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Response Assessment Challenges in Clinical Trials of Gliomas

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Abstract Accurate, reproducible criteria for determining tumor response and progression after therapy are critical for optimal patient care and effective evaluation of novel therapeutic agents. Currently, the most widely used criteria for determining treatment response in gliomas is based on two-dimensional tumor measurements using neuroimaging studies (Macdonald criteria). In recent years, the limitation of these criteria, which only address the contrast-enhancing component of the tumor, have become increasingly apparent. This review discusses challenges that have emerged in assessing response in patients with gliomas and approaches being introduced to address them.

Keywords High-grade glioma · Response criteria · Pseudoprogression

Introduction

Gliomas are the most frequent and deadly form of malignant primary brain tumors in adults, with an annual incidence of about five to six cases per 100,000 [1, 2]. Despite optimal therapy, most patients eventually succumb to their disease. There is an urgent need to develop more effective treatments.

Currently, the effectiveness of therapies for these tumors is determined either by measuring overall survival, or more commonly, by determining the radiographic response rate or progression-free survival (PFS) [3, 4]. There is a need for accurate response criteria to determine tumor response and progression after therapy. This review discusses emerging challenges in determining treatment response in both high- and low-grade gliomas.

Evaluation of Response in High-Grade Gliomas

High-grade gliomas (glioblastomas, anaplastic astrocytomas, anaplastic oligodendrogliomas, and oligoastrocytomas) account for more than 75% of malignant primary brain tumors [2]. Accurate and reproducible response criteria are critical for optimal patient care and effective evaluation of novel therapeutic agents [5]. The standard criteria used to determine response in systemic malignancies involve one-dimensional tumor measurements. Response Evaluation Criteria in Solid Tumors (RECIST) criteria were first introduced in 2000 [6] and recently updated in 2009 (RECIST version 1.1) [7]. Several studies have compared the RECIST criteria with two-dimensional, three-dimensional, and volumetric measurements in high-grade gliomas [8–10]. These studies generally show good concordance between the RECIST criteria and two-dimensional and volumetric measurements in patients with high-grade gliomas [8–10]. However, studies prospectively validating the RECIST criteria in high-grade gliomas have not been performed and these criteria are rarely used in clinical trials.

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Macdonald Criteria

Currently, the most widely used criteria for assessing response in high-grade gliomas involve two-dimensional measurements of enhancing tumor (the product of the maximal cross-sectional enhancing diameters) on CT or MRI scans [11]. These Macdonald criteria also account for the use of corticosteroids and changes in the neurologic status of the patient. They provide an objective radiologic assessment of tumor response and enable comparison of response rates among clinical trials. Since their introduction almost 20 years ago, these have been the most widely used response criteria in clinical trials of glioma.

In the Macdonald criteria, *complete response* is defined as the complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks. There must be no new lesions and the patient must be clinically stable or improved and not on any corticosteroids other than those used for adrenal replacement. *Partial response* is defined as ≥50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. There must be no new lesions, the patient must be clinically stable or improved, and on stable or reduced doses of corticosteroids. *Progression* is defined as a≥25% increase in the sum of the products of perpendicular diameters of enhancing lesions, the appearance of any new lesions, or clinical deterioration. *Stable disease* applies to patients who do not qualify for complete or partial response, or progression, and are stable clinically.

Limitations

There is increasing consensus that the Macdonald criteria have important limitations [5••, 12•, 13•, 14••]. These limitations include interobserver variability, the lack of assessment of the nonenhancing component of the tumor, the difficulty of measuring irregularly shaped tumors, lack of guidance for the assessment of multifocal tumors, and the difficulty in measuring enhancing lesions in the wall of cystic or surgical cavities. Most importantly, the Macdonald criteria use only contrast-enhancement as a surrogate for tumor size. A significant increase in the size of contrast enhancement (≥ 25%) is considered tumor progression and requires 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 affected by differences in radiologic techniques or the amount of contrast agents administered. Increased enhancement can also be caused by various processes not caused by the tumor itself, such as postsurgical changes, infarction, treatment-related inflammation, seizure activity, subacute radiation effects, and radiation necrosis [15–18]. In addition, the extent of contrast enhancement can be significantly affected by changes in corticosteroid doses [19, 20]. The limitations of equating changes in the enhancing area with changes in tumor size have become even more evident with the increased incidence of pseudoprogression in patients receiving chemoradiotherapy and the use of antiangiogenic therapies that affect the permeability of tumor vasculature. These limitations are discussed in greater depth below.

