

End Point Assessment in Gliomas: Novel Treatments Limit Usefulness of Classical Macdonald's Criteria

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Recent trials in glioma have revealed significant limitations in the end points used. This requires a critical and comprehensive review of how brain tumor trials are conducted, particularly of which end points are defined and how response and progression are defined.

LIMITATIONS OF MACDONALD'S RESPONSE AND PROGRESSION CRITERIA

In 1990, Macdonald et al¹ reported criteria for response assessment in glioma. These criteria, which rely primarily on computed tomography (CT)–based two-dimensional WHO response criteria, marked the transition from a subjective interpretation of clinical and radiologic changes toward more objective radiologically based criteria. Macdonald's criteria use the enhancing tumor area as the primary measure, while considering the use of steroids and changes in the neurologic status. Although these criteria have limitations (particularly the difficulty of measuring the often irregular shape of gliomas), they have become widely accepted. However, recent observations have revealed fundamental limitations to Macdonald's criteria.^{2,3} At the core of Macdonald's criteria are changes in enhancement, and indeed, all too often, the enhancement of high-grade tumors is perceived as a measure of tumor. However, enhancement is nonspecific and primarily reflects a disrupted blood-brain barrier. Enhancement can be influenced by changes in corticosteroid dose and radiologic technique.^{4,5} Enhancement can also be induced by a variety of nontumoral processes: inflammation, seizure activity, postsurgical changes, and radiation necrosis.^{6–9} As a result, changes in the enhancing area cannot be equated with changes in tumor size or tumor growth/activity. Macdonald's criteria have proved to be of limited value in the following clinical situations.

Pseudoprogression and Radiation Necrosis

Studies of patients with glioblastoma treated with the current standard of care—chemoradiation combined with temozolomide—have shown consistently that immediately after the end of radiother-

apy, 20% to 30% of patients suffer from pseudoprogression.^{10,11} This is defined as an increase of enhancement within the irradiated field that spontaneously subsides without new antitumor treatments (Fig 1). Pseudoprogression appears to be less frequent after fractionated external-beam radiotherapy only.¹² Moreover, after combined chemoradiation, radiation necrosis also seems to occur more frequently and earlier than it does after fractionated external-beam radiotherapy only.¹³ This limits the validity of progression-free survival (PFS) as the primary end point in clinical trials and has significant implications for eligibility in salvage treatment trials; patients should not be eligible for such trials in the first months after the end of radiotherapy. Most trials currently use a 3-month minimum interval, which is admittedly an arbitrary period.

Enhancement Resulting From Local Treatment

The observation of postsurgical enhancement confounding assessment of response has resulted in the exclusion from phase II studies using response as the primary end point of patients after surgery, unless an immediate postoperative scan (ie, within the first 24 to 48 hours) is obtained.^{7,14–16} However, local treatment–induced enhancement is not limited to surgical resection. Transient increases in enhancement (flare) not reflecting tumor progression have been reported in multiple studies of local intratumoral treatment.^{17–20} Therefore, PFS may not be an appropriate end point in such trials. The same holds true for interstitial brachytherapy and stereotactic radiosurgery, which may induce radiation necrosis mimicking tumor progression.²¹

Pseudoresponse After Treatment With Agents Affecting Angiogenesis and Blood Vessels

Studies of agents that modify signal transduction through the vascular endothelial growth factor (VEGF) signaling pathways (eg, bevacizumab and cediranib) have shown that initiation of therapy often produces a rapid decrease in enhancement, resulting in high response rates.^{22,23} However, these responses result at least partially from a rapid normalization of abnormally permeable blood vessels or

