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SPECIAL ARTICLE

Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group

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ABSTRACT

Currently, the most widely used criteria for assessing response to therapy in high-grade gliomas are based on two-dimensional tumor measurements on computed tomography (CT) or magnetic resonance imaging (MRI), in conjunction with clinical assessment and corticosteroid dose (the Macdonald Criteria). It is increasingly apparent that there are significant limitations to these criteria, which only address the contrast-enhancing component of the tumor. For example, chemoradiotherapy for newly diagnosed glioblastomas results in transient increase in tumor enhancement (pseudoprogression) in 20% to 30% of patients, which is difficult to differentiate from true tumor progression. Antiangiogenic agents produce high radiographic response rates, as defined by a rapid decrease in contrast enhancement on CT/MRI that occurs within days of initiation of treatment and that is partly a result of reduced vascular permeability to contrast agents rather than a true antitumor effect. In addition, a subset of patients treated with antiangiogenic agents develop tumor recurrence characterized by an increase in the nonenhancing component depicted on T2-weighted/fluid-attenuated inversion recovery sequences. The recognition that contrast enhancement is nonspecific and may not always be a true surrogate of tumor response and the need to account for the nonenhancing component of the tumor mandate that new criteria be developed and validated to permit accurate assessment of the efficacy of novel therapies. The Response Assessment in Neuro-Oncology Working Group is an international effort to develop new standardized response criteria for clinical trials in brain tumors. In this proposal, we present the recommendations for updated response criteria for high-grade gliomas.

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INTRODUCTION

Gliomas are the most common form of malignant primary brain tumors in adults, with an annual incidence of approximately four to five per 100,000 people.[1,2] The evaluation of treatment in high-grade gliomas currently relies either on the duration of patient survival or, more commonly in patients with recurrent disease, the radiographic response rate or progression-free survival (PFS).[3,4] In 1990, Macdonald et al[5] published criteria for response assessment in high-grade gliomas (Table 1). These criteria provided an objective radiologic assessment of tumor response and were based primarily on contrast-enhanced computed tomography (CT) and the two-dimensional WHO oncology response criteria using enhancing tumor area (the product of the maximal cross-sectional enhancing diameters) as the primary tumor measure.[6,7] These criteria also considered the use of corticosteroids and changes in the neurologic status of the patient. The Macdonald Criteria enabled response rates to be compared between clinical trials and have been widely used in high-grade glioma studies since their introduction.

Although the Macdonald Criteria were developed primarily for CT scans, they have been extrapolated to magnetic resonance imaging (MRI), which is now the standard neuroimaging modality used to assess treatment response in high-grade gliomas. Like CT scans, areas of the tumor with abnormal vascular architecture and disrupted integrity of the blood-brain barrier are depicted as the contrast-enhancing component on MRI.[8]

In systemic cancers, one-dimensional tumor measurements have become the standard criteria to determine response. The Response Evaluation Criteria in Solid Tumors (RECIST) first introduced the use of one-dimensional measurements in 2000[9] and were recently revised (RECIST version 1.1).[10] Several studies have compared the RECIST criteria with

Table 1. Current Response Criteria for Malignant Gliomas (Macdonald Criteria)[5]

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; no corticosteroids; and stable or improved clinically
Partial response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no new lesions; stable or reduced corticosteroid dose; and stable or improved clinically
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; and stable clinically
Progression	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions; any new lesion; or clinical deterioration

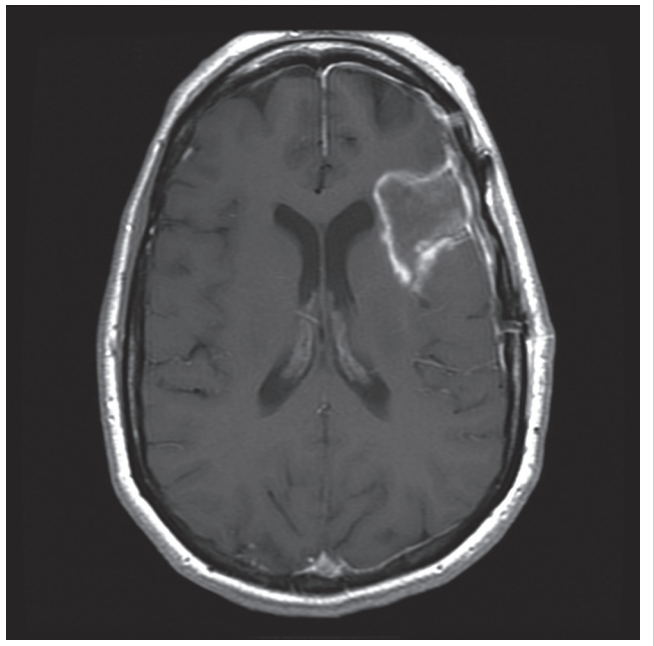

Fig 1. A 38-year-old patient with left frontal glioblastoma showing irregular enhancement in wall of the cavity that is difficult to measure. Although the entire cavity is often measured, it would be preferable if only the enhancing nodule in the posterior wall of the cavity were measured. If it is smaller than 10 mm in bidirectional diameters, the lesion would be considered nonmeasurable.

