Radiology: Criteria for Determining Response to Treatment and Recurrence of High-Grade Gliomas

Joshua Lucas, MD*, Gabriel Zada, MD

KEYWORDS

• High-grade gliomas • Response criteria • Neuroimaging

High-grade glioma (HGG) is the most common form of primary brain tumor in adults. The World Health Organization (WHO) classification for central nervous system gliomas includes 2 grades that constitute HGG: anaplastic astrocytoma (WHO grade 3) and glioblastoma multiforme (WHO grade 4). The evaluation of response to treatment for patients with these tumors is of high clinical value in several respects. First, a patient's response to a particular treatment must be able to be analyzed objectively and easily communicated among practitioners. If one particular treatment fails to produce favorable results, an alternative treatment strategy can be pursued. Also, an objective scale must be available for clinical trials of new treatments. Traditional end points for the assessment of efficacy in clinical trials are progression-free survival (PFS), radiographic response rate (RRR), and overall survival (OS). Unlike OS, PFS and RRR depend on reproducible and accurate imaging measurements to analyze tumor progression.[1]

The development and refinement of specific radiographic response criteria have spanned several decades and several imaging modalities, and have evolved considerably over the past 3 decades. Contrast-enhanced computed tomography (CT) scans were initially used to analyze tumor progression. Criteria that had been developed for CT imaging were expanded to include T1-weighted magnetic resonance imaging (MRI) with gadolinium contrast.[2] Both methods detect disruption of the blood-brain barrier by evaluating areas of tumor enhancement. Newer response criteria, including the recently published Response Assessment in Neuro-Oncology (RANO) criteria, attempt to address limitations of prior response criteria and use fluid-attenuated inversion recovery (FLAIR) and T2-weighted MRI combined with T1-weighted MRI with gadolinium contrast to evaluate tumor size. Further study of advanced MR techniques, such as perfusion/permeability imaging and diffusion-weighted imaging, and functional assessment of tumors with MR spectroscopy (MRS) and positron emission tomography (PET) scanning, will likely allow for more accurate response criteria to be developed in the future. In this review, various schemes that have been developed and implemented to determine response to treatment and recurrence of HGG, and the status of current and emerging neuroimaging modalities used to make these assessments, are reviewed.

DEVELOPMENT OF CRITERIA FOR DETERMINING RESPONSE

Starting in the 1970s, several investigators have attempted to create practical criteria for assessing tumor response to treatment based on

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Department of Neurosurgery, University of Southern California, 1200 North State Street, Suite 3300, Los Angeles, CA 90033, USA
* Corresponding author.
E-mail address: joshuawlucas@gmail.com

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combinations of neuroimaging studies, patient clinical status, and relative interventions, such as corticosteroid administration. Although the basic principles of each of these schemes have remained more or less consistent with regard to determining treatment response versus tumor progression, the neuroimaging modalities used to make these determinations and specific criteria have evolved considerably. Starting with the Levin criteria in the late 1970s to the most recent implementation of the RANO criteria in 2010, the various criteria for assessing tumor response to multimodality treatment regimens are discussed in the following sections.

Levin Criteria (1977)

An early attempt to classify response to treatment of HGGs was published by Levin and colleagues[3] in 1977. The grading scheme they developed incorporated 4 separate modalities, including the neurologic examination, a radionuclide brain scan, an electroencephalogram, and a CT scan. Each was individually analyzed and any change from baseline was graded on a scale from +3 ("markedly better") to –3 ("markedly worse"). The CT scan was analyzed specifically for interval changes in tumor size, central lucency, degree of edema, degree of contrast enhancement, and size of the ventricular system. The corticosteroid dosages required by the patient at the time of grading were also accounted for as part of the assessment. This system represents one of the earliest published attempts at characterizing response to treatment of HGGs with the use of CT imaging.

WHO Oncology Response Criteria (1979)

In 1979, WHO developed criteria for grading response to therapy that was not specific for HGG, but applicable to all types of cancer.[4,5] Assessment of tumor size was based on 2-dimensional analysis of the tumor. The product of the 2 largest cross-sectional diameters of a specific enhancing lesion seen on CT scan was used as the primary measure of tumor size.

