

Updated response assessment criteria for high-grade glioma: beyond the MacDonald criteria

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Abstract: High-grade glioma continues to be a challenging disease with few effective treatment options and a poor prognosis, necessitating intensive research into alternate therapies. The Response Assessment in Neuro-Oncology (RANO) committee was formed to create a robust endpoint assessment criteria in Neuro-Oncology in order to streamline the assessment of new therapies in a uniform fashion. The aim of this committee is to create standardized guidelines to assess clinical and imaging response in the treatment of brain tumors, which can then be applied in clinical trials. Since the first RANO report was published in 2010, its criteria have been widely adopted and utilized in clinical trials worldwide. Standardized application of the RANO response assessment criteria in clinical trials will result in the generation of strong clinical data, which can subsequently be pooled and analyzed to attain a more accurate assessment of treatment efficacy. In this review, we summarize the current RANO guidelines in patients with high-grade glioma, highlighting the key clinical and imaging criteria used for RANO evaluation and introducing the role of newer imaging and biomarkers.

Keywords: Response Assessment in Neuro-Oncology (RANO); Neuro-Oncology; high-grade glioma; brain tumor

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Introduction

High-grade glioma remains a highly challenging disease for neuro-oncologists and neurosurgeons alike, with a dismal prognosis. Despite decades of research and development, the median survival of patients with newly diagnosed glioblastoma multiforme (GBM) remains poor, with a range from 12 to 14 months (1). Maximal safe surgical resection followed by concurrent chemoradiotherapy [temozolomide (TMZ) with radiation therapy (RT)] and adjunct chemotherapy (TMZ) remains the current standard of care in these patients, with little change since the advent

of the Stupp protocol in 2005 (1). Prognosis is even poorer in patients with recurrent GBM, with a 6-month PFS of approximately only 15% and a median overall survival (OS) ranging between 24–40 weeks (2,3). Consequently, there is a clear and urgent need for further development and investigation of promising new therapies, with a focus on identifying those therapies which are most likely to have a significant impact on GBM outcome. Tumor response to various therapeutic interventions is typically assessed using different imaging modalities, but intra-axial tumors such as GBM are most often evaluated using contrast enhanced magnetic (4). While imaging response is critical, other

modalities have been incorporated in the assessment of treatment response. In their seminal paper published in 1977, Levin *et al.* (5) reported an equal predictive value of neurological examination, radionuclide scintiscan, CT scan and electroencephalogram (EEG) when used individually in determining tumor response to chemotherapy in 100 patients with malignant brain tumors. However, combining two of three modalities (i.e., neurological examination, CT scan, radionuclide scintiscan, etc.) conferred an improved predictive value, resulting in predicted response to therapy in 82% of patients (5). Taken together, these results would suggest that comprehensive response criteria should include multi-modal assessment to achieve a more accurate assessment of response.

Tumor response criteria

In 1981, the World Health Organization (WHO) published their first tumor response criteria, defining response to therapy as a change in the product of bidimensional tumor measurements while on treatment. This criterion was vague and was subsequently modified in several forms, aimed to address tumors in general irrespective of tumor type or location (6). In 1990, Macdonald *et al.* (7) reported a novel criteria to assess tumor response based on the combination of two dimensional tumor measurement on contrast enhanced CT or MRI, clinical status, and change in corticosteroid requirement following treatment. Based on these parameters, they classified response as complete, partial, stable and progressive disease (PD) (7). Complete response (CR) was defined as disappearance of all enhancing tumor off steroids, partial response (PR) as reduction of $\geq 50\%$ on stable or reduced steroid dose, PD as $\geq 25\%$ increase in size on stable or increased steroids, and stable disease as all other situations. Furthermore, the criteria incorporated clinical outcomes, requiring that patients be additionally neurologically stable or improved in order to qualify as PR or CR, and conversely that neurologic decline be categorized as PD. Importantly, the response by the Macdonald criteria required scans at least 1 month apart with reductions of greater than 50% without an increase in steroid use, in an attempt to identify sustained, significant reductions in tumor size independent of response to steroid (7). At the time, when some patients were followed by CT scans and even the MRI resolution was not what it is today, this stringent criterion was intended to eliminate the chance that the margin of error of tumor volume measurements would result in misclassification as a true

response. Due to the objectivity of the Macdonald criteria in determining the response to therapy, these criteria were widely accepted in different clinical trials to make comparisons across different therapeutic interventions. These criteria have also been extensively used in recent clinical trials for Response Assessment in Neuro-Oncology (RANO) (8).

