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Response Assessment in Neuro-Oncology Clinical Trials

Patrick Y. Wen, Susan M. Chang, Martin J. Van den Bent, Michael A. Vogelbaum, David R. Macdonald, and Eudocia Q. Lee

ABSTRACT

Development of novel therapies for CNS tumors requires reliable assessment of response and progression. This requirement has been particularly challenging in neuro-oncology for which contrast enhancement serves as an imperfect surrogate for tumor volume and is influenced by agents that affect vascular permeability, such as antiangiogenic therapies. In addition, most tumors have a nonenhancing component that can be difficult to accurately quantify. To improve the response assessment in neuro-oncology and to standardize the criteria that are used for different CNS tumors, the Response Assessment in Neuro-Oncology (RANO) working group was established. This multidisciplinary international working group consists of neuro-oncologists, medical oncologists, neuroradiologists, neurosurgeons, radiation oncologists, neuropsychologists, and experts in clinical outcomes assessments, working in collaboration with government and industry to enhance the interpretation of clinical trials. The RANO working group was originally created to update response criteria for high- and low-grade gliomas and to address such issues as pseudoresponse and non-enhancing tumor progression from antiangiogenic therapies, and pseudoprogression from radio-chemotherapy. RANO has expanded to include working groups that are focused on other tumors, including brain metastases, leptomeningeal metastases, spine tumors, pediatric brain tumors, and meningiomas, as well as other clinical trial end points, such as clinical outcomes assessments, seizures, corticosteroid use, and positron emission tomography imaging. In an effort to standardize the measurement of neurologic function for clinical assessment, the Neurologic Assessment in Neuro-Oncology scale was drafted. Born out of a workshop conducted by the Jumpstarting Brain Tumor Drug Development Coalition and the US Food and Drug Administration, a standardized brain tumor imaging protocol now exists to reduce variability and improve reliability. Efforts by RANO have been widely accepted and are increasingly being used in neuro-oncology trials, although additional refinements will be needed.

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INTRODUCTION

Despite extensive efforts, progress in developing more effective therapies for tumors of the CNS has been disappointingly slow. There are many reasons for this lack of progress, including tumor characteristics, such as intrinsic resistance to most available therapies, molecular heterogeneity, and redundant signaling pathways; lack of predictive preclinical models; poor passage of most therapeutic agents across the blood–tumor barrier; and a relative lack of interest from pharmaceutical companies because of the relatively small patient population and the poor record of success to date.[1] Over the past decade, there has also been a growing consensus that the lack of reliable and widely accepted response criteria and clinical trial end points is another limiting factor in identifying more effective therapies in neuro-oncology.[2,3] This review summarizes the current efforts to improve response assessment in neuro-oncology clinical trials, including those led by the international Response Assessment in Neuro-Oncology (RANO) working group,[4,5] as well as some of the remaining challenges.

DEVELOPMENT OF GUIDELINES AND RESPONSE CRITERIA

The process of developing guidelines and response criteria within each RANO working group is detailed in their respective publications.[4,6-9] In brief, each working group is an international, multidisciplinary effort that consists of neuro-oncologists, medical oncologists, neurosurgeons, radiation oncologists, neuropsychologists, neuropathologists, and experts in quality-of-life measures who work in collaboration with government

and industry. After the completion of literature review and critique, each working group convened to formulate consensus proposals for response criteria through an iterative process. Subsequent efforts are focused on incorporating the response criteria into clinical trials and validating them.

HIGH-GRADE GLIOMAS

High-grade gliomas (HGGs) account for the majority of malignant primary brain tumors.[10] Although response assessments in clinical trials in oncology are based on one-dimensional tumor measurements as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria,[11] until recently, tumor measurements in neuro-oncology were based on two-dimensional measurements that used the criteria proposed in 1990 by Macdonald et al.[12] These criteria determined response by using enhancing tumor area—the product of the maximal cross-sectional enhancing diameters—together with changes in the neurologic status of patients and corticosteroid use.[12] A number of studies have compared RECIST criteria with two-dimensional, three-dimensional, and volumetric measurements and have found generally good concordance between methods.[4,13-15] Nonetheless, because of concerns regarding the irregular shapes of such tumors as glioblastoma, the Macdonald Criteria remained the most widely used response criteria.

Over time, it became apparent that the Macdonald Criteria had a number of important limitations.[4,16] It did not provide guidance on the definition of progression that was necessary for entry into clinical trials, measurability of disease, definition of target lesions, or the handling of patients who were suspected of experiencing pseudoprogression—the transient increase in contrast enhancement observed in 10% to 30% of patients with glioblastoma immediately after treatment with chemoradiotherapy[17] (Fig 1A). The Macdonald Criteria also did not take into account the pseudoresponse observed with antiangiogenic therapies, such as bevacizumab, that rapidly reduce vascular permeability and contrast enhancement.[4] These agents can produce a marked decrease in contrast enhancement as early as 1 to 2 days after the initiation of therapy that does not necessary reflect a true reduction of tumor burden. Of most importance, the Macdonald Criteria measured only contrast-enhancing tumor and did not take into account nonenhancing disease. This is especially problematic for WHO grade II and III gliomas. In addition, up to 40% of patients who were treated with agents, such as bevacizumab, that reduce vascular permeability develop progressive increase only in T2/fluid-attenuated inversion recovery (FLAIR) signal and not contrast enhancement as the initial manifestation of progression, a phenomenon termed nonenhancing tumor progression[18] (Fig 1B).