The criteria proposed by WHO identified 4 response categories. Complete response (CR) was characterized by complete disappearance of the lesion on subsequent CT scans. Partial response (PR) was characterized by a greater than 50% reduction in tumor size. Progressive disease (PD) indicated that tumor size had increased by more than 25% on repeat imaging. Stable disease (SD) was characterized by a reduction in size of less than 50% or an increase in size of less than 25%. Macdonald and colleagues[2] would be the first group to apply these categories of progression to brain tumors specifically.

Macdonald Criteria (1990)

In 1990, Macdonald and colleagues[2] published a new set of criteria demonstrating that the WHO criteria of 1979 could be applied directly to brain tumors, specifically HGGs. Like the WHO criteria, the Macdonald criteria used the maximal cross-sectional enhancing diameters of a specific lesion on CT scan as the primary tumor measure. In addition to radiographic response, Macdonald and colleagues[2] incorporated the clinical assessment of the patient and the current corticosteroid dose into the response grading scheme.

The categories of response in the Macdonald criteria are similar to the WHO Oncology Response criteria with regard to changes in tumor size. CR was defined as complete disappearance of tumor, with the additional requirements of no corticosteroids and stable or improved neurologic examination. PR was characterized by greater than 50% reduction in tumor size along with no new lesions, stable or reduced corticosteroid requirements, and stable or improved neurologic examination. PD was defined as any of the following: greater than 25% enlargement of tumor size, a new lesion, or clinical deterioration. SD was defined as a stable clinical examination that did not qualify as CR, PD, or PR.

Over the next several years, the Macdonald criteria would be met with some criticism.[6,7] Because of reliance on 2-dimensional assessment of tumor size, irregularly shaped tumors are difficult to assess and may therefore result in a high degree of interobserver variability. The criteria also provide little guidance for measuring tumors within or adjacent to cystic cavities or surgical cavities, and for multifocal tumors. Another limitation of the Macdonald criteria is that the primary tumor measurement relies only on enhancing portions of the tumor, so nonenhancing portions are not taken into consideration. Furthermore, the degree of contrast enhancement can be very nonspecific. Factors that may influence enhancement include corticosteroid dosages, the amount of contrast used during the scan, postsurgical changes, treatment-related inflammation, seizure activity, ischemia, subacute radiation effects and radiation necrosis, and antiangiogenic agents.[8–13]

The Macdonald criteria have since been adapted to include MRI with gadolinium contrast, under the same assumption that breakdown of the blood-brain barrier and disrupted vascular architecture will also manifest as contrast enhancement. Because corticosteroids can influence the

amount of contrast enhancement, Macdonald and colleagues[2] proposed that patients be kept on stable doses of corticosteroids when assessing for response. When new doses of corticosteroids were required, Macdonald and colleagues[2] originally proposed waiting 2 weeks for reassessment; however, new evidence suggests that 5 days are likely sufficient. The Macdonald criteria were the most widely used method of assessing response until the RANO criteria were published in 2010.

Response Evaluation Criteria in Solid Tumors (2000, 2009)

The Response Evaluation Criteria in Solid Tumors (RECIST) were introduced in 2000,[14] and then revised in 2009[15] for the evaluation of systemic cancers. In contrast to the WHO Oncology Response criteria, the RECIST criteria are based on the longest unidirectional single diameter in the axial plane. When multiple lesions are present, the diameters are summed to provide the primary tumor size measurement. As part of the RECIST criteria, the categories of response also differed from WHO criteria in that PR was defined as a greater than 30% decrease in the sums of maximal diameters of tumors, PD was characterized by a greater than 20% increase in the sums of diameters of tumors, and SD was defined as a lesion not classified as PD or PR.