In 2000, the International Working Party published new criteria, known as Response Evaluation Criteria in Solid Tumors (RECIST), aiming to simplify and standardize the evaluation of solid tumor treatment response. The RECIST criteria differed from the original WHO tumor response criteria by calling for unidimensional instead of bidimensional measurements to assess tumor burden, defining a minimum size for measurable lesions, and creating a limit of ten lesions to follow in the case of metastatic disease, with only five in a single organ. Several prospective studies validated the replacement of bidimensional with unidimensional measurements, which further translated well to phase II studies of solid tumors. A RECIST Working Group was formed to regularly update these criteria based on new evidence, and revised guidelines have included modifications such as assessing tumor size using the sum of the diameters of each lesion in a given target tissue. Based on these criteria, PR is defined as $\geq 30\%$ decrease in this sum; with PD defined as a 20% increase in sum requiring an absolute increase of 5 mm or appearance of a new lesion. The use of a unidimensional measurement and the summation of multiple lesions may have less relevance for intracranial malignancy in which the complex morphology of these tumors, and their tendency to infiltrate rather than forming new discrete lesions, limits the utility of the RECIST criteria. While these criteria have since been applied sporadically to high-grade glioma, it was ultimately designed with non-CNS solid-tumors in mind, and as a result has not been widely accepted by the neuro-oncology community (6,8).

While both the MacDonald and RECIST criteria have contributed to the standardization of evaluating tumor response, they both have notable limitations in the current treatment of high-grade glioma/GBM. Specifically, the MacDonald criteria is based entirely on enhancing tumor dimensions, which may be confounded in both directions by treatment-related enhancement changes, known as pseudoprogression (PsP), and alternatively by infiltrative disease beyond the areas of enhancement. The RECIST criteria, while useful for solid tumor malignancies, does not incorporate enhancement patterns or volume in its

Table 1 Summary of Response Assessment in Neuro-Oncology criteria for high grade glioma

Define measurable vs. non-measurable disease

Measurable disease: lesions with well-defined margins and uniformly enhancing areas measuring ≥ 10 mm in two perpendicular dimensions

Non-measurable disease: surgical resection cavities, cystic or necrotic regions of tumor on MRI unless these regions are surrounded by nodular enhancement measuring ≥ 10 mm

Identify and differentiate pseudoprogression (PsP) from true tumor progression when evaluating contrast enhancement following concomitant chemoradiation therapy (10)

Must include evaluation of T2/FLAIR signal changes during response assessment

Post-operative baseline MRI scan should be obtained with 24–48 h (not ≥ 72 h) following the procedure to minimize the confounding effects of surgery induced enhancement (11–14)

Evaluate changes in the requirement of steroid dose as an indirect marker of clinically significant tumor burden

Clinicians should continue to use their judgment to incorporate clinical assessments throughout treatment

Table 2 Current response assessment in neuro-oncology projects

Response Assessment in Neuro-Oncology (RANO) criteria for leptomeningeal disease (LMD)

RANO criteria for meningioma

Neurological Assessment in Neuro-Oncology (NANO)

RANO criteria for patient reported outcomes (PRO) measures

RANO criteria for seizure assessment

RANO criteria for response based on corticosteroids/
glucocorticoids dosage

assessment, which may be critical in the case of GBM. Given these shortcomings along with advancement in neuroimaging, it was deemed necessary to redefine the endpoint assessment criteria in Neuro-Oncology. A multinational working group was formed to re-evaluate and re-define these criteria, termed the RANO criteria (9).

RANO criteria for glioma

Based on contrast enhanced MRI, the RANO committee laid down the following criteria for response assessment which are summarized in *Table 1*.

The RANO committee is actively working to establish guidelines for end-point assessment that can further be applied beyond high-grade glioma (15,16), to patients with brain metastases (17,18) and low-grade gliomas (19) (*Table 2*). These guidelines will be discussed in detail in following sections.

Imaging and clinical criteria used for RANO assessment

MRI T1W gadolinium (Gd) contrast enhancing imaging

Based on T1W Gd-contrast enhancing images (slices 5 mm apart with 0 mm skip), measurable disease is defined as enhancing lesions with well-defined margins and two perpendicular diameters of ≥ 10 mm. As detailed previously, cystic and necrotic regions of the tumor or surgical cavity are considered non-measurable, unless they demonstrate wall enhancement that exceeds 10 mm. Lesions which can be measured in only one dimension, with ill-defined margins, or maximum dimension < 10 mm are also considered as non-measurable disease. Based on abovementioned criteria, patients with complete resection of enhancing tumor on post-operative scan can be considered only for studies looking at OS or PFS as endpoints, due to the lack of measurable imaging response to follow (9). Despite this, patients having undergone a complete resection can still be followed for recurrence, and thereby “progression” (20,21).