two-dimensional measurements, three-dimensional measurements, and volumetric measurements in high-grade gliomas.[11-13] These studies suggest that there is good concordance among the different methods in determining response in adult patients with both newly diagnosed and recurrent high-grade gliomas,[12,13] as well as in pediatric brain tumors.[11] However, an exception is seen with three-dimensional measurements, which seem to be inferior to one- and two-dimensional and volumetric measurements.[12,14] Nonetheless, studies prospectively validating the RECIST criteria in gliomas have not been performed. Currently, the Macdonald Criteria using two-dimensional measurement remain the most widely used method for evaluating tumor response in clinical trials of high-grade gliomas, partly because they enable the results of ongoing studies to be easily compared with historical data.

LIMITATIONS OF THE MACDONALD CRITERIA

From their inception, it was apparent that the Macdonald Criteria had a number of important limitations. These limitations, which have recently been reviewed in detail,[15-17] include the difficulty of measuring irregularly shaped tumors, interobserver variability, the lack of assessment of the nonenhancing component of the tumor, lack of guidance for the assessment of multifocal tumors, and the difficulty in measuring enhancing lesions in the wall of cystic or surgical cavities because the cyst/cavity itself may be included in the tumor measurement (Fig 1). In the Macdonald Criteria, a significant increase (at least 25%) in the contrast-enhancing lesion is used as a reliable surrogate marker for tumor progression, and its presence mandates a change in therapy. However, contrast enhancement is nonspecific and primarily reflects the passage of contrast material across a disrupted blood-tumor barrier. Enhancement can be influenced by changes in corticosteroid doses, antiangiogenic agents (discussed later), and changes in radiologic techniques.[18,19] Increased enhancement can also be induced by a variety of nontumoral processes such as treatment-related inflammation, seizure activity, postsurgical changes, ischemia, subacute radiation effects, and radiation necrosis.[20-23] As a result, there are significant limitations in equating changes in enhancing area with changes in tumor size or tumor growth. The limitations of the Macdonald Criteria have become even more apparent with the increased incidence of pseudoprogression in patients receiving radiotherapy with temozolomide and the recent introduction of antiangiogenic therapies that affect the permeability of tumor vasculature. This has led to the current effort to revise the response criteria for high-grade gliomas.[17] The major issues are discussed in the following sections.

Pseudoprogression and Radiation Effects

Standard therapy for glioblastoma involves maximal safe tumor resection followed by radiotherapy with concurrent and adjuvant temozolomide.[24,25] Twenty to 30% of patients undergoing their first postradiation MRI show increased contrast enhancement that eventually subsides without any change in therapy (Fig 2). This phenomenon, termed pseudoprogression, likely results from transiently increased permeability of the tumor vasculature from irradiation, which may be enhanced by temozolomide, and complicates the determination of tumor progression immediately after completion of radiotherapy.[26-30] Pseudoprogression may be accompanied by progressive clinical signs and symptoms and seems to be more frequent in patients with a methylated *MGMT* gene promoter.[30] This treatment-related effect has implications for patient management and may result in premature discontinuation of effective adjuvant therapy. This limits the validity of a PFS end point unless tissue-based confirmation of tumor progression is obtained. It also has significant implications for selecting appropriate patients for participation in clinical trials for recurrent gliomas. Failure to exclude patients with pseudoprogression from these studies will result in a falsely high response rate and PFS