To address the limitations of the Macdonald Criteria, the RANO working group proposed updated response criteria for HGGs in 2010.[4] These RANO Criteria are summarized in Table 1. The RANO criteria built on the Macdonald Criteria by using two-dimensional tumor measurements, but included a definition of progression for patients being considered for enrollment in clinical trials (≥ 25% increase in the product of perpendicular diameters compared with baseline or best response); definitions for measurable disease (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); and allowance of up to five target lesions. To address pseudoprogression, the RANO criteria recommended that within the first 12 weeks after irradiation, patients should be excluded from clinical trials for recurrent disease unless progression is clearly outside the radiation field or there was clear histologic documentation of progression. To account for pseudoresponse after antiangiogenic therapies, patients who achieved partial or complete responses required a confirmatory scan at least 4 weeks later to ensure that responses were sustained. In addition, the RANO criteria defined progression not only as a 25% increase in contrast-enhancing area over baseline or best response, but also included any significant enlargement of nonenhancing T2/FLAIR signal on magnetic resonance imaging (MRI) that was attributed to tumor growth. Given the difficulty of measuring nonenhancing disease progression, no objective criteria were proposed—a significant limitation of the RANO criteria. Of importance, there were also recommendations for dealing with equivocal imaging changes, which allowed patients to stay on study with a repeat scan in ≥ 4 weeks. If progression is subsequently confirmed, the time of progression is backdated to the time point at which the issue was first suspected. This prevents patients from being discontinued prematurely from studies when imaging findings are equivocal. Since its introduction, the RANO criteria have been adopted in the majority of clinical trials of HGG.

In 2014, the Jumpstarting Brain Tumor Drug Development Coalition and the US Food and Drug Administration conducted a workshop to evaluate clinical trial neuroimaging end points.[2,19-21] There was general consensus that the RANO criteria was reasonably reproducible and accurate, despite some limitations. Further work was deemed necessary to define the value of including T2/FLAIR progression in the definition of progression as well as the role of advanced MRI techniques. Of most importance, it highlighted the need, in the field, to standardize neuroimaging to reduce variability and increase reliability. This led to the development of a standardized brain tumor imaging protocol that is increasingly being used in neuro-oncology clinical trials, especially in Europe and North America.[22,23]

A number of outstanding issues regarding response assessment in HGG remain to be addressed. These include the optimal management of pseudoprogression from chemoradiation and immunotherapies, determination of the value of T2/FLAIR assessment and volumetric imaging and T1 subtraction maps, and establishment of a more objective score for the assessment of clinical deterioration.

Pseudoprogression

The ability to differentiate pseudoprogression as a result of radiochemotherapy from true tumor progression remains a significant challenge.[24,25] Advanced MRI techniques, such as dynamic susceptibility contrast (perfusion) and dynamic contrast-enhanced MRI,[26-28] as well as amino acid positron emission tomography,[29,30] have shown promise but additional work is necessary to standardize these approaches and improve their sensitivity and specificity. In addition, issues of cost and accessibility will need to be addressed before they can be widely adopted in clinical trials. Given the difficulty in determining pseudoprogression from progression
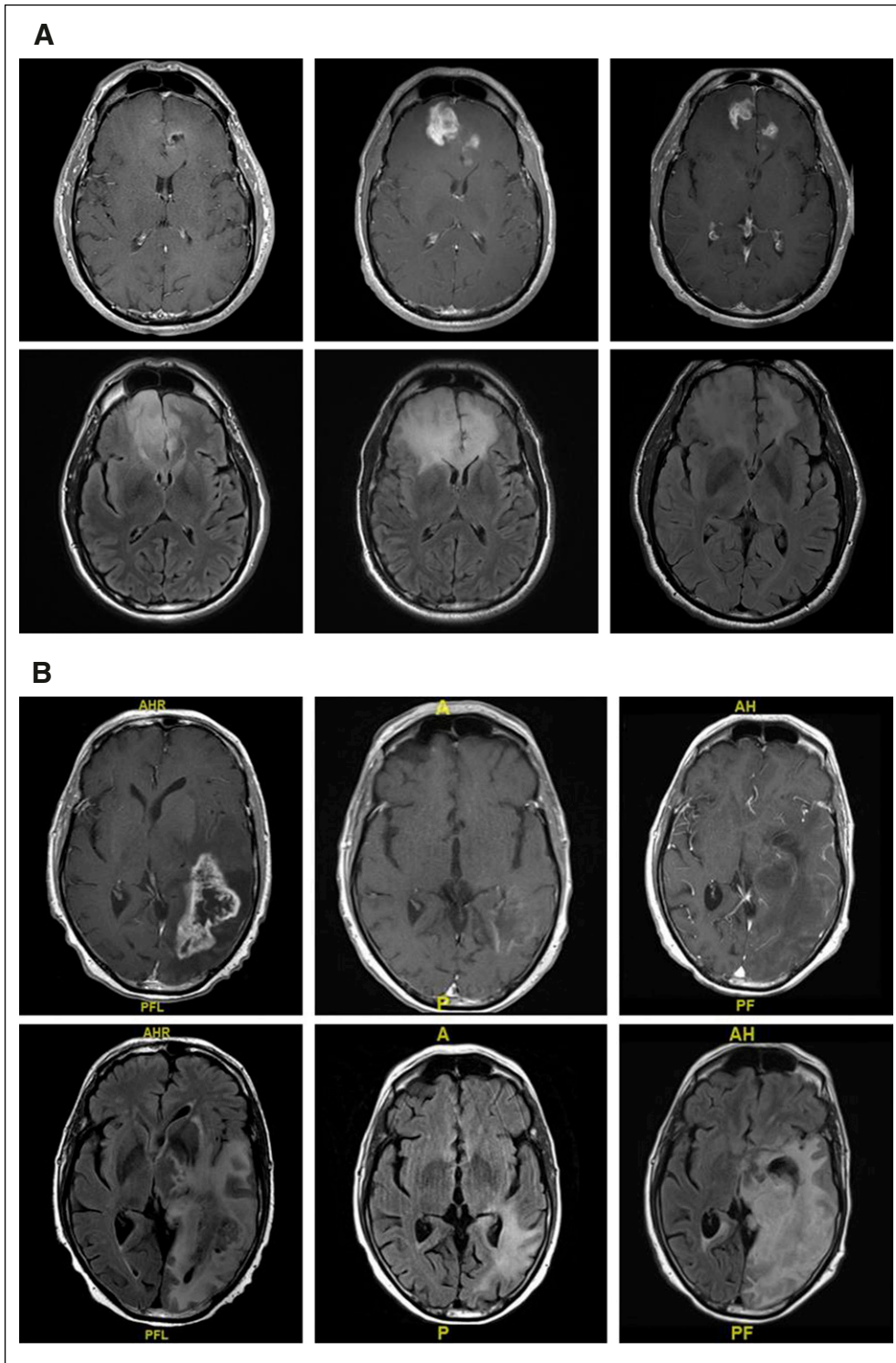
Fig 1. (A) T1 postcontrast and fluid-attenuated inversion recovery (FLAIR) images before (left), 2 months after (middle), and 3 months (right) after completing radiation and concurrent temozoloimde in a patient with a newly diagnosed glioblastoma (GBM). The extent of enhancement initially increases, but then improves with time to suggest that the initial post-treatment changes represented pseudoprogression. (B) T1 postcontrast and FLAIR images before (left), after one cycle (middle), and after five cycles (right) of bevacizumab in a patient with recurrent GBM. Although enhancement remains nonmeasurable after five cycles of treatment, the extent of FLAIR only continues to expand in this case of nonenhancing disease progression. (C) T1 postcontrast and FLAIR images before (left), 1 month after (middle), and 3 months (right) after completing radiation and concurrent nivolumab in a patient with a newly diagnosed GBM. Tumor resection pathology revealed almost all treatment effect.