An additional challenge in assessing response based on contrast enhancement frequently arises in patients who have undergone investigational surgical interventions such as convection-enhanced delivery (CED) of therapeutic agents (gene or immune), chemotherapy wafers, and radiosurgery, which can result in changes in enhancement independent of tumor response (22,23). In these patients in particular, it becomes critical to differentiate between true and pseudo tumor progression. PsP often appears as a contrast-enhancing lesion on MRI, and is seen in up to 20–30% of

patients following concomitant chemoradiation therapy for GBM (particularly in MGMT methylated tumors) (10,24,25). These treatment-induced changes following chemoradiation appear to peak between 3 (26) and 6 months (27), which forms the basis of the RANO criteria stipulating a timeframe of 12 weeks. However, PsP can still occur outside of the stated window and remains a potential confounding variable affecting response assessment (28).

Although disease measurement using RANO criteria is similar to that described by Macdonald criteria (two-dimensional) and different from that described by RECIST criteria (one-dimensional) (7,9,29), various studies have shown strong correlation between these methods and tumor response (29–31). Two-dimensional measurement of tumor response has been widely adopted in clinical trials (20); yet there are intuitive advantages to 3D and volumetric tumor measurements in their ability to more effectively capture minor changes in the tumor dimensions following treatment, and to further quantify more subtle changes in non-measurable enhancing disease. The increased accuracy conferred by volumetric measurements becomes more apparent in the case of non-uniform tumors that take on complex shapes in a three-dimensional space, as in the case of intracranial tumors such as glioma, as well as tumors with mixed morphology including cysts, cavitation, and necrosis, and finally in multifocal or recurrent tumors (32). Another advantage of volumetric or 3D tumor measurement is that these measurements are independent of head position during image acquisition between serial follow up scans, which otherwise may lead to erroneous two-dimensional measurements (33). However, despite these benefits, volumetric assessment of tumor volumes is labor intensive and requires manual drawing of tumor volumes slice by slice on different software platforms, which may be challenging in routine clinical practice and perhaps more difficult to standardize (32,34). Nevertheless, with the inevitable ongoing advances in software platforms that streamline the measurement process, volumetric assessment of tumor response following treatment is likely to become the standard of care in near future.

MRI T2W/FLAIR imaging

An increasing use of anti-angiogenic therapeutic agents such as bevacizumab in patients with recurrent GBM (34,35) has led to several challenges in terms of response assessment on follow up imaging due to the impact of these agents on contrast enhancement, which unlike other therapies can

lead to an artificial reduction in enhancement (*Figure 1*). These anti-VEGF agents reduces the vascular permeability of abnormally leaky vessels in patients with GBM leading to a significant decrease in contrast enhancement on follow up imaging, known as pseudo response (36,37). This pseudoresponse led to a significant objective response rate (ORR) of 29–42% using bevacizumab on MR imaging (38,39), without a significant impact on OS in patients with high-grade glioma (39–41). This dissociation between imaging response and clinical response suggests that in these patients, enhancement is not a reliable marker for tumor burden.

Patients on anti-angiogenic therapy typically demonstrate this pseudo response for a minimum of 4 weeks on follow up MRI (9). Conversely, anti-angiogenic agents reduce the incidence of pseudo progression, and consequently any evidence of increased enhancement in patients on these agents can be considered true tumor progression (42). Furthermore, patients on anti-angiogenic therapy for GBM have a very different pattern of tumor recurrence or progression, being more infiltrative and non-enhancing (5–10%) on MRI than otherwise (40,43–48), although there is no evidence to suggest that this has an impact on overall outcomes in patients on anti-angiogenic therapy for GBM (29,48–53). Given these complex changes resulting from anti-angiogenic therapy, to assess tumor response and recurrence/progression in patients who are on anti-angiogenic therapy for recurrent high-grade glioma, it is prudent to look beyond the contrast enhancement on MRI images using T2/FLAIR images (39).