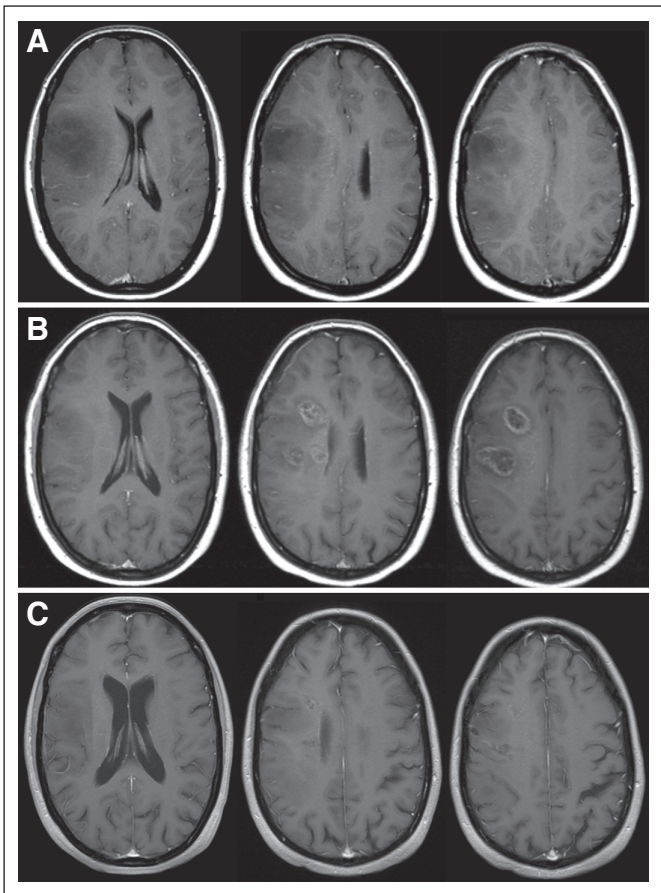


Fig 1. Example of pseudoprogression after radiotherapy only. (A) Patient with biopsy-proven gemistocytic astrocytoma showing mass effect on magnetic resonance imaging (MRI) < 2 months before start of radiotherapy underwent 50.4-Gy radiotherapy in fractions of 1.8 Gy. (B) On first follow-up MRI 2 months after end of radiotherapy, new enhancing lesions were present. (C) These disappeared 7 months later without any additional treatment. The patient was asymptomatic throughout this episode and did not receive steroids.

regional cerebral blood volume, not from antitumor effects. Moreover, in several patients, increases in the nonenhancing portion of tumor were observed in T2- or fluid-attenuated inversion recovery (FLAIR)-weighted magnetic resonance imaging (MRI), suggestive of infiltrative tumor progression despite the continuing radiologic response of the enhancing lesions (Fig 2).²⁴ This may explain the disappointing disparity between the unprecedented high response rates produced by these agents in recurrent glioblastoma and the modest (if any) survival benefit reported. To some extent, similar effects have been observed after treatment with platelet-derived growth factor inhibitors.²⁵ Again, the difficulty in assessing progression limits use of 6-month PFS as the primary end point, and in response assessment, changes in T2- or FLAIR-weighted MRI sequences must also be considered.²⁶

Another issue is the occurrence of rebound enhancement and edema on discontinuation of the VEGF-signaling inhibitor, which requires special attention if patients are enrolled onto clinical trials after nonresponse to VEGF-inhibiting agents. In the example illustrated by Figure 3, after a sufficiently long washout interval, a new baseline scan is needed to avoid the unjustified designation of failure of subsequent treatment because of rebound enhancement and edema.

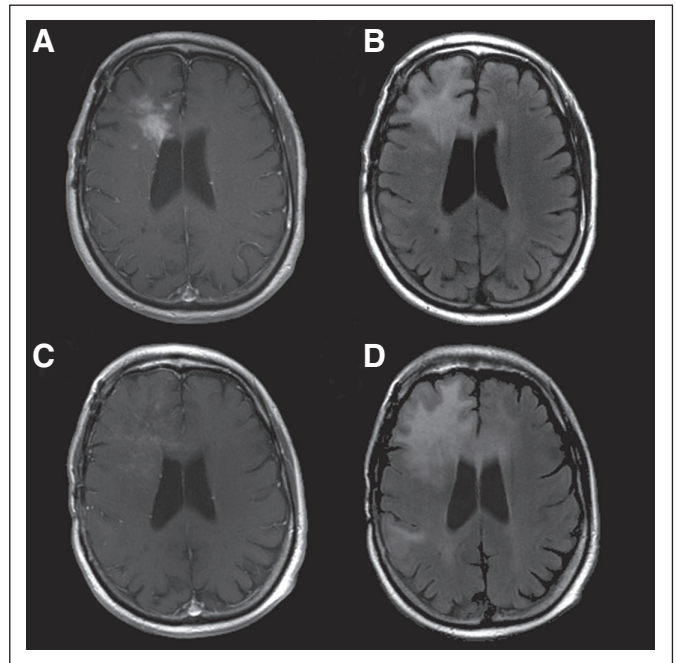


Fig 2. Patient 57 years of age with secondary glioblastoma before (A) T1-weighted magnetic resonance imaging (MRI) with contrast and (B) fluid-attenuated inversion recovery [FLAIR]-weighted MRI and after 7 months of treatment with bevacizumab and irinotecan, showing reduction in size of initial contrast-enhancing mass but also demonstrating (C) subtle diffuse enhancement and (D) significantly increased FLAIR crossing the corpus callosum. This was associated with increased cognitive impairment. Patient was not receiving corticosteroids at time of either scan.

Nonenhancing Tumors: Low-Grade Glioma

Macdonald's criteria were designed primarily to evaluate high-grade gliomas and focus on changes in enhancing tumor volume. However, low-grade gliomas usually do not show contrast enhancement in CT or MRI. Untreated, these tumors often have low growth rates, on the order of 3 to 5 mm per year.²⁷ Because it would take a considerable period of time to reach the Macdonald-specified 25% increase in area, this obscures the detection of progression. Moreover, low response rates have been observed in several trials despite significant clinical benefit (particularly seizure reduction) and prolonged disease control.²⁸⁻³⁰ One problem seems to be that residual abnormalities, which may persist after successful treatment, cannot be distinguished from active tumor in T2- or FLAIR-weighted MRI.