on the first MRI scan after chemoradiotherapy, Ellingson et al[31] have proposed that, instead of using the postoperative MRI as the baseline scan, the baseline scan should be the first postradiation MRI. If the next scan shows progression and the patient is clinically stable, then the patient will remain on treatment and only be taken off study if the subsequent scan confirms progression. This approach reduces the challenges posed by pseudoprogression on the first postradiation scan but requires validation.

The recent introduction of immunotherapies in neuro-oncology has led to the realization that a subset of patients who receive these therapies can also develop pseudoprogression, which is characterized by transient enlargement of the tumor or the appearance of new lesions that ultimately regress[32] (Fig 1C). To address this phenomenon in neuro-oncology, the immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria were recently proposed[33] (Appendix Fig A1, online only). These criteria
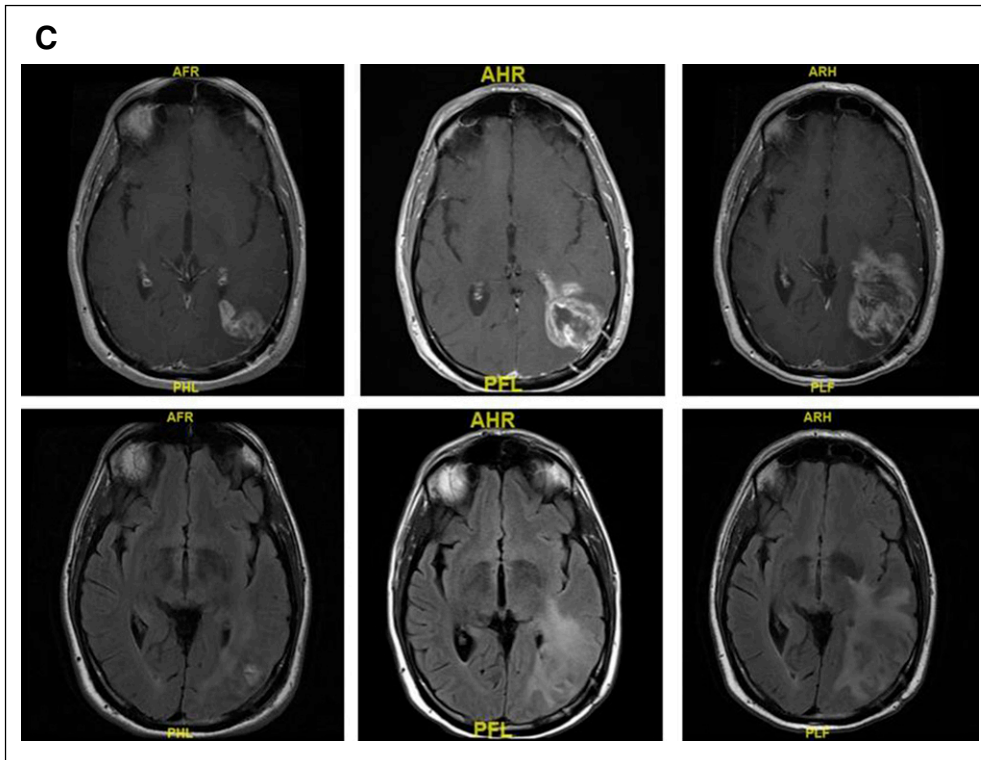
Fig 1. (Continued)

were based on the immune-related response criteria that were proposed for systemic cancers as well as on attempts to prevent patients in clinical trials from being discontinued prematurely as a result of the experience of pseudoprogression by requiring that progression be confirmed.[32] The iRANO criteria suggest that within the first 6 months of initiating an immunotherapy—when pseudoprogression is most likely to occur—if MRI scans show radiologic progression (a 25% increase in area or appearance of new lesions), provided the patient is clinically stable, the patient can stay on treatment and be observed closely with repeat MRI scans in 3 months or sooner. If the subsequent scans confirm progression, the date of progression will be backdated to the date of initial progressive disease. The iRANO criteria have been incorporated into a number of ongoing immunotherapy trials of patients with brain tumor, which has allowed its value to be assessed.