Based on these unique challenges and the complex enhancement changes resulting from treatment, RANO committee has crucially integrated T2/FLAIR imaging as a part of tumor response assessment criteria. Based on T2/FLAIR imaging, tumor progression is defined as a significant increase in the dimensions of non-enhancing lesion, which cannot be attributed to radiation related changes, ischemic injury, infection, demyelination, seizures, post-operative and other treatment related changes (9). However, despite these guidelines, it is often a challenge to differentiate between true tumor progression and treatment effects based on changes seen on T2W/FLAIR MRI images. This challenge is more pronounced in the setting of patients with recurrent GBM who have been previously treated with multiple treatment modalities such as surgery, chemotherapy and RT including stereotactic radiosurgery.

To address the issues that arises with non-tumor causes

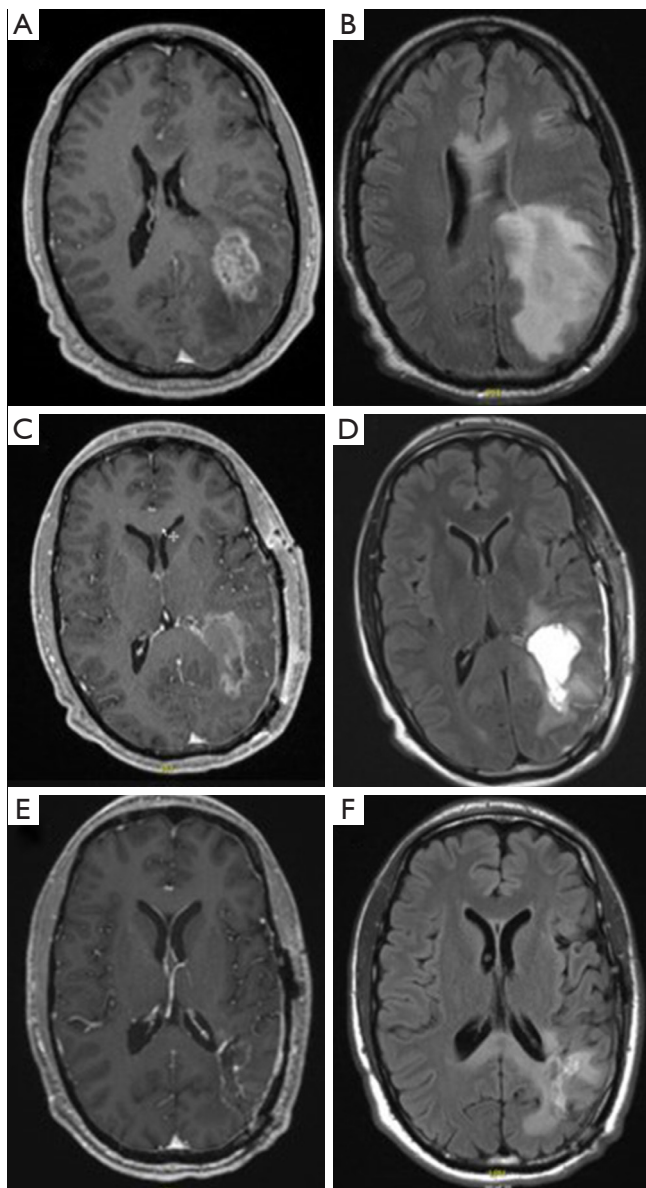


Figure 1 MRI images of a 48-year-old left handed male who developed symptomatic tumor recurrence following biopsy and concurrent radiotherapy/temozolomide for GBM. He subsequently underwent craniotomy and resection of the tumor mass. (A) MRI T1W with Gd contrast; (B) T2/FLAIR; (C,D) MRI performed 1 month after surgery was concerning for tumor progression on T2/FLAIR and he was started on bevacizumab; (E) follow up MRI at 3 months showed improvement in contrast enhancement with tumor progression, which would suggest a radiographic response. Yet, (F) there was evidence of progression on T2/FLAIR, which indicated progression per the RANO criteria. GBM, glioblastoma multiforme; Gd, gadolinium.