Enhancement Caused by Local Effects of Therapies

After surgical resection of gliomas, increased enhancement usually develops in the wall of the surgical cavity within 48–72 h [15, 21–23]. It is generally recommended that a baseline MRI scan should be obtained within 24–48 h after surgery (no later than 72 h) to avoid interpretation of postoperative changes as residual enhancing disease. Unfortunately, these recommendations are not often followed.

Increasingly, as diffusion-weighted imaging (DWI) is incorporated into the immediate postoperative MRI scans, it has become apparent that ischemic changes are relatively common [13•, 17]. These changes may lead to subsequent enhancement that can be mistaken for postoperative residual tumor or tumor recurrence. The routine incorporation of DWI in the postoperative MRI scan help differentiate these ischemic changes from residual postoperative disease.

A number of locally administered therapies can result in transient increases in enhancement that can be difficult to distinguish from recurrent disease. These therapies include chemotherapy wafers (polifeprosan 20 with carmustine implant), immunotoxins delivered by convection-enhanced delivery such as cintredekin besudotox, regionally administered gene and viral therapies, and local immunotherapies, as well as focal irradiation with brachytherapy and stereotactic radiosurgery [5••, 14••, 24–30]. In addition, systemic immunotherapies may potentially induce an inflammatory response that results in increased enhancement and may be mistaken for recurrent or progressive disease. Differentiating treatment effects from recurrent disease can be difficult. Imaging modalities such as perfusion imaging, MR spectroscopy, and positron emission tomography (PET) scans may sometimes be helpful [31–34]. However, no imaging modality currently has adequate sensitivity and specificity to conclusively differentiate recurrent tumor from treatment effects, and surgery may be necessary to obtain tissue for a definitive diagnosis.

Pseudoprogression and Radiation Necrosis

Pseudoprogression

Currently, the standard therapy for glioblastoma involves maximal tumor resection followed by radiotherapy with concurrent and adjuvant temozolomide [35]. About 40% to 50% of patients undergoing their first MRI 4 weeks after completion of radiotherapy show increased contrast enhancement [36•, 37, 38•]. In half of these patients, the increased enhancement represented true tumor progression. However, in the other half of patients, the increased enhancement eventually subsided with no change in therapy, suggesting that it resulted from transiently increased permeability of the tumor vasculature from irradiation [36•, 38•]. This phenomenon, termed *pseudoprogression*, is enhanced by the addition of temozolomide to radiotherapy [36•, 39–41], but can also be seen with radiotherapy alone [42, 43]. Patients with pseudoprogression are frequently asymptomatic, but when extensive, pseudoprogression can be associated with neurologic deterioration (Fig. 1).

Pseudoprogression is now recognized as a common and important clinical problem that complicates the determination of tumor progression immediately after completion of radiotherapy and has important implications for patient management [5••, 35•, 37•]. Failure to recognize pseudoprogression may result in patients being prematurely discontinued from an effective therapy, decreasing the perceived benefit of the treatment involved. Conversely, enrollment of patients with pseudoprogression into clinical trials for recurrent tumors will lead to artificially improved outcomes, and the false perception that the agent under investigation is active.

There is intense interest in finding methods to differentiate pseudoprogression from true tumor progression. Imaging techniques such as MR spectroscopy, diffusion imaging, and PET are being evaluated [44] but have not been particularly helpful [39]. A more promising approach may be dynamic susceptibility-weighted contrast-enhanced perfusion MRI, which determines relative cerebral blood volume [45, 46].