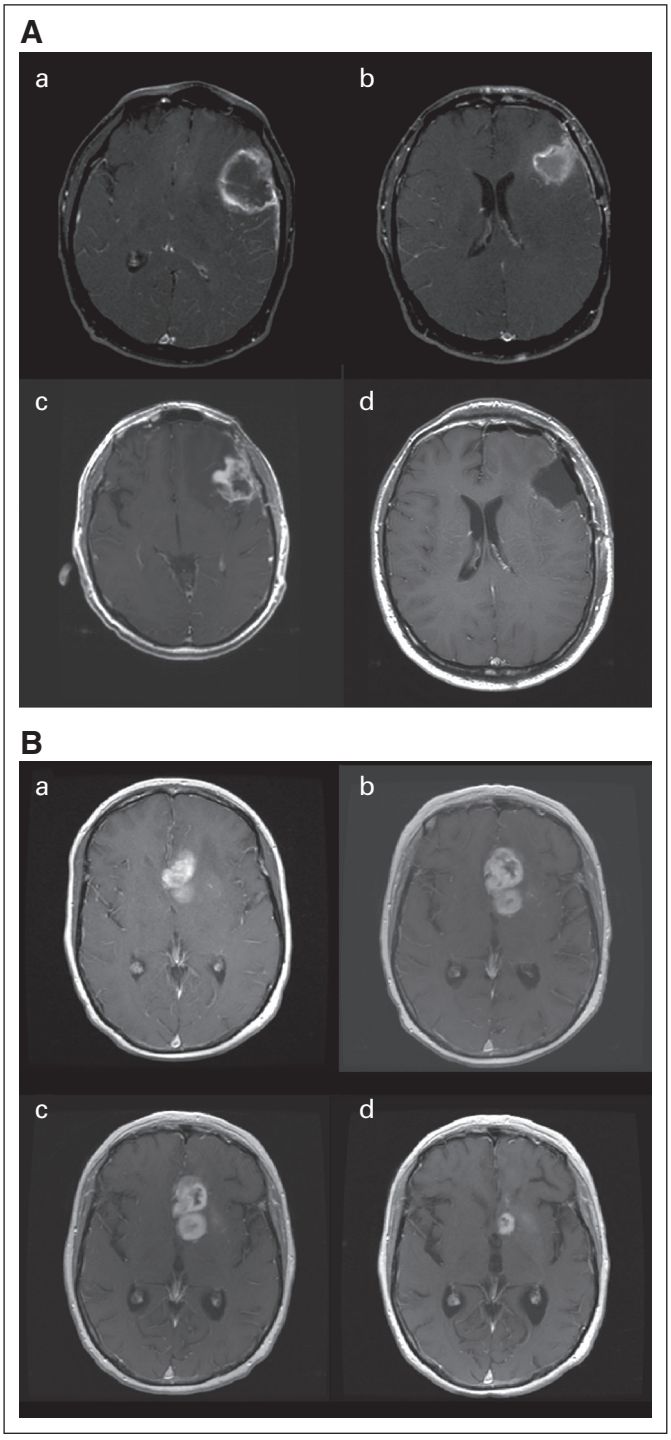

Fig 2. (A) Pseudoprogression after chemoradiotherapy: axial T1-contrast enhanced magnetic resonance imaging (MRI) a) before surgery; b) after surgery; c) after radiotherapy and concomitant temozolomide showing increased enhancement; d) re-operation showing only necrotic tissue and no tumor. (B) Pseudoprogression after chemoradiotherapy: axial T1-contrast enhanced MRI showing deep left frontal glioblastoma a) 2 days after stereotactic biopsy; b) 4 weeks after radiotherapy and concomitant temozolomide showing increased enhancement, raising the possibility of progression; c) after 4 additional weeks of treatment with adjuvant temozolomide showing stable disease; d) after 8 cycles of adjuvant temozolomide showing significant reduction in tumor size.

and the possibility that an agent will be incorrectly considered to be active. To address this issue, the proposed new response criteria suggest that within the first 12 weeks of completion of radiotherapy, when pseudoprogression is most prevalent, progression can only be determined if the majority of the new enhancement is outside of the radiation field (for example, beyond the high-dose region or 80% isodose line) or if there is pathologic confirmation of progressive disease (Table 2). It is recognized that the proposed histologic criteria have important limitations, but they provide guidance on the type of findings that are suggestive of progressive disease. For patients in whom pseudoprogression cannot be differentiated from true tumor progression, enrollment onto trials for recurrent gliomas should not be permitted. Patients who remain clinically stable and/or are suspected to have pseudoprogression based on metabolic or vascular imaging should continue with their current therapy.

Enhancement As a Result of Surgery and Other Therapies

Increased enhancement often develops in the wall of the surgical cavity 48 to 72 hours after surgery.[20,31-33] To avoid interpretation of

Table 2. Criteria for Determining First Progression Depending on Time From Initial Chemoradiotherapy

First Progression	Definition
Progressive disease < 12 weeks after completion of chemoradiotherapy	Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (eg, solid tumor areas [ie, > 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.
Progressive disease ≥ 12 weeks after chemoradiotherapy completion	1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids. 2. Increase by ≥ 25% in the sum of the products of perpendicular diameters between the first postradiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids. 3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence. 4. For patients receiving antiangiogenic therapy, significant increase in T2/FLAIR nonenhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (eg, effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

Abbreviation: FLAIR, fluid-attenuated inversion recovery.