of T2/FLAIR changes, RANO investigators attempted to define changes pointing towards true tumor progression. Features such as involvement of the cortical ribbon, non-enhancing lesion beyond the radiation field, presence of mass effect, signal intensity between gray matter and vasogenic edema, non-uniform signal intensity, and lack of typical finger-like projections suggestive of edema are advocated as findings more accurately pointing towards true tumor progression (47). The RANO investigators further aimed to define which changes are considered significant in an effort to elucidate the difference between tumor and non-tumor causes of T2/FLAIR changes. The RANO committee has also attempted to standardize methods of quantification on T2/FLAIR images to facilitate comparison on serial follow-up imaging (54-56). Techniques such as quantitative maps of differential T2 relaxation times between the normal brain, edematous brain and infiltrative tumor have been generated prior to and during therapy in order to subtract out the non-specific causes of signal change to identify areas of true tumor progression (57,58). Voxel-based, pre- and post-T2 subtraction analysis displayed in color-coded maps have been utilized to define the extent of true tumor progression as well as to quantify the effect of antiangiogenic treatment on edema demonstrated on T2/FLAIR images (54,56). However, further studies are needed to demonstrate consistent correlation between changes on the T2 relaxation maps and its impact on survival in order to avoid over or under-estimation of treatment effect based on these newer methods.

Positron emission tomography (PET) scan

Given the limitations of MRI imaging in the assessment of tumor response following anti-angiogenic treatment detailed above, ^{18}F -fluorodeoxy-glucose (^{18}F -FDG) PET, ^{18}F -fluorothymidine (^{18}F -FLT) PET and ^{18}F -fluoroethyl-L-tyrosine (^{18}F -FET) PET scans have been explored in various studies as an alternate method to evaluate tumor response to various antiangiogenic therapies. ^{18}F -FLT-PET scans have been shown to identify tumor response earlier than standard anatomical contrast enhanced MRI and are also predictive of both OS and PFS (59). Similarly, ^{18}F FDOPA PET scans have significant correlation between changes in uptake during anti-angiogenic therapy and OS (60).

The RANO working group in association with European Neuro-Oncology society (EANO) recently published guidelines regarding the clinical use of PET in patients

with glioma (61). Amino acid based PET scans (FET and ^{18}F DOPA) allow for increased tumor differentiation, target definition and follow up response when compared to glucose based PET scan (^{18}F -FDG). Although amino acid PET scans have been shown to have better sensitivity, specificity and accuracy in differentiating glioma and inflammatory tissues compared to ^{18}F -FDG-PET scan, both modalities have notable overlap in uptake values in low and high-grade glioma. However, overall, there is increased uptake in higher-grade glioma (WHO III/IV) compared to lower grade lesions (WHO II). Dynamic analysis of ^{18}F -FET PET scans can augment discerning between high and low grade gliomas. Similar to other PET modalities, ^{18}F DOPA PET scan has also been found to be useful in assessing response in patients on antiangiogenic therapy. Finally, amino acid PET improves the diagnostic accuracy of pseudo progression, progression and radiation necrosis (61).

Despite the evident usefulness of these modalities as an adjunct in assessing the tumor response, the widespread applicability of these PET scans are often limited by availability, lack of trained personnel and cost associated with these procedures.

Standardized brain tumor imaging protocol (BTIP)

A recent meeting hosted by the National Cancer Institute which included representatives from the FDA, multiple brain tumor interest groups, radiologists, and a select group of Neuro-Oncology experts yielded recommendations for a standardized BTIP intended to be used in multicenter therapeutic studies to evaluate the efficacy of treatments in patients with malignant brain tumors (62). The standardization in imaging protocol more readily allows for pooling and rapid comparisons of data from the multiple centers participating in brain tumor clinical trials. Recommendations included a minimum of pre contrast 3DT1w (IR-GRE), axial 2D FLAIR (TSE), axial 2D DWI and post contrast axial 2DT2w (TSE), 3DT1w (IR-GRE) for 1.5 T and 3 T MRI scans. These recommendations advocated additional 2DT1w, GRE T2 scans, etc. on a tailored basis (62). This protocol has since been rapidly incorporated in the majority of new clinical trials involving malignant glioma. Currently, there are no guidelines for acquiring diffusion tensor imaging (DTI) in brain tumor trials. In general, 30–32 diffusion directions with one b-value ($1,000 \text{ s/mm}^2$) and minimizing TE (60–100 ms) yield reproducible fractional anisotropy (FA) and apparent diffusion coefficient (ADC) images (63,64).

Role of corticosteroids/glucocorticoids

Glucocorticoids have been used in routine clinical practice to reduce tumor-associated edema and improve neurological functions in patients, particularly in those with newly diagnosed or recurrent high-grade gliomas (1,38). Dexamethasone has been shown to decrease tumor-associated edema in a dual fashion by reducing the expression of vascular permeability factor (VPF) by the tumor cells, while also minimizing the ability of the vasculature to respond to these vasoactive factors (65). *In vitro* studies also have demonstrated that glucocorticoids inhibit the proliferation, migration and invasion of glioma (66). However, despite these benefits, given the well-described morbidity and intolerance to long-term steroid use, a reduction in the requirement of steroid dose during treatment is often considered as a favorable response to the given treatment modality (9).