T2/FLAIR

Incorporation of T2/FLAIR changes in the determination of progression was one of the major changes proposed by the RANO criteria for HGG; however, because of the difficulty of measuring T2/FLAIR accurately, no objective criteria were proposed. Instead, worsening of T2/FLAIR was a subjective assessment that is characterized by a significant increase in T2/FLAIR nonenhancing lesion that is felt to be a result of tumor growth and not because of comorbid events—for example, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects.[4] As it is often difficult to differentiate T2/FLAIR changes that result from tumor growth from other causes, there is significant interobserver variability and unclear benefit, which has

led to some proposals to eliminate this aspect of the RANO criteria.[31,34] For agents that generally do not affect vascular permeability, such as most cytotoxic agents and many targeted agents, nonenhancing tumor progression is unlikely and the measurement of T2/FLAIR is likely unnecessary. With immunotherapies for which an inflammatory component that results in increased T2/FLAIR is likely, using T2/FLAIR to determine tumor progression is probably inappropriate; however, when antiangiogenic agents, such as bevacizumab, are being evaluated, up to 40% of patients experience progression initially with nonenhancing disease,[18] and determination of progression using the RANO criteria results in significantly shorter progression-free survival compared with the Macdonald Criteria.[35] T2/FLAIR may potentially still have a role for this class of agents that affect vascular permeability and for grade III gliomas. A number of studies are ongoing that attempt to better quantify T2/FLAIR[36] as well as to assess its value in response determination with respect to survival outcomes and its ease of use and reproducibility.

Volumetric MRI and T1 Subtraction Maps

Given the irregular shape of brain tumors and the difficulties in evaluating tumors using two-dimensional measurements, there has been longstanding interest in using volumetric imaging, and, more recently, T1-subtraction maps, to more accurately determine T1 contrast-enhancing tumor[37,38]; however, whereas some studies have failed to show a benefit of volumetric imaging, these were not performed with standard protocols, and additional studies will be required to determine whether the additional cost and complexity of volumetric measurements will enhance response assessment.[13,14,39]

Table 1. Criteria for Response Assessment Incorporating Magnetic Resonance Imaging and Clinical Factors

Criterion	CR	PR	SD	PD
T1-Gd +	None	≥ 50% ↓	< 50% ↓ to < 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†
Summary of HGG response criteria	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 achieve CR; the best response possible is SD.	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 scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically.	Requires all of the following: Does not qualify for CR, PR, or progression; stable nonenhancing (T2/FLAIR) lesions on the 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 SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.	Defined by any of the following: ≥ 25% increase in the 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, etc) 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. Modified with permission Wen et al.[4] American Society of Clinical Oncology. All rights reserved.

Abbreviations: ↓, decrease; ↑, increase; CR, complete response; FLAIR, fluid-attenuated inversion recovery; HGG, high-grade glioma; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease; T1-Gd +, T1 postgadolinium.

*Progression occurs when this criterion is met.

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

NEUROLOGIC ASSESSMENT

Although response rate, progression-free survival, and overall survival are well-established end points, there is increasing recognition of the importance of clinical outcome assessments that help measure the benefits of treatments on the basis of patients' quality of life, neurocognitive status, or function. Clinical status is a criterion for the proposed response assessment in several RANO efforts, including those for HGG,[4] low-grade glioma (LGG),[6] brain metastases,[7] and leptomeningeal disease.[8] Whereas clinician-reported measures, such as Karnofsky performance status, are commonly used in clinical trials and correlate with overall survival, Karnofsky performance status is not a sensitive or specific measure of response to treatment[40] and may not accurately capture the neurologic status of a patient.

To this end, the Neurologic Assessment in Neuro-Oncology (NANO) working group developed a more objective, quantifiable proxy for clinical status in patients with brain tumors.[9] NANO is

a simple neurologic assessment conducted and reported by a trained health care professional who evaluates the patient in nine domains: gait, strength, upper extremity ataxia, sensation, visual fields, facial strength, language, level of consciousness, and behavior. Each domain contains a score from 0 to 3 or 0 to 2, depending on the domain, with higher scores indicating worse neurologic function (Table 2). The cumulative score can be compared over time to determine whether clinical status is stable, better, or worse as part of the response assessment. In pilot studies, NANO is associated with high interobserver agreement.[9] The value of NANO is being determined in a number of trials that have incorporated this tool.