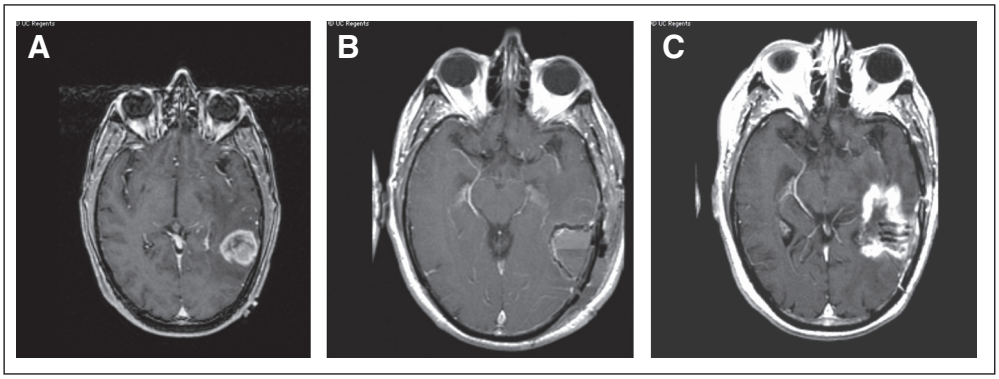

Fig 3. Pseudoprogression after brachytherapy. (A) Axial T1 contrast-enhanced magnetic resonance imaging (MRI) showing enhancing tumor before surgery. (B) Immediate postoperative magnetic resonance imaging (MRI) showing acute surgical changes and placement of iodine-125 brachytherapy seeds. (C) MRI performed 18 months later showing increased enhancement. Reoperation showed no tumor.

postoperative changes as residual enhancing disease, a baseline MRI scan should ideally be obtained within 24 to 48 hours after surgery and no later than 72 hours after surgery. The inclusion of diffusion-weighted imaging in the immediate postoperative MRI scan can be helpful in determining whether new enhancement developing in the subsequent weeks or months is caused by sequelae of ischemia or by tumor recurrence.[16,22] In addition, a transient increase in enhancement that can be difficult to distinguish from recurrent disease can also occur after locally administered therapies. These include chemotherapy wafers, immunotoxins delivered by convection-enhanced delivery, regionally administered gene and viral therapies, immunotherapies, and focal irradiation with brachytherapy and stereotactic radiosurgery (Fig 3).[17,34-38] Imaging modalities such as perfusion imaging, magnetic resonance spectroscopy, and positron emission tomography scans may sometimes be helpful in differentiating treatment effects from recurrent tumor.[39-42] However, no imaging modality currently has sufficient specificity to conclusively differentiate recurrent tumor from treatment effects, and surgical sampling may occasionally be needed to obtain a definitive diagnosis.

Pseudoresponses After Treatment With Antiangiogenic Therapies

Antiangiogenic agents, especially those targeting vascular endothelial growth factor (VEGF), such as bevacizumab, and the VEGF receptor, such as cediranib, can produce marked decrease in contrast enhancement as early as 1 to 2 days after initiation of therapy and commonly result in high radiologic response rates of 25% to 60%.[43-46] These apparent responses to antiangiogenic therapy may be partly a result of normalization of abnormally permeable tumor vessels and not always necessarily indicative of a true antiglioma effect (Fig 4). As a result, radiologic responses in studies with antiangiogenic agents should be interpreted with caution. There is a disappointing disparity between the unprecedented high response rates these agents produce in recurrent glioblastoma and the modest survival benefits, if any, that have been reported.[47] Although the duration of response or stability (PFS) or overall survival may be a more accurate indicator of a true anti-glioma effect, there is emerging data suggesting that the degree of initial response may also correlate with survival.[48] As with the Macdonald Criteria, the proposed criteria suggest that radiologic responses should persist for at least 4 weeks before they are considered as true responses.

Failure to Measure Nonenhancing Tumor

High-grade gliomas are infiltrative in nature, and their presence does not always result in disruption of the blood-brain barrier. In fact, determination of the extent of this nonenhancing component of the tumor, usually depicted on the MRI T2-weighted and fluid-attenuated inversion recovery (FLAIR) image sequences, can be difficult because peritumoral edema and delayed radiation white matter changes have similar radiographic appearances. Because the Macdonald Criteria do not account for the nonenhancing component of the tumor, this is especially problematic for low-grade gliomas (WHO grade 2) and anaplastic gliomas (WHO grade 3), where a significant portion of the tumor is typically nonenhancing.