In the BRAIN study involving patients with recurrent GBM treated with bevacizumab, the authors attempted to evaluate the use of corticosteroids during treatment. Response required $\geq 50\%$ reduction in corticosteroid dose for $\geq 50\%$ of the time while on study medication or complete discontinuation of corticosteroids for $\geq 25\%$ of time (67), resulting in sustained reduction in 30.2% of patients with 16.3% of patients sustained off steroids altogether while on bevacizumab. Another Phase III randomized, partially blinded clinical trial (REGAL) compared treatment with cediranib monotherapy, lomustine monotherapy, or combined treatment and reported the results as a function of corticosteroid use. In this study, both cediranib monotherapy and combination therapy (cediranib plus lomustine arm) resulted in a significant decrease in steroid use (26% and 23% reduction from baseline respectively) compared to 5% increase seen with lomustine monotherapy alone (68). The results of such studies emphasize the importance of incorporating the use of steroids as surrogate for clinical response. The RANO working committee is in the process of defining the criteria for steroid responders (complete and PR) in order to formulate formal RANO recommendations.

Assessment of neurological status

The importance of a thorough clinical neurological examination in evaluating the functional status of the patient and their overall health cannot be overemphasized (69). Acknowledging this, the RANO working committee

included clinical status as a component of response assessment to the given treatment modality. Various assessment measures such as Karnofsky Performance Scale (KPS), Medical Research Council scale for Muscle Strength Council (MRC), common terminology criteria for adverse events (CTCAE), patient reported outcomes (PROs) [European Organization for Research and Treatment of Cancer Brain tumor module (EORTC-BN), MD Anderson Symptom Inventory (MDASI)] and neurocognitive test battery (Hopkins Verbal Learning Test-Revised: HVLTR), Trail making test A and B and multilingual aphasia examination and oral word association test) have been utilized (18).

Unlike patient reported subjective assessment methods, patient performance on these neurocognitive scales is a reliable measure to assess and compare the overall neurological functioning of patients across different clinical studies (70,71). There are, however, several challenges in terms of applicability of these objective neurocognitive measures, such as variability in clinical presentations, frequency of these tests and variability in different studies, rapid disease progression in patients with recurrent GBM, patient compliance, strict adherence to protocol, floor and ceiling effects among different tests and comparability among these tests (18).

Taking into account these logistical issues, and in an attempt to create a standardized assessment protocol, the RANO committee has proposed that clinical trials should include a pre specified assessment schedule throughout the study, baseline cognitive assessments, measures to ensure patient and investigators compliance and adherence to the protocol, as well as protocols to stratify the patients based on their performance on these neurocognitive scales. It would be practical to perform these assessments in conjunction with follow-up imaging to minimize the visit burden to the patient and maximize compliance.

Neurological assessment in neuro-oncology (NANO)

The NANO working group created an objective scale to better assess clinical response and disease progression in an effort to generate consistency between future studies. The NANO scale is based on clinical assessment of domains such as level of consciousness, behavior, language, facial strength, visual fields, strength, sensation, ataxia (upper extremity) and gait. These domains are evaluated on a scale ranging from zero to three, with zero representing normal and three representing grossly abnormal. This scale is intended

to be integrated into the standardized RANO criteria and to complement the evaluation of MRI progression with clinical outcome measures including quality of life (QOL), neurocognitive functions, system burden inventories, in order to create a more comprehensive picture of treatment outcome. In this scale, response requires significant improvement defined as ≥ 2 level change in at least one domain, without concomitant worsening in other domains. Neurological progression is defined as significant worsening with ≥ 2 level change in any one domain, or change to the highest score in that same domain. Stable disease encompasses those that do not meet criteria for either response or progression, while patients in whom there are limitations on the ability to perform an accurate neurologic assessment are classified as non-evaluable.