The revised RECIST guidelines defined a minimum of 2 and a maximum of 5 lesions to be counted in cases of multiple lesions. Also, pathologic lymph nodes were incorporated into the assessment. To prevent overcalling progression, the revised RECIST guidelines also suggest a 5-mm absolute minimum increase requirement to diagnose PD. Several studies have suggested that the RECIST criteria have good concordance with both 2-dimensional measurements (Macdonald criteria) and volumetric measurements when determining response in both adult and pediatric high-grade gliomas.[16–18]

DEVELOPMENT OF THE CURRENT STANDARD CRITERIA (RANO CRITERIA)

Limitations of the Macdonald Criteria

Multimodality therapy for HGGs has evolved dramatically since the publication of the Macdonald criteria. Standard first-line therapy for high-grade gliomas currently involves maximal tumor resection followed by radiotherapy and concurrent and adjuvant temozolomide.[19] Therapy with antiangiogenic agents, such as bevacizumab and cediranib, or additional chemotherapy regimens, is reserved for patients demonstrating recurrence or tumor progression following first-line therapy. Recently observed effects of these current treatment modalities, namely pseudoprogression and pseudoresponse, have presented new challenges to the practicality of the Macdonald criteria in determining response to treatment.

Pseudoprogression

Pseudoprogression refers to the phenomenon whereby an increase in contrast enhancement does not accurately reflect actual tumor progression, and is thought to occur as a result of increased vascular permeability in tumors primarily following treatment with radiation and temozolomide.[20,21] Several studies have reported that 20% to 30% of patients treated with radiation and temozolomide develop pseudoprogression on the first postradiation MRI,[22,23] and that pseudoprogression is most likely to occur 4 to 12 weeks after completion of radiation therapy. Pseudoprogression will eventually resolve on subsequent MRI. To be considered pseudoprogression, the new region of enhancement must be within the radiation field.[21] Of note, this phenomenon occurs more often in patients with methylated MGMT-promoter tumors.[22]

The clinical significance of pseudoprogression may be profound. Nontumoral enhancement mistaken for PD may result in premature discontinuation of adjuvant therapy that is actually effective. Also, pseudoprogression may have implications for response reporting in clinical trials, especially in trails using PFS and RRR as primary end points.[24]

To evaluate tumor progression in these patients, FLAIR and T2-weighted sequences can be obtained on MRI. Progressive increases in nonenhancing FLAIR and T2-weighted signals reflect actual tumor progression.[25–27] An increase in these signals must be differentiated from other potential causes, including the effects of radiation, decreased corticosteroids, demyelination, ischemia, infection, seizures, and postoperative changes. Changes in FLAIR and T2-weighted imaging that suggest infiltrating tumor include mass effect, infiltration of the cortical ribbon, and an involvement of an area outside the radiation field.[28] In addition, newer imaging modalities, such as MR perfusion and permeability imaging, can more easily distinguish between real progression and pseudoprogression.

Pseudoresponse

Pseudoresponse refers to a decrease in contrast uptake that does not reflect actual tumor regression. This phenomenon occurs most commonly in patients treated with antiangiogenic therapies, such as bevacizumab (an anti–vascular endothelial

growth factor [VEGF] monoclonal antibody) and cedirinib (an anti-VEGF receptor monoclonal antibody), and can be seen as early as 1 to 2 days after initiation of antiangiogenic therapy.[28] Pseudoresponse is thought to be the result of normalization of vessel permeability and not a true antitumor response.[29,30] Also, increasing evidence suggests that anti-VEGF therapies increase blood vessel co-option by tumor cells. Co-opted vessels are believed to be less permeable and therefore less visible on contrast-enhanced MRI.[31–33]

RANO Group Criteria

The RANO group was an international effort to develop new standardized response criteria for clinical trials in brain tumors and response to therapy in individual patients with brain tumors.[28] In 2010, the RANO group published response criteria based on the Macdonald criteria but expanded these to define more-specific methods of measurement. The RANO criteria set more-specific guidelines for exact measurement of tumor size, and made significant changes to address the limitations of the Macdonald criteria (**Tables 1** and **2**).