As experience with antiangiogenic therapies has grown, especially with agents targeting VEGF and VEGF receptor, it has become apparent that a subset of patients who initially experience reduction in tumor contrast enhancement subsequently develop progressive increase in nonenhancing T2 or FLAIR signals suggestive of infiltrative tumor (Fig 5).[49-51] Increasing evidence suggests that anti-VEGF therapy may increase the tendency of tumor cells to co-opt existing blood vessels, resulting in an invasive nonenhancing phenotype.[52-54] Unlike the Macdonald Criteria, which do not take into account progressive nonenhancing disease, the new response assessment will consider enlarging areas of nonenhancing tumor as evidence of tumor progression (Tables 3 and 4). However, precise quantification of the increase in T2/FLAIR signal can be difficult and must be differentiated from other causes of increased T2 or FLAIR signal, such radiation effects, decreased corticosteroid dosing, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects, before making a determination of progressive disease. Changes in T2/FLAIR signal that suggest infiltrating tumor include mass effect (as determined by sulcal effacement, ventricular compression, and thickening of the corpus callosum), infiltration of the cortical ribbon, and location outside of the radiation field. Although it would be preferable to have an objective measure of progressive nonenhancing recurrent disease similar to contrast-enhancing disease, the Response Assessment in Neuro-Oncology (RANO) Working Group felt that this was not possible at present given the limitations of current technology.

The initiation of these changes can be subtle, and convincing non–contrast-enhancing growth may require one or two confirmatory scans. If nonenhancing progression is determined after retrospective review of images, the scan at which these changes were first detected should serve as the progression scan.

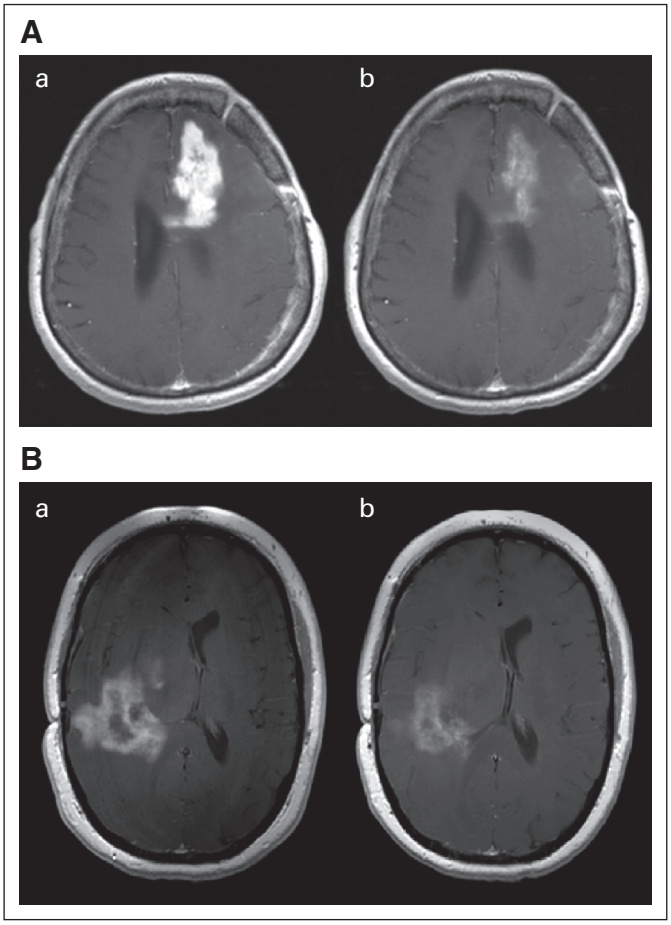

Fig 4. (A) Pseudoresponse. Axial T1-weighted contrast enhanced MRI of left frontal recurrent glioblastoma a) before and b) one day after therapy with cediranib (pan-VEGFR inhibitor) showing significant reduction in contrast enhancement. The reduction in contrast enhancement within 1 day of therapy is more likely to be caused by reduced vascular permeability to contrast than to a true antitumor effect. (Slide courtesy of A. Gregory Sorensen, Massachusetts General Hospital; Adapted with permission from Batchelor et al. Cancer Cell 11:83-95, 2007[43]). (B) Pseudoresponse. Axial T1-weighted contrast enhanced MRI of right parietal glioblastoma a) before and b) 1 day after therapy with XL184 (vascular endothelial growth factor receptor [VEGFR] and MET inhibitor) showing significant reduction in contrast enhancement. (Slide courtesy of A. Gregory Sorensen, Massachusetts General Hospital).

Progressive nonenhancing tumor is often associated with neurologic deterioration, and consequently, the clinical status of the patients may help in determining progressive disease. Given the lack of validated measures of neurologic function, a precise definition of neurologic deterioration is not included in the proposed response criteria. However, it is recommended that a decline in the Karnofsky performance score (KPS), Eastern Cooperative Oncology Group performance status, or WHO performance score be considered in determining clinical deterioration. The specific details are discussed later in the section defining progression.