In conjunction with the RANO neurologic assessment working group, the RANO leptomeningeal metastases (RANO-LM) working group has modified NANO for patients with LM to be used as part of the response assessment.[8] Ten domains are included: gait, strength, sensation, vision, eye movements, facial strength, hearing, swallowing, level of consciousness, and behavior. Similarly, each domain is scored from 0 to 3 or 0 to 2 on

Table 2. Neurologic Assessment in Neuro-Oncology Scale to Assess Neurologic Function for Integration Into Response Assessment in Neuro-Oncology Criteria

Domain	Score			
	0	1	2	3
Gait	Normal	Abnormal but walks without assistance	Abnormal and requires assistance (companion, cane, walker, etc)	Unable to walk
Strength	Normal	Movement present but decreased against resistance	Movement present but none against resistance	No movement
Ataxia (upper extremity)	Able to touch finger to nose without difficulty	Able to finger to nose touch but difficulty	Unable to touch finger to nose	NA
Sensation	Normal	Decreased but aware of sensory modality	Unaware of sensory modality	NA
Visual fields	Normal	Inconsistent or equivocal partial hemianopsia (≥ quadrantanopsia)	Consistent or unequivocal partial hemianopsia (≥ quadrantanopsia)	Complete hemianopsia
Facial strength	Normal	Mild or moderate weakness	Severe facial weakness	NA
Language	Normal	Abnormal but easily conveys meaning to examiner	Abnormal and difficulty conveying meaning to examiner	Abnormal; if verbal, unable to convey meaning to examiner; or nonverbal (mute/global aphasia)
Level of consciousness	Normal	Drowsy (easily arousable)	Somnolent (difficult to arouse)	Unarousable/coma
Behavior	Normal	Mild or moderate alteration	Severe alteration	NA

NOTE. Modified from Nayak et al[9] by permission of Oxford University Press.
Abbreviation: NA, not applicable.

the basis of the level of function. RANO-LM is discussed in further detail in the LM section.

LGGs

Recent advances in the understanding of the molecular pathogenesis of LGGs[41] has led to renewed interest in developing novel therapies for patients with these tumors. The RANO working group proposed response criteria for LGG (Table 3) that are similar to that for HGG but that measures T2/FLAIR rather than contrast enhancement as these tumors rarely enhance. In addition, because responses are often relatively modest, minor response criteria that are characterized by a decrease in

T2/FLAIR tumor of 25% to 50% was introduced. Although T2/FLAIR provides the clearest and most reproducible definition of LGG, distinguishing tumor from radiation-induced changes, postsurgical changes, demyelination, ischemic injury, and other comorbid events can be difficult. As validated imaging modalities that more accurately reflect tumor burden are developed, these criteria can be revised. With LGGs, clinical outcome assessments, such as neurocognitive function, quality of life, and seizure control, assume greater importance for the determination of the response to treatment. The RANO group recently proposed guidelines for using seizure control as a metric to assess the efficacy of tumor treatment in LGG trials by using a composite score of seizure classification, frequency, outcome, and severity.[42]

Table 3. Summary of the Proposed Response Assessment in Neuro-Oncology Response Criteria for Low-Grade Gliomas

Criterion	CR	PR	MR	SD	PD
T2/FLAIR	Disappearance of all lesions	≥ 50% ↓ in perpendicular diameters of lesion, sustained for 4 weeks	25%-50% ↓ in perpendicular diameters of lesion	< 25% ↓ to < 25% ↑	≥ 25% ↑*
New lesion	None (apart from those consistent with radiation effects, and no new or increased enhancement)	None (apart from those consistent with radiation effects, and no new or increased enhancement)	None (apart from those consistent with radiation effects, and no new or increased enhancement)	None (apart from those consistent with radiation effects, and no new or increased enhancement)	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	Stable or ↑	↓* (not attributable to other causes apart from the tumor, or decrease in corticosteroid dose)
Requirement for response	All	All	All	All	Any†

NOTE. Modified from Van den Bent et al[6] with permission from Elsevier.
Abbreviations: ↓, decrease; ↑, increase; CR, complete response; FLAIR, fluid-attenuated inversion recovery; MR, minor response; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease.
*Progression occurs when this criterion is met.
†Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

BRAIN METASTASES

Before the RANO brain metastases (RANO-BM) working group convened in 2011, clinical trials of patients with brain metastases were notable for their heterogeneity with respect to patient population, imaging modality, frequency of assessment, definitions of progression, and response (WHO[43] v modified Macdonald Criteria[12] v RECIST[11] v ad hoc radiographic assessment criteria), among other features.[44,45] Even though BMs are the most common malignant brain tumor, affecting up to one third of adults with cancer,[46] the field lacked the common definitions and guidelines for response assessment and clinical trial design that are needed for quality and consistency in trial reporting. RANO-BM proposed response assessment on the basis of literature review and consensus opinion.[7] For clinical trials of systemic agents, the group recommended the use of RECIST 1.1[11] for non-CNS response assessment and RANO-BM for CNS response assessment. With features that were adopted from RECIST and RANO-HGG to meet the particular needs of patients with solid tumor brain metastases, RANO-BM response assessment is based on the sum diameter of one-dimensional measurements, corticosteroid dosing, and clinical status[7] (Table 4). Guidance is also provided for cases in which patients were treated with stereotactic radiosurgery or immunotherapy to avoid equating treatment effect with tumor progression.

Several controversies arose during the development of these criteria. As a result of concerns over reproducibility and the interpretation of changes in small lesions as well as to maintain consistency with RECIST 1.1, measurable disease was defined in RANO-BM as a contrast-enhancing lesion that can be accurately measured in at least one dimension with a minimum size of 10 mm. The working group acknowledged that many patients present with subcentimeter brain metastases and, therefore, RANO-BM provides guidance for investigators who choose to lower the minimum size limit of measurable disease to 5 mm. Similarly, the use of one-dimensional versus volumetric assessments was debated within the working group. Ultimately, one-dimensional measurements formed the basis of RANO-BM criteria as the group felt that the existing data on volumetric assessments were not strong enough to justify the real-time cost and complexity

as discussed previously with respect to RANO-HGG. However, RANO-BM does provide guidance for those investigators who wish to include volumetric assessment within their trials.