An international prospective study used the NANO scale domains during a scheduled office visit as a secondary outcome in an attempt to determine the variability between observers and to assess the practicality of performing these assessments. This study has reported the inter-observer agreement ranging between 90.7% and 99.5% (moderate to substantial strength of agreement) across various neurological domains in 220 patients (unpublished data, SNO meeting RANO update 2016). The group concluded based on these findings that the NANO scale can be easily incorporated into clinical practice and can reliably be performed not only by neurologists, but by other physicians as well. Currently, the NANO scale is included as an exploratory end-point in various phase I and II clinical trials in patients with GBM, brain metastasis and PCNSL.

RANO criteria for seizure assessment

Seizure outcome definitions based on the International League against Epilepsy (ILAE) (72) classification range from seizure freedom with no auras (Score 1) to greater than 100% increase from baseline seizure with or without auras (Score 6) (73). Given the propensity of certain tumors to cause seizures, particularly when enlarging or recurring, seizure control has been proposed as an outcome measure in determining treatment response in clinical trials of patients with low-grade glioma (74). This assessment further incorporates a variety of health related QOL and symptom burden scales (Fact-Br, BN20 and MDASI-BT) that emphasize symptoms and neurologic function (74). Seizure frequency is evaluated prior to the initiation of treatment (12 months to the most recent 3 months) and following treatment and stratified in 10% decrements (classes 4 and 5)

or increments (classes 5 and 6) compared to baseline. Rare seizures are given a class 3 score. A composite score (2 to 19) is then calculated incorporating the seizure classification score (1 to 3), frequency score, ILAE outcome score (1 to 6) and MD Anderson symptom inventory score (MDASI, 0 to 10) (74). The composite score is then used to define CR as patients who are completely seizure free, while PR requires at least one level improvement on the outcome scale compared to baseline. The authors have proposed a pilot trial to assess the validity of this seizure assessment as a tool for measuring outcomes in conjunction with clinical assessment in patients with brain tumors.

RANO criteria for PRO measures

The objective of this international multidisciplinary working committee is to create standard PRO criteria in patients with a variety of intracranial tumors (glioma, brain metastasis meningioma and CNS lymphoma). These PROs are based on several subjective measures such as clinical symptoms, functions and health related QOL measures from patient's perspective. They are further tailored to the type of study being performed. This committee works with the other RANO committees as well as external committees in order to generate study design recommendations that take into account PROs. In this capacity this group aims to systematically review the use of PRO measures in prior brain tumor studies and to review the validity and reliability of using these measures in order to create standardized guidelines for using PRO measures in clinical trials for brain tumors (75).

Clinical application of RANO criteria for gliomas

With regard to end-points for response assessment to evaluate therapeutic efficacy, parameters such as ORR, OS and progression free survival (PFS) have been used traditionally in various studies.

ORR is an early end-point based on the radiological response and is linked to the direct therapeutic effect of the modality (16,76). The advantages of using ORR as the end-point include that ORR is not affected by the natural history of the disease and it remains the fastest criterion to assess response in early phase II clinical trials. However, as discussed previously, imaging results are fraught with confounding effects of treatment itself, as well as the inherent differences in tumor enhancement characteristics. Furthermore, some agents, including targeted therapies,

have the intended effect of achieving tumor control rather than regression. Isolated imaging-based metrics for outcomes would be biased against such therapies, which may otherwise have significant value. Blinded centralized radiologic review is a useful strategy to address these methodological issues including bias, but may not be feasible or cost-effective for phase II trials. This highlights the need for a multi-modal assessment of outcome.

OS is most frequently used as an end-point in Neuro-Oncology practice and clinical trials and is often considered as gold standard (76) as measurements are simple and precise. OS as an end-point is particularly useful in patients with PD such as GBM with relatively rapid recurrence and shorter survival time. Improvement in OS in such patients can be attributed to the therapeutic efficacy; however, this end-point is often affected by various concomitantly used salvage therapies and therefore need to be cautiously interpreted. Also variability in terms of inclusion criteria, performance level of patients during enrollment, number and types of salvage therapies used made comparison with historical controls using OS as end point challenging (16). Therefore to circumvent these issues, using OS at a defined time period along with standardizing various salvage therapies made it possible to compare OS with historical controls. However, PFS is usually preferred for such comparisons. PFS has several advantages over OS, including an attenuated time to event, potentially larger effect sizes, and outcomes independent of salvage therapy use (16,76). While PFS is not clearly a surrogate marker of OS, PFS at fixed time points (such as PFS 6 months) correlates well with OS based on previous studies (77-79). Despite this, the definition of PFS depends once again on imaging-based outcomes, lending it to the same inherent issues as previously outlined.