PROCESS OF DEVELOPMENT OF THE UPDATED RESPONSE CRITERIA IN HIGH-GRADE GLIOMAS

Because of the limitations of the Macdonald Criteria, there has been an international effort in neuro-oncology to improve imaging response assessments for high-grade glioma and to enhance the interpretation of clinical trials involving novel agents that affect the blood-brain barrier such as antiangiogenic therapies. The RANO Working Group consists of neuro-oncologists, neurosurgeons, radiation oncologists, neuroradiologists, neuropsychologists, and experts in quality-of-life measures, in collaboration with government and industry. The RANO Working Group includes members with leadership roles in the major neuro-oncology organizations and brain tumor cooperative groups in both the United States and Europe. Recognizing the challenges in other neuro-oncologic clinical scenarios, imaging response recommendations are also being generated for low-grade glioma and the evaluation of surgically based therapies and will be reported separately.

In the following section, we outline a proposal for updated response criteria in high-grade gliomas from the RANO Working Group. It must be emphasized that this represents a work in progress. In coming years, as new volumetric and physiologic imaging techniques (eg, perfusion, permeability, and diffusion imaging; magnetic resonance spectroscopy; and metabolic imaging)[55,56] and other end points such as neuropsychological testing and quality-of-life measures are developed and validated in neuro-oncology, the RANO Working Group anticipates incorporating these parameters into the response criteria.

STANDARDIZATION OF IMAGING DEFINITIONS

Specific lesions must be evaluated serially, and comparative analysis of changes in the area of contrast enhancement, as well as the nonenhancing component, should be performed. As with the Macdonald Criteria, the product of the maximal cross-sectional enhancing diameters will be used to determine the size of the contrast-enhancing lesions.

Measureable and Nonmeasurable Disease for Contrast-Enhancing Lesions

Measurable disease is defined as bidimensionally contrast-enhancing lesions with clearly defined margins by CT or MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip. As with RECIST version 1.1, in the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness.[10] In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general, such lesions should be considered nonmeasurable unless there is a nodular component measuring $\geq$ 10 mm in diameter. The cystic or surgical cavity should not be measured in determining response.

Nonmeasurable disease is defined as either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm.

Patients without measurable disease, such as those who undergo a gross total resection, cannot respond and can only achieve stable disease as their best radiographic outcome. Therefore, if response rate is the primary end point of the study, patients with measurable disease are required for study eligibility. If duration of