LM

Response assessment in LM is particularly difficult for a variety of reasons. The clinical presentation and neuroimaging features in patients with LM are varied. Although CSF cytology, when positive for malignant cells, is definitive for disease confirmation, false negatives are common in as much as 50% of patients.[47,48] Imaging changes often do not correlate with the clinical status of the patient, and LM can be difficult to measure quantitatively.[48]

With these challenges in mind, the proposed response criteria from the LM working group recommended assessment using three elements: standardized neurologic examination, CSF cytology or flow cytometry, and radiographic evaluation[8] (Appendix Table A1, online only). Steroid dose contributed to assessment only in hematologic cancers. Although cytologic responses can be clinically relevant, RANO-LM also recognized that the sensitivity of CSF cytology is poor. As the neuroimaging features of LM varies from patient to patient, many radiographic features contribute to radiographic assessment on the basis of change in size and extent of disease, including nodular lesions (defined as measurable when greater than 5 mm × 10 mm), leptomeningeal enhancement, cranial nerve enhancement, hydrocephalus, and nerve root enhancement. Progressive disease is defined by worsening neurologic examination as a result of LM or worsening neuroradiographic assessment. The working group lacked consensus on how to define progression or refractory disease on the basis of CSF cytology or flow cytometry. The current criteria suggest defining progression/refractory disease by conversion of negative to positive cytology or failure to convert positive cytology to negative after induction therapy—although it is unclear how to define response assessment in a patient with persistently positive CSF cytology or flow cytometry who are otherwise clinically and radiographically stable to improved.

Table 4. Summary of the Proposed Response Assessment in Neuro-Oncology Response Criteria for Brain Metastases

Criterion	CR	PR	SD	PD
Target lesions	None	≥ 30% decrease in sum LD relative to baseline	< 30% decrease relative to baseline, but < 20% increase in sum LD relative to nadir	≥ 20% increase in sum LD relative to nadir*
Nontarget lesions	None	Stable or improved	Stable or improved	Unequivocal PD*
New lesion(s)†	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	NA‡
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any‡

NOTE. Reprinted from Lin et al[7] with permission from Elsevier.
Abbreviations: CR, complete response; LD, longest dimension; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease.
*Progression occurs when this criterion is met.
†New lesion = new lesion not present on prior scans and visible in at least two projections. If a new lesion is equivocal, for example, because of its small size, continued therapy may be considered and follow-up evaluation will clarify whether it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone do not define progression.
‡Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

		Reports/Guidelines Published to	Limitations of Current Criteria (if	
Focus of Working Group	Working Group	Date	published)	Future Plans
HGGs	RANO-HGG	Limitations of end point assessments for HGGs[6]	Optimal management of pseudoprogression from chemoradiation and immunotherapies remains challenging	Validation and refinement of proposed criteria
		Proposal for response assessment criteria for HGGs[4]	The value of T2/FLAIR assessment is unclear	
		Review of clinical trial design and end points for HGGs[49,50]	The value of 2D v volumetric assessment is unclear	
			There is a need for a more objective score for assessing clinical deterioration	
LGGs	RANO-LGG	Proposal for response assessment criteria for diffuse LGGs[6]	Measurement of T2/FLAIR can be difficult	Validation and refinement of proposed criteria
			The value of 2D v volumetric assessment is unclear	
			There is a need for a more objective score for assessing clinical deterioration	
Seizures	RANO Seizures	Proposal for a method of seizure assessment as a metric in brain tumor treatment trials[42]	Patients may under-report their seizure frequency, especially if associated with alteration of consciousness	Feasibility study of the seizure assessment tool in clinical practice
				Validation and refinement of proposed criteria
BMs from solid tumors	RANO-BM	Reviews of challenges to solid tumor BMs in clinical trials[44,45]	The value of one-dimensional v two-dimensional v volumetric assessment remains to be determined	Recommendations for clinical trial design in BM trials
		Proposal for response assessment criteria for brain metastases[7]	Optimal methods for distinguishing radiation necrosis from tumor progression	Validation and refinement of proposed criteria
			Optimal assessment and management of pseudoprogression from radiosurgery and immunotherapies	
			The need for a more objective score for assessing clinical deterioration	
			The challenge of discordant responses between CNS and non-CNS	
LMs from solid or hematologic tumors	RANO-LM	Review of end points and response criteria of published randomized clinical trials in patients with leptomeningeal disease[48]	Lack of sensitivity and specificity for CSF cytology and flow cytometry	Validation and refinement of proposed criteria
		Proposal for response assessment criteria for LMs[8]	How best to categorize patients with persistently positive CSF cytology who are clinically and radiographically stable or improved	
			Lack of sensitivity and specificity in current imaging for evaluation of leptomeningeal disease	
			Role of newer methodologies, such as CSF circulating tumor cells or new soluble CSF markers	
			Complexity of the criteria potentially reducing implementation in clinical trials	
Immunotherapy in neuro-oncology	iRANO	Proposal for immunotherapy response assessment in neuro-oncology[33]	For immunotherapeutics or tumor types where pseudoprogression is unlikely, delaying a change in therapy could be harmful to patients	Validation and refinement of proposed criteria

Table 5. Summary of RANO Efforts Across Working Groups

(continued on following page)