For instance, the RANO group concluded that the use of maximum cross-sectional enhancing diameters on T1-weighted contrast-enhanced MRI was supported most by published evidence and should continue to be the primary tumor measure. The group also extended the Macdonald criteria to include both CT and MRI. For the least amount of variability, the group recommended that lesions be measured with the same scanner or at least one with the same magnetic strength. Strict guidelines were set for tumor measurements in cases of multiple lesions. The RANO criteria specify that a minimum of 2 lesions and a maximum of 5 lesions should be selected. Ideally, the largest lesions are selected, but favor should be given to those lesions that can be most reliably measured. The sum of the products of the cross-sectional diameters is used as the primary tumor measure. The group also set guidelines for measurement of small lesions. They determined that lesions must be visible on 2 consecutive 5-mm axial slices on CT or MRI. If larger slices are used, the size of the lesion at baseline should be at least double the slice thickness. Guidelines were also set for measurement of lesions with cystic components and those associated with surgical cavities. The RANO criteria state that the cyst or surgical cavity should not be measured, and lesions with cysts or surgical cavities must have a nodular component more than 10 mm in diameter to be included.

To address the phenomenon of pseudoprogression in patients treated with radiation and temozolomide, the RANO criteria specify that PD cannot be confirmed within the first 12 weeks following treatment unless new enhancement is found outside of the 80% isodose radiation field or tumor is unequivocally confirmed pathohistologically. Also, clinical decline alone without evidence of radiologic progression within the first 12 weeks was determined not to be sufficient for the classification of PD.

For patients receiving antiangiogenic therapies, specific additions were made to the RANO criteria to address pseudoresponse. According to the new criteria, FLAIR and T2-weighted MRI were included in all classifications of response. Lesions must have stable or decreased FLAIR and T2-weighted signals to be classified as CR, PR, or SD. A significant increase in FLAIR and T2-weighted signals was considered enough evidence to classify the tumor as PD, provided that other potential causes were excluded.

Aside from the addition of FLAIR/T2-imaging sequences and more strict requirements for defining PD, classifications within the RANO criteria remained largely the same as with the Macdonald criteria. CR was again classified as complete disappearance of tumor, no new lesions, absence of corticosteroids, and a stable or improved clinical examination. PR was defined as a greater than 50% decrease in tumor size, no new lesions, stable or decreased corticosteroid doses, and stable or improved clinical examination. PD was characterized by a greater than 25% increase in tumor size, new lesions, increased dosages of corticosteroids, or worsening clinical examination. SD comprised anything that did not belong to another category.

Of note, the RANO criteria defined a new category of nonmeasurable lesions as predominantly cystic lesions, lesions measureable in 1 dimension only, lesions having no clearly defined margins, or lesions with a maximum perpendicular diameter smaller than 1 mm. According to the RANO criteria, patients with nonmeasurable disease can achieve a “stable” classification as their best radiologic outcome.

EMERGING NEUROIMAGING MODALITIES TO ASSESS TUMOR RESPONSE

Authors of the RANO criteria and the RECIST criteria, the 2 most recent guidelines to be published, analyzed whether other forms of measurement, such as advanced MRI techniques, volumetric measurement, or functional assessment, would be more accurate as primary tumor

Table 1
RANO classifications of tumor response

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[a]; 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[a] 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

All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
Abbreviations: FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.
[a] Stable doses of corticosteroids include patients not on corticosteroids.
Data from Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology working group. J Clin Oncol 2010;28(11):1963–72.

measures for response criteria. The 2 studies concluded that current lack of published evidence, availability, and standardization prohibits the use of these advanced measurements in current response criteria. As more data become available regarding the ability for emerging advanced neuroimaging techniques to accurately predict tumor response to therapy and differentiate this from pseudoprogression and pseudoresponse, various response criteria schemes will require periodic reassessment and are likely to remain in flux. As expected, future studies will undoubtedly incorporate these imaging modalities into updated response criteria for HGGs.

MR Perfusion and Permeability

MR perfusion

HGGs are characterized by an increase in neovascularization on both a macrovascular and microvascular scale. MR perfusion scanning yields an estimated relative cerebral blood volume that

Table 2
Summary of the proposed RANO response criteria

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

Abbreviations: CR, complete response; FLAIR, fluid-attenuated inversion recovery; NA, not applicable; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease; ↓, decreased; ↑, increased.

[a] Progression occurs when this criterion is present.