O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status is another test that may help differentiate pseudoprogression from true tumor progression

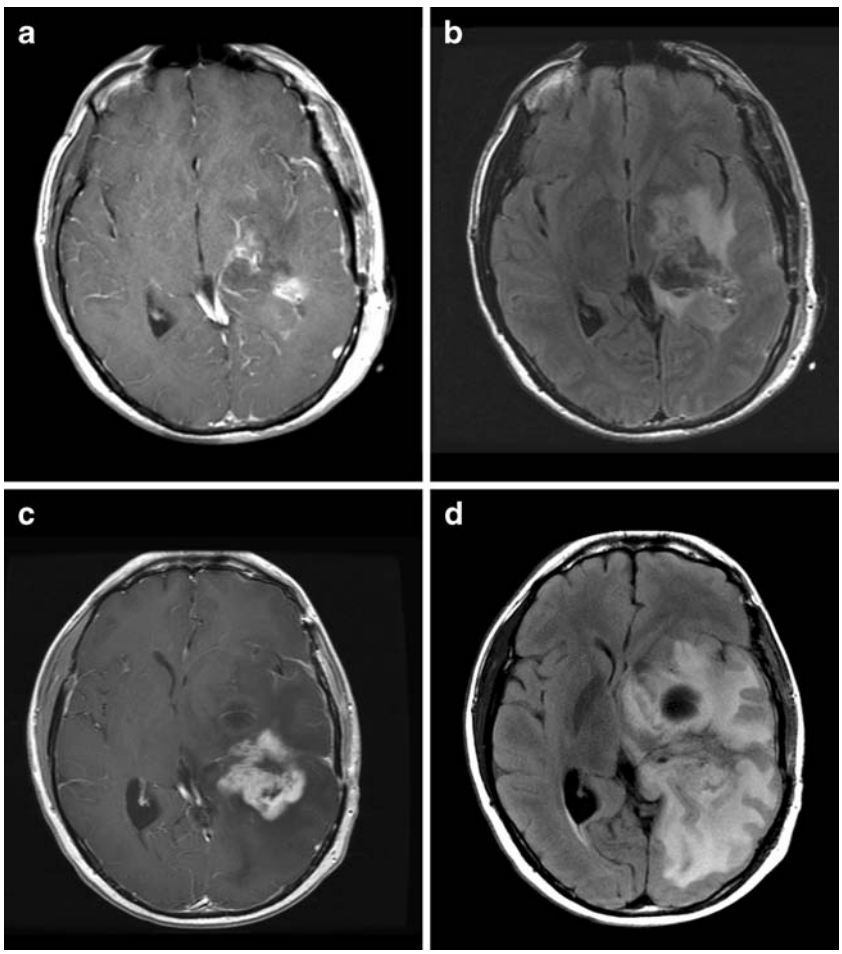

Fig. 1 A 39-year-old man with a deep left frontal/temporal glioblastoma after subtotal resection (**a**, axial T1 with contrast; **b**, axial fluid attenuated inversion recovery [FLAIR]) and 4 weeks after radiotherapy with concomitant temozolomide (**c**, axial T1 with contrast; **d**, axial FLAIR) showing significant increase in enhancement and edema. The patients underwent a reoperation. The pathology showed mainly necrosis, suggesting that the radiologic changes were primarily caused by pseudoprogression

[38•]. In a series of 103 patients with glioblastoma, Brandes et al. [38•] found almost 50% of these patients had worsening of the first postradiotherapy scan. Of the patients who developed pseudoprogression, 66% had tumors with methylated MGMT promoters, whereas 34% had unmethylated MGMT promoters. In contrast, of the patients who developed true progression, 89% had an unmethylated MGMT promoter and only 11% had a methylated MGMT promoter [38•]. Moreover, those patients with pseudoprogression had improved survival compared with those who did not. These data suggest that patients with a methylated MGMT promoter are more likely to have pseudoprogression. Although further studies will be necessary to validate these findings, MGMT methylation status may be useful in differentiating pseudoprogression from true progression.