Application of Macdonald's Criteria After Complete Resection of Enhancing Disease

Macdonald's criteria define disease progression as an increase in enhancing tumor area of $\geq 25\%$ or the appearance of new enhancing lesions. Surgical techniques have evolved such that so-called gross total resection (eg, resection of all of the enhancing disease) is performed on a more regular basis.³¹ If there is no enhancement present at postoperative imaging study, any enhancement on subsequent scans—no matter how small or nonspecific—by definition implies tumor progression. Currently, there are no generally accepted criteria to determine progression after gross total resection.

In theory, both alternative imaging tools and alternative trial designs and end points could be used to overcome these imaging issues. Indeed, more sophisticated MRI techniques and metabolic

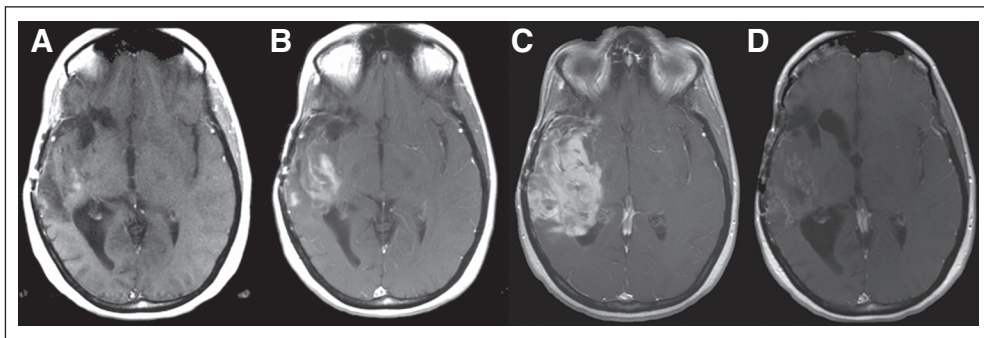


Fig 3. Example of rebound enhancement after discontinuation of anti-vascular endothelial growth factor (VEGF) agent. (A) Axial T1-weighted magnetic resonance imaging with contrast of patient with recurrent right temporal glioblastoma who initially responded to aflibercept (VEGF Trap; Regeneron, Tarrytown, NY); (B) at recurrence when aflibercept was discontinued; and (C) 4 weeks after, showing significant increase in contrast enhancement. (D) Patient began receiving bevacizumab with significant reduction in enhancement 4 weeks later, suggesting that worsening was in part result of aflibercept discontinuation and not just of tumor progression.

positron emission tomography with radioactively labeled amino acid tracers may provide answers to some of these issues, but these techniques are not widely available, nor have they been validated for use in trials of glioma.^{32,33} Their value remains to be established in future studies.

PFS OR OVERALL SURVIVAL AS THE PRIMARY END POINT

Whether PFS can be an appropriate primary end point in phase III trials—or whether overall survival (OS) should be the primary end point in these trials as a matter of principle—is an ongoing discussion in oncology. The evaluation of the effect of a particular treatment on OS may be influenced by subsequent salvage treatments. Until recently, the lack of effective treatments in glioma made this a hypothetical consideration in glioma trials. However, the bevacizumab studies in recurrent glioblastoma have suggested that salvage treatments may indeed affect OS.²³ In contrast, some recent trials of newly diagnosed glioma have shown improved PFS after initially intensified treatment without an impact on OS.^{34–36} None of these trials have clarified whether this increase in PFS signified clinical benefit for the patients. Prolonging PFS may be beneficial to a patient if the toxicity of initial treatment is low, good function is maintained as long as the tumor is controlled, and progression is associated with a significant deterioration in function or quality of life. Unfortunately, until recently, most studies of treatment for newly diagnosed gliomas did not gather adequate functional or quality-of-life data to assess these issues. Moreover, validated and accepted tools to assess neurologic deterioration-free survival are currently not available.

NEED FOR STUDY-SPECIFIC END POINTS

Clearly, different and study-specific end points are required depending on the type of trial, investigational treatment, and clinical setting (newly diagnosed or recurrent high-grade or low-grade glioma). If classical cytotoxic drugs that do not interfere with enhancement are tested in recurrent glioblastoma, then a classical approach with 6-month PFS as the primary end point can be used. In newly diagnosed glioblastoma, analyses have suggested that 12-month OS may be considered as a surrogate end point, although this end point would be subject to the effects of salvage treatments.^{37,38} PFS is not adequate

in trials of local treatments, trials of newly diagnosed glioma managed with chemoradiation combined with temozolomide, or trials with antiangiogenic agents. In these cases, the diagnosis of progression as assessed by conventional MRI is too uncertain. Crossover is an issue if the investigational agent is active in recurrent disease or is likely to be used in the control arm at time of progression. If so, no OS benefit may be observed, despite clear activity of the investigational agent. In these circumstances, trial design should emphasize other parameters of clinical benefit for patients.

To address these issues and develop specific guidelines for end points in various types of neuro-oncology trials, an international working party has been formed to develop recommendations for each of these situations. It is expected that through this effort, widely accepted criteria will again become available for use in clinical trials in the coming years.

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