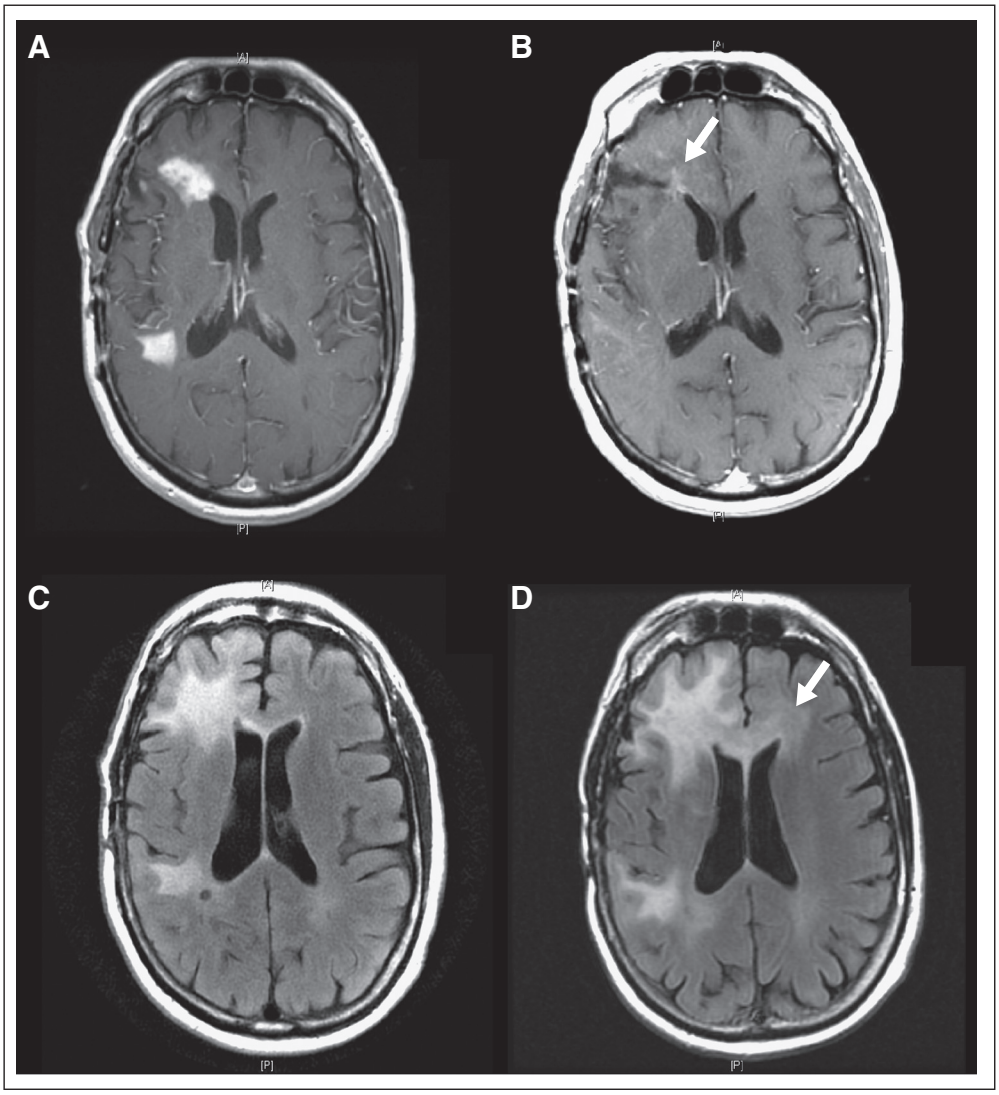

Fig 5. A 54-year-old patient with recurrent glioblastoma showing nonenhancing progression after bevacizumab therapy. Axial contrast-enhanced, T1-weighted images show (A) scan at recurrence showing multifocal right frontal glioblastoma; (B) decreased enhancement after 7 months of therapy that qualifies by Macdonald Criteria as partial response; (C) axial fluid-attenuated inversion recovery image at baseline and (D) after 7 months of therapy showing nonenhancing tumor progressing through corpus callosum to the left frontal lobe.

tumor control or survival is the primary end point, then patients with both measurable and nonmeasurable disease would be eligible for assessment because the determination of disease progression would be the primary interest.

Number of Lesions

If there are multiple contrast-enhancing lesions, a minimum of the two largest lesions should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined, similar to the criteria proposed for systemic tumors in RECIST version 1.1.[10] However, given the heterogeneity of high-grade gliomas and the difficulty in measuring some lesions, a maximum of five of the largest lesions may be measured. In general, the largest enlarging lesion(s) should be selected. However, emphasis should also be placed on lesions that allow reproducible repeated measurements. Occasionally, the largest lesions may not lend themselves to reproducible measurements, and the next largest lesions that can be measured reproducibly should be selected.

For patients with recurrent disease who have multiple lesions of which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response. The other lesions will be considered nontarget lesions and should also be recorded. Rarely, unequivocal progression of a nontarget lesion requiring discontinuation of therapy or development of a new contrast-enhancing lesion may occur, even in the setting of stable disease or partial response in the target lesions. These changes would qualify as progression.

CRITERIA FOR DETERMINING FIRST PROGRESSION DEPENDING ON TIME FROM INITIAL CHEMORADIOTHERAPY

As mentioned earlier, 20% to 30% of patients develop pseudoprogression after chemoradiotherapy, especially within the first 3 months after completion of radiotherapy.[27] Given the difficulty of differentiating pseudoprogression from true progression in the first 12 weeks after irradiation, we propose excluding these patients from clinical trials for recurrent disease unless the progression is clearly outside the radiation field (eg, beyond the high-dose region or 80% isodose line)

Table 3. Criteria for Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

NOTE. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.

Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.

*Stable doses of corticosteroids include patients not on corticosteroids.

or there is pathologic confirmation of disease progression. Table 2 lists these recommendations.

CRITERIA FOR ENTRY ONTO CLINICAL TRIALS FOR RECURRENT HIGH-GRADE GLIOMA

Currently, patients with any worsening of their imaging studies are eligible for entry onto clinical trials for recurrent gliomas, even if the change is minimal. We propose that patients should be required to have a 25% increase in the sum of the products of perpendicular diameters of the contrast-enhancing lesions, while on stable or increasing doses of corticosteroids, before they are considered to have progressive disease and are entered onto clinical trials for recurrent/progressive disease. Patients with new contrast-enhancing nonmeasurable disease may be considered for clinical trials in which PFS is the primary end point. Clinical deterioration or increase in corticosteroid dosing alone would not be sufficient to indicate progressive disease for entry onto clinical studies.