[b] Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Data from Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology working group. J Clin Oncol 2010;28(11):1963–72.

reflects the amount of capillaries with a given space on imaging.[30] The amount of hyperperfusion in a tumor is a marker for tumor aggressiveness and behavior. Only solid, non-necrotic, noncystic areas of tumors can be assessed. Parametric response mapping, created with perfusion scan postprocessing, has been reported to be useful in distinguishing real progression from pseudoprogression.[34]

MR permeability

Another characteristic of HGGs is increased vascular leakiness, caused by abnormal permeability of immature capillaries. Increasing amounts of vascular leakage have been shown to correlate with increasing grade in HGGs.[35] T1-weighted dynamic contrast-enhanced MRI is used to produce a variable called the transport constant (Ktrans), which corresponds to the quantity of contrast extravasation and, in turn, vascular permeability.[36,37] Corrected perfusion maps that account for extravascular extravasation of contrast have been shown to correlate more accurately with tumor grade.[38,39]

MR Diffusion-Weighted Imaging

Diffusion-weighted MRI studies the movement of water molecules within tissue, and can be used to analyze response to therapy within tumor cells. Effective therapies can potentially change the cellular density of HGGs, the architecture of individual tumor cells, and the state of water within tumor cells. In many cases, these changes are visible on diffusion-weighted imaging (DWI) before morphologic changes in the tumor are able to be visualized.[40] The apparent diffusion coefficient (ADC) is the standard of measurement with DWI, as it provides a measure of the diffusion properties of water in brain tissue at the voxel level. Multiple voxels can be analyzed to create an ADC map.[30]

ADC maps have been shown to be effective in differentiating radiation-induced necrosis from recurrent lesions.[41–43] Contrast enhancement can be seen in the walls of the surgical cavity 48 to 72 hours postoperatively.[44,45] Baseline MRI should therefore be obtained within 24 to 48 hours, and no later than 72 hours.[28] The addition of DWI to this MRI can identify areas of ischemia that will become contrast enhancing several weeks postoperatively.[12] Without DWI, these areas of ischemia are often confused with enhancing tumor.

MR Spectroscopy

MRS provides information about the biochemical composition of tumors. Markers used for analysis include glucose (tumor metabolism), choline (membrane turnover and proliferation), creatine (energy homeostasis), N-acetyl-aspartate (intact glioneural structures), and lactate or lipids (necrosis).[30] Current limitations of MRS include signal-to-noise ratios that require large voxel sizes, which eliminate the ability to image small tumors.

PET Scanning

PET scanning assesses the metabolic state of HGGs.[30] To localize areas of tumor with increased anaerobic metabolism, 18F-fluorodeoxyglucose (18F-FDG) is commonly used. Localized hypoxia within HGGs forces cells to convert to anaerobic

metabolism.[46] Also, anaerobic glycolysis occurs in spite of adequate oxygen levels in advanced cancers.[47] Tumor cells therefore have increased uptake of 18F-FDG, which can be seen on PET imaging.

Also used as markers are 11C-methionine, 18F-fluoroethyltyrosine (18F-FET), and 18F-fluorothymidine. Upregulation of DNA and protein synthesis in cancer cells creates an increased turnover of nucleosides and amino acids, and these markers are subsequently incorporated into new genetic and protein products. The 11C-methionine and 18F-FET are more specific than 18F-FDG because they are more selectively taken up by tumor cells than by healthy brain tissue. Disadvantages of PET include scarce availability, cost, and mild exposure to radioactive material.[30]

SUMMARY

The development of radiologic criteria for the assessment of response to treatment in HGGs has evolved considerably over the past decades. Currently, T1-weighted MR imaging with gadolinium contrast combined with FLAIR and T2-weighted sequences is the standard imaging modality used to assess tumors. Considerable evolution in the criteria of various tumor response grading schemes have been observed since the widespread implementation of CT imaging in the 1970s. The 2010 RANO criteria, the most recent attempt to provide comprehensive guidelines for the measurement and analyses of HGGs, have incorporated methods by which to exclude the phenomena of pseudoprogression and pseudoresponse. The RANO criteria can be implemented in both direct patient care and clinical trials. Future studies assessing emerging advanced neuroimaging techniques, combined with more widespread availability, will facilitate the development of future evidence-based radiologic response criteria with more accuracy in differentiating tumor response versus progression.

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