Current state of RANO in the assessment of brain tumor response

RANO for measuring response of high-grade gliomas

Given the limitations of the above criteria, the development of the RANO criteria attempts to circumvent some of these issues by including metrics which address both "measurable" and "non-measurable" lesions, in a time frame that minimizes the influence of treatment related effects and steroids while emphasizing durable (>4 weeks) outcomes. In this manner, RANO builds upon the positive elements of prior criteria while expanding applicability to the complex assessment of GBM response.

The inclusion of “non-measurable” disease in the RANO criteria is a significant change from prior proposed criteria. A recent study assessed the RANO criteria using outcome data of patients with recurrent GBM from a prospective randomized phase II trial (AVF3708) to determine the influence of these added measurements on assessment of ORR and PFS compared to the old Macdonald criteria (80). In this study, the addition of T2/FLAIR assessment by RANO resulted in statistically significant reductions in median PFS (28%) and ORRs, with a sustained correlation between progression and survival. The T2/FLAIR assessment resulted in earlier detection of progression in a subgroup of patients leading to this reduction, with detection of at least 35% of patients with non-enhancing tumor progression that would not have met progression criteria under Macdonald (80).

One concern regarding the RANO criteria has been the use of 2D measurements over volumetric measurements. A recent study from the randomized controlled phase II BELOB trial evaluating bevacizumab, lomustine, and combination therapy studied 2D *vs.* volumetric methods for response assessment using OS as the primary endpoint. This study compared 2D RANO with assessment by contrast-enhancing volume, subtraction volume, contrast enhancing and FLAIR volume, and subtraction and FLAIR volume. At second follow-up, only results from the RANO criteria and combination contrast/FLAIR analysis were sufficiently reliable (power >80%). Volumetric methods, with or without subtraction, did not provide significant improvement as a prognostic marker in bevacizumab-treated patients. Notably, the 2D RANO assessment was performed by “raters with extensive clinical experience”, which was proposed by the authors as a possible reason for enhanced performance of the 2D method in comparison with prior studies (81).

Current challenges in assessing response to therapy in patients undergoing resection of recurrent tumors

A major challenge with the applicability of RANO criteria is the ability to differentiate true tumor progression from pseudo progression (treatment after-effects) due to lack of reliable imaging modalities. As per the RANO criteria, true tumor progression within 12 weeks following chemoradiation/RT is diagnosed only if there is obvious tumor seen on histopathology examination. There are questions regarding period of 12 weeks as pseudo

progression can occur after 12 weeks as well, histopathology definition of unequivocal evidence and cases in which histopathology is negative for tumor also need to be defined. Intratumoral heterogeneity with a mixture of tumor and treatment effects coupled with lack of defined diagnostic criteria in patients with recurrent tumor creates significant challenges for neuropathologists. In addition, biopsy from different regions of the same tumor may show different pathology and therefore sampling of the appropriate portion of the tumor becomes highly relevant in the diagnosis. Incorporating immunohistochemical markers (cell proliferation, inflammation, gliosis, etc.) with histopathology analysis, and validating correlation between histopathology, radiographic and clinical outcome are steps forward in overcoming the challenges associated with diagnosis and management of patients with recurrent glioma. These challenging issues are likely to be addressed with increasing experience of RANO criteria in future clinical trials.

Summary

Availability of effective and reliable criteria to assess response of high-grade glioma to various treatment modalities is critical in Neuro-Oncology practice not only to evaluate the role of currently available therapeutic options but also to assess and compare newer treatment modalities across different clinical trials. The guidelines laid down by the RANO working group opened the horizons for exploring novel response assessment tools including imaging techniques. The RANO committee is actively working to incorporate standardized neurological and functional assessment scales into the standard RANO criteria, to integrate imaging, clinical and functional response measures. Future RANO versions shall incorporate some of the rapid developments in this area towards a uniform and standardized assessment scheme, which can be integrated in future clinical trials. Various newly introduced RANO criterions shall undergo further refining and modification in the process of standardization, as these criteria are incorporated in future clinical trials. RANO is also in the process of developing standardized criteria to assess response in patients with leptomeningeal disease, meningioma and a variety of pediatric brain tumors.

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None.

Footnote

Conflicts of Interest: MA Vogelbaum is co-founder and a member of the steering committee of RANO. He receives no compensation for this activity. MA Vogelbaum is co-founder of Infuseon Therapeutics and has patent interests in drug delivery devices licensed to Infuseon. The other authors have no conflicts of interest to declare.

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