During the past 2 years, an international Response Criteria in Neuro-Oncology (RANO) working group has been developing updated criteria for determining response in brain tumors [5••, 13••, 46]. Given the difficulties in differentiating pseudoprogression from true progression, the RANO working group has suggested that patients should generally be excluded from clinical trials during the first 3 months after radiotherapy, when pseudoprogression is most likely. Patients suspected of having pseudoprogression, or who have little or no symptoms, can continue on their present therapy and be followed closely with serial MRIs [5••].

Radiation Necrosis

As the name implies, radiation necrosis is associated with frank necrosis of tissue. It appears as increased contrast enhancement with surrounding edema and can be difficult to differentiate from recurrent tumor [16]. Radiation necrosis is generally a late effect of radiotherapy, occurring months to years after completion of treatment, in contrast to pseudoprogression that occurs within the first 3–6 months of therapy [16, 39, 48]. It is estimated to occur in less than 5% of patients undergoing standard radiotherapy for high-grade gliomas (6000 cGy in 200 cGy fractions) [49]. Therapies that increase the radiation dose to the tumor bed, such as interstitial brachytherapy or stereotactic radiosurgery, are associated with a higher incidence of radiation necrosis. Other factors such as large volumes and certain locations are also associated with a higher risk. Radiation necrosis from interstitial brachytherapy and stereotactic radiosurgery usually occurs several months after therapy [50]. As with pseudoprogression, differentiating radiation necrosis from recurrent disease can be difficult. PET with ^{18}F-fluorodeoxyglucose has relatively low sensitivity and specificity [51]. Dual-phase PET may potentially be more useful [52]. Amino acid PET such as ^{11}C-methionine [53] and ^{18}F-fluoroethyl-l-tyrosine [54] also show promise. MR spectroscopy [55] and perfusion imaging [46] are also being evaluated. When the diagnosis remains in doubt, surgery may be required to obtain tissue for histology.

Pseudoresponses After Treatment with Antiangiogenic Therapies

High-grade gliomas produce large amounts of vascular endothelial growth factor (VEGF). This increases vascular permeability and contributes to the contrast enhancement and peritumoral edema associated with these tumors. Antiangiogenic agents, especially those targeting VEGF, such as bevacizumab and aflibercept, or the VEGF receptors (VEGFR), such as cediranib, can significantly reduce vascular permeability. Recent trials with these agents have produced high radiologic response rates of 25% to 60% [56–59]. However, these apparent responses to antiangiogenic therapy may be due partly to normalization of abnormally permeable tumor vessels, decreasing contrast enhancement, and not necessarily to a true antiglioma effect because the reduction in contrast enhancement can occur as early as 1 day after initiation of therapy [5••, 14••, 57]. This phenomenon has been termed *pseudoresponse*. There is emerging evidence that patients who respond to bevacizumab have increased survival, suggesting that there is also a real antitumor effect [60]. Nonetheless, radiologic responses in studies with antiangiogenic agents will have to be interpreted with caution. The high response rates observed with these agents have been associated with little or no survival benefit, suggesting that at least some of the radiologic improvement may be artifactual [5••, 61]. Although response rate will remain an important criteria for assessing efficacy of therapeutic agents, for antiangiogenic agents the duration of response or stable disease (PFS) or overall survival may be a more accurate indicator of a true antitumor effect.

Nonenhancing Tumor

A major limitation of the Macdonald criteria is a failure to account for the nonenhancing tumor. Most World Health Organization grade III gliomas, and some glioblastomas, have extensive areas of nonenhancing tumor which are not currently unaccounted. In addition, as experience with anti-VEGF and VEGFR therapies increase, it has become apparent that some patients treated with these agents experience an initial reduction in contrast enhancement followed by the development of nonenhancing infiltrating disease, which appear as areas of increasing T2/fluid attenuated inversion recovery (FLAIR) signal abnormality [5••, 62•, 63–65]. These changes are frequently associated with clinical deterioration. There is increasing preclinical

evidence suggesting that anti-VEGF therapy may increase the tendency of tumor cells to coopt existing blood vessels, resulting in invasive, non-enhancing tumor [66, 67•, 68•, 69]. Differentiation of the T2/FLAIR signal caused by infiltrating tumor from other causes can be difficult. Almost all patients with recurrent malignant glioma will have increased T2/FLAIR signal on MRIs from radiation effects. Other conditions that should be considered before making a determination of progressive disease include demyelination, ischemic injury, decreased corticosteroid dosing, infection, seizures, postoperative changes, or other treatment effects. Currently, no imaging modality can reliably differentiate increased T2/FLAIR caused by infiltrating tumor from other causes, although emerging data suggest that apparent diffusion coefficient maps may be useful [70].