Focus of Working Group	Working Group	Reports/Guidelines Published to Date	Limitations of Current Criteria (if published)	Future Plans
Neurologic assessment	NANO	Development of standardized neurologic assessment	Not yet designed for pediatric patients Unclear whether the NANO score provides additional information over clinician assessment of neurologic deterioration or changes in Karnofsky performance status Unclear whether neurologic assessment correlates with radiographic outcomes or survival	Validation and refinement of proposed criteria
Pediatric CNS tumors	RAPNO	Challenges in defining end points and response assessment for clinical trials in pediatric neuro-oncology[51]		Development of response assessment for trials of pediatric gliomas
Spine tumors	SPINO	Challenges in standardizing imaging-based assessment of local control and pain for spinal metastases[52]		Development of consensus criteria for tumor imaging, clinical assessment, and symptom- and imaging-based response criteria to help standardize future clinical trials
Meningiomas	RANO-Meningioma	Review of PFS6 benchmarks in meningioma clinical trials[53] Review of meningioma treatments and patient outcomes after standard surgery and radiotherapy to help inform clinical trial design[54]		Development of standardized end point and response criteria for meningioma
PET	RANO PET	Recommendations for use of PET imaging in gliomas[29]		Guideline for PET imaging of meningiomas Guideline for technical procedures of PET imaging in gliomas
Surgery	RANO-Surgery Group	Recommendations for surgically related end point assessment[55]		Development of response criteria for locally delivered therapies
Histologic assessment of postoperative patients				Recommendations for assessing response to therapy using tissue obtained from surgery in patients with recurrent glioma
Corticosteroid use	RANO Steroid			Development of corticosteroid use as an end point in clinical trials Validation and refinement of proposed criteria
Patient-reported outcomes	RANO Patient-Reported Outcomes			Review of available patient related outcomes Recommendations for selecting clinical outcome assessments in clinical trials

Abbreviations: BM, brain metastases; HGG, high-grade glioma; LGG, low-grade glioma; LM, leptomeningeal metastases; NANO, Neurologic Assessment in Neuro-Oncology; PET, positron emission tomography; PFS, progression-free survival; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SPINO, Spine Response Assessment in Neuro-Oncology.

OTHER RANO EFFORTS

Several other RANO working groups are developing response criteria and clinical trial guidelines for use in neuro-oncology clinical trials.[5] These efforts are summarized in Table 5.

VALIDATION OF RESPONSE CRITERIA

By using RECIST as a model for validating and, ultimately, updating response criteria, each working group will monitor the implementation of their respective guidelines. Thus far, RANO-HGG and RANO-LGG are the standard response criteria used in glioma studies. Increasingly, clinical trials are implementing RANO-BM and NANO criteria. Each working group will use data from these prospective clinical trials to evaluate the usefulness, relevance, and applicability of their criteria, including correlation of response with progression-free survival and overall survival. RANO-BM is currently working with RECIST to analyze historical data sets as a means of validating these criteria.[7]

FUTURE DIRECTIONS

During the past decade, the efforts of the RANO working group and others to develop consensus criteria for assessing response and

progression in CNS tumors, together with the development of the standardized brain tumor imaging protocol, have improved reliability and reduced variability in determining outcomes in neuro-oncology clinical trials. Nonetheless, there are important challenges still to be addressed. The role of advanced imaging, including volumetric measurements and digital subtraction maps, in defining contrast-enhancing tumor need to be determined. The value of dynamic susceptibility contrast and dynamic contrast-enhanced MRI and amino acid positron emission tomography in diagnosing pseudoprogression also requires additional studies, and for these techniques to be incorporated routinely into clinical trials, standardization will be necessary. The value of including T2/FLAIR progression for agents that affect vascular permeability remains to be determined. A number of proposals, such as the iRANO, RANO-BM, NANO, and RANO-LM criteria, require validation in clinical trials, as will newer proposals that address the use of seizures, corticosteroid use, and patient-reported outcomes as potential trial end points. For slow-growing tumors that are unlikely to decrease significantly in size in response to therapy, studies are underway to evaluate whether a reduction in the rate of growth after the initiation of treatment may indicate benefit.

These advances in response assessment will hopefully help accelerate the identification of more effective therapies for patients with CNS tumors.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Financial support: All authors
Administrative support: All authors
Provision of study materials or patients: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Affiliations

Patrick Y. Wen and **Eudocia Q. Lee**, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; **Susan M. Chang**, University of California, San Francisco, San Francisco, CA; **Michael A. Vogelbaum**, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH; **Martin J. Van den Bent**, Erasmus University Medical Center Cancer Institute, Rotterdam, the Netherlands; and **David R. Macdonald,** London Regional Cancer Program, Western University, London, Ontario, Canada.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Response Assessment in Neuro-Oncology Clinical Trials

Patrick Y. Wen
Consulting or Advisory Role: Agios, AstraZeneca, Alexion Pharmaceuticals, Genentech, Insys Therapeutics, Monteris Medical, Novartis, Novogen, Vascular Biogenics, VBI Vaccines
Speakers' Bureau: Merck
Research Funding: Agios (Inst), Angiochem (Inst), AstraZeneca (Inst), Genentech (Inst), Novartis (Inst), ImmunoCellular Therapeutics (Inst), Kadmon (Inst), Karyopharm Therapeutics (Inst), Merck (Inst), Eli Lilly (Inst), Oncoceutics (Inst), Sanofi (Inst), Vascular Biogenics (Inst)

Susan M. Chang
Consulting or Advisory Role: Agios, Blaize, Neuro-Oncology, Tocagen, Edge
Research Funding: Agios (Inst), Tocagen (Inst), Novartis (Inst), Quest Diagnostics (Inst), Roche (Inst)

Martin J. Van den Bent
Consulting or Advisory Role: AbbVie, Actelion, Blue Earth Diagnostics, Cavion, Roche, Celldex, Bristol-Myers Squibb, Novartis, MSD
Research Funding: AbbVie (Inst)