A particularly difficult problem involves patients receiving first-line antiangiogenic agents who develop predominantly nonenhancing disease at progression. This can be difficult to differentiate from treatment effects. If it seems clear that the nonenhancing changes represent tumor progression, these patients would also be eligible for enrollment onto clinical trials for recurrent disease, although their tumor will be considered nonmeasurable. As noted previously, although it would be preferable to have a more objective measure of progressive nonenhancing recurrent disease similar to contrast-enhancing disease, the RANO Working Group felt that this was not possible at present given the limitations of current technology.

DEFINITION OF RADIOGRAPHIC RESPONSE

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement at either pretreatment baseline or after initiation of therapy should be used for determination of progression. Table 3 lists the criteria for radiographic changes after therapy. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4-week intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which this issue was first raised. The determination of radiographic response after treatment with agents, such as antiangiogenic therapies, that affect vascular permeability is particularly difficult. In these patients, consideration should be given to performing a second scan at 4 weeks to confirm the presence of response or stable disease.

All measurable and nonmeasurable lesions should be assessed using the same techniques as at baseline. Ideally, patients should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

Complete Response

Complete response requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; and patient must be off corticosteroids or on physiologic replacement doses only, and stable or improved clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

Partial Response

Partial response requires all of the following: ≥ 50% decrease, compared with baseline, in the sum of products of perpendicular

Table 4. Summary of the Proposed RANO Response Criteria

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.
*Progression occurs when this criterion is present.
†Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and patient must be on a corticosteroid dose not greater than the dose at time of baseline scan and is stable or improved clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

Stable Disease

Stable disease occurs if the patient does not qualify for complete response, partial response, or progression (see next section) and requires the following: stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan and clinically stable status. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Progression

Progression is defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids; a significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events; the appearance of any new lesions; clear progression of nonmeasurable lesions; or definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression.

Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary.

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group and WHO performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

Patients with nonmeasurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of ≥ 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip) will also be considered to have experienced progression. The transition from a nonmeasurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (eg, a 9 × 9 mm lesion [nonmeasurable] increasing to a 10 × 11 mm lesion [measurable]). Ideally, the change should be significant (> 5 mm increase in maximal diameter or ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions). In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression.

If there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation (eg, evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression should be the time point at which this issue was first raised.

MULTIFOCAL TUMORS

For multifocal lesions, progressive disease is defined as ≥ 25% increase in the sum of products of perpendicular diameters of all measurable lesions compared with the smallest tumor measurements after initiation of therapy (Table 3). The appearance of a new lesion or unequivocal progression of nontarget lesions will also be considered progression. Partial response is defined as ≥ 50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable lesions sustained for at least 4 weeks with stable or decreasing corticosteroid doses.

ROLE OF VOLUMETRIC AND ADVANCED MRI ASSESSMENT

Given the limitations of two-dimensional tumor measurements, there is significant interest in volumetric anatomic assessment. The use of volumetric assessment would allow more accurate determination of the contrast-enhancing and nonenhancing volumes and overcome the limitations of two-dimensional measurements of lesions surrounding a surgical cavity.[14-16] However, the RANO Working Group and colleagues in neuroradiology do not believe that there is sufficient standardization and availability to recommend adoption of volumetric assessment of tumor volume at present. Nonetheless, this is an important area of research. Eventually, as volumetric imaging becomes more standardized and widely available and as data validating this approach emerge, it may be possible to incorporate volumetric measurements in the response assessment of high-grade gliomas.

Emerging data also suggest that advanced MRI techniques such as perfusion imaging (dynamic susceptibility MRI), permeability imaging (dynamic contrast-enhanced MRI), diffusion imaging, magnetic resonance spectroscopy, and [^{18}F]-fluorothymidine and amino acid positron emission tomography may predict tumor response or allow the differentiation of nonenhancing tumor from other causes of increased FLAIR signal. These techniques will require rigorous clinical validation studies before they can be incorporated into response criteria used in clinical trials in high-grade gliomas.

OTHER METHODS OF DETERMINING EFFICACY

Growing data suggest that other end points such as neurocognitive function, quality of life, and corticosteroid use may be used to measure clinical benefit. At present, these end points are not sufficiently validated to be incorporated into the current response criteria but could be added in the future as further data emerge.

CONCLUSION

We propose updated response assessments for the evaluation of therapies in high-grade gliomas incorporating MRI characteristics to address the recognized and accepted limitations of the current Macdonald Criteria. These recommendations were generated as part of an international neuro-oncology effort with consensus building and are an attempt to develop standardized assessment criteria. Implementation into future clinical trials will be critical so we can validate the criteria as a surrogate to end points such as survival and, ultimately, improve the accuracy and efficiency of the early evaluation of novel therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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