2] Over the next 2 decades, innovations in computed tomography (CT) and magnetic resonance (MR) imaging improved both brain tumor characterization and radiotherapy techniques.[3] However, further attempts using

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alternative methods of radiotherapy failed to improve outcomes.[4] In 2005, Stupp and colleagues[5] showed improved survival with the addition of concurrent and adjuvant temozolomide (TMZ) to radiotherapy and this regimen, combined with maximal surgical resection, has since become the current standard of care for newly diagnosed glioblastoma. In 2009, the antiangiogenic agent bevacizumab received US Food and Drug Administration approval for the treatment of recurrent/progressive glioblastoma. Therapeutic assessment of high-grade gliomas (HGGs) relies on patient survival or, in cases of recurrent tumor, often the radiographic response rate or progression-free survival (PFS).[6,7] The adoption of chemoradiation with TMZ and antiangiogenic agents into the therapeutic armamentarium has resulted in a reevaluation of conventional contrast-enhanced MR imaging and response criteria.

The most widely used method to assess therapeutic response in HGGs has been to examine changes in contrast-enhancing area, typically on conventional contrast-enhanced MR imaging.[8] Progression on imaging is defined as either a 25% increase in the size of enhancement or new foci of enhancement (**Table 1**).[8] In addition, corticosteroids and neurologic status are also taken into consideration. Taken together, this schema is known as the MacDonald criteria. When proposed in 1990, these criteria represented a shift from a subjective evaluation of clinical and radiologic data toward a more objective, image-based methodology.[9]

LIMITATIONS OF THE MACDONALD CRITERIA

Since their introduction, several limitations of the MacDonald criteria have been identified.[10,11] These limitations include interobserver variability, failure to measure nonenhancing portions of tumor (particularly significant for evaluation of low-grade gliomas [LGGs]), difficulty in measuring tumors with irregular shapes, lack of guidance in the evaluation of multifocal tumors, assessment of progression after gross total resection of all enhancing tumor, and difficulties with measuring enhancing lesions in the walls of cysts/surgical cavities because the cysts/cavities may be incorporated into the tumor size measurement.

The most critical limitation rests on the MacDonald criteria's reliance on contrast enhancement as a criterion of therapeutic response. Although contrast enhancement is a sensitive marker of blood-brain barrier (BBB) disruption, it is not a specific finding of active tumor, and can be the result of many other processes including treatment-related effect, ischemia, seizure, inflammation, and postoperative changes.[12–16] In

Table 1
MacDonald criteria

Response	Criteria
Complete response	All of the following are required: Complete disappearance of all enhancing measurable and nonmeasurable disease that is sustained for a minimum of 4 wk No new lesions No use of corticosteroids Stable or improved clinically
Partial response	All of the following are required: ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for a minimum of 4 wk No new lesion Stable or reduced corticosteroid dose Stable or improved clinically
Stable disease	All of the following are required: Does not qualify for complete response, partial response, or progression Stable clinically
Progression	Any of the following: ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions Any new lesion Clinical deterioration

Adapted from Macdonald DR, et al. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 1990;8(7):1277–80.