Michael A. Vogelbaum
Leadership: Infuseon Therapeutics
Stock or Other Ownership: Infuseon Therapeutics
Honoraria: Tocagen, Neuralstem, Medicenna
Research Funding: Tocagen (Inst)
Patents, Royalties, Other Intellectual Property: Patents on a drug delivery device (Inst)

David R. Macdonald
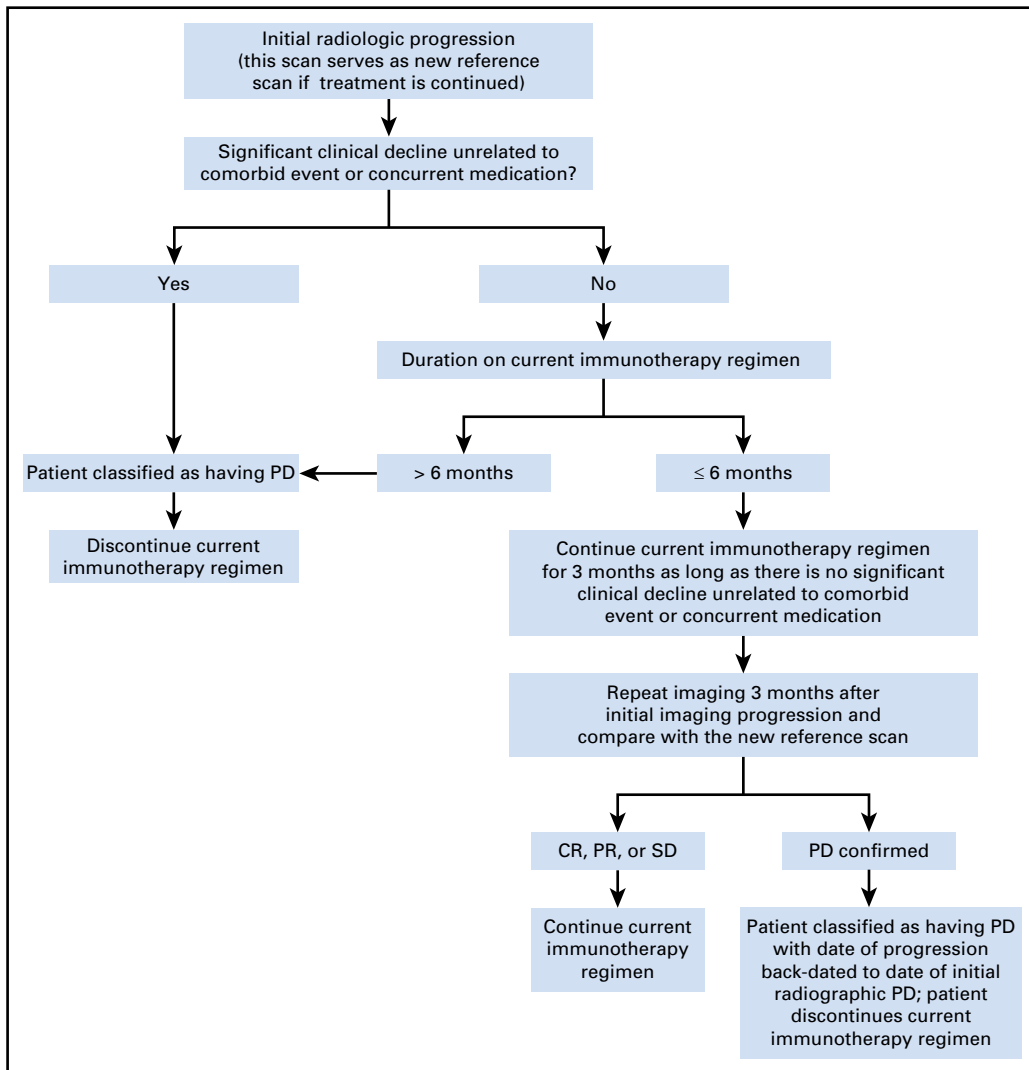No relationship to disclose

Eudocia Q. Lee
Consulting or Advisory Role: Genentech

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Appendix

Fig A1. Response Assessment in Neuro-Oncology treatment algorithm for the assessment of progressive imaging findings in neuro-oncology patients treated with immunotherapy. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. Reprinted from Okada et al[33] with permission from Elsevier.

Table A1. Summary of Response Determination in Leptomeningeal Disease

Assessment	Response	Neurologic Examination–Defined Progression	CSF-Defined Disease Progression	Radiologic-Defined Disease Progression	Symptoms^	Stable Disease
		Progressive or Refractory Disease				
Neurologic exam	Improved	Worse	Stable	Stable	Stable	Stable
CSF						
Cytology (all cancers)	Negative	Negative	Positive (lack consensus)	Negative	Negative	Negative or positive (solid tumors only)
Flow cytometry (in hematologic cancers only)	Negative	Negative	Positive	Negative	Negative	Negative
CNS imaging	Definite Improvement	Stable	Stable	Definite worsening	Stable	Stable or equivocally worsening or improved
Corticosteroid dose (in hematologic cancers only)	None or decreased	Stable or increased	Stable or increased	Stable or increased	Stable	Stable or decreased
Symptom assessment	Improved	Worse or stable	Worse or stable	Worse or stable	Worse	Stable

NOTE. Reprinted from Chamberlain et al[8] by permission of Oxford University Press.
CSF cytology negative Defined as either true negative or atypical. CSF cytology positive Defined as true positive or suspicious. Stable Defined as stable or indeterminate. Symptoms^Stable; no change: −1 to +1 in symptom inventory. Worse: −2 to −3 in symptom inventory. Improved: +2 to +3 in symptom inventory.