Updated Response Criteria in High-Grade Gliomas

As noted above, the increasing recognition of the limitations of the Macdonald criteria has led to an international effort in neuro-oncology to improve imaging response assessments for gliomas. This multidisciplinary RANO working group recently proposed updated response criteria for high-grade gliomas [5••]. These criteria remain based on two-dimensional tumor measurements because it was felt that volumetric measurements were currently insufficiently standardized and available for widespread use.

The main features of the updated criteria include 1) precise definitions of measurable and nonmeasurable disease; 2) guidance on the selection of the number of lesions in patients with multiple lesions; 3) exclusion of most patients within the first 3 months after radiotherapy from clinical trials to avoid including patients with pseudoprogression; 4) strict criteria for determining when a patient has progressed and becomes eligible for enrollment into clinical trials; 5) more precise definition of response and progression; and 6) inclusion of nonenhancing disease as criteria for determining tumor response.

These criteria are considered a work in progress. As new volumetric and physiologic imaging techniques [71, 72], as well as other end points such as neuropsychologic testing and quality-of-life measures, become validated and more widely available, these parameters will be incorporated into future criteria determining response in high-grade gliomas.

Evaluation of Response in Low-Grade Gliomas

Low-grade gliomas (LGG) include grade I and II astrocytomas, oligodendrogliomas, and oligoastrocytomas. These tumors present a particular challenge when determining the efficacy of therapies. Most phase 3 studies include overall survival as an end point [73, 74]. However, the slow growth of these tumors results in very long studies. Ideally, earlier measures of efficacy such as response and PFS would be used to improve the efficiency of conducting studies in this group of patients.

Determining response in LGG poses several problems. First, most of these tumors are nonenhancing. As a result, the Macdonald criteria, based on measurement of two-dimensional enhancing tumor, does not strictly apply. Many studies have used a modified Macdonald criteria, in which the criteria for contrast-enhancing tumors are applied to the nonenhancing T2/FLAIR abnormality. Second, these tumors often have irregular or ill-defined margins, making tumor measurements difficult. Third, these tumors tend to respond slowly to treatment and the reduction in tumor size is often less than that seen in high-grade gliomas. As a result, the 50% reduction in cross-sectional area required by the Macdonald criteria for determining partial response, and the 25% increase in determining progression are relatively insensitive measures for evaluating the efficacy of particular therapies. Fourth, effective therapies may lead to improvement in neurocognitive function, quality of life, and reduction in seizure frequency without significant changes in tumor size. These clinical benefits are currently not captured by the standard Macdonald criteria.

The RANO working group [14••, 47] is in the process of developing updated criteria to improve the assessment of response in LGG. It is likely that in addition to changes in the assessment of tumor size, these criteria may suggest incorporating measurements of neurocognitive function, quality-of-life measurements, and seizure frequency. It is hoped that these new criteria improve the accuracy and efficiency of evaluating new therapies in patients with LGG.

Conclusions

Recently, there have been important advances in the treatment of gliomas. However, these new therapies, such as chemoradiation for newly diagnosed glioblastomas and anti-VEGF agents for recurrent high-grade gliomas, have complicated the assessment of response in clinical trials of glioma. The RANO working group has proposed updated response criteria in gliomas to address some of these challenges [5••]. These criteria will continue to evolve and may eventually incorporate volumetric measurements, advanced MRI, and assessment of neurocognitive function and quality-of-life

measurements as these become validated and more widely available.

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- • Of importance
- •• Of major importance

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