Response Assessment in Neuro-Oncology Criteria and Clinical Endpoints

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KEYWORDS

• RANO • Response assessment • Endpoints • Gliomas • Brain metastases

KEY POINTS

- The Response Assessment in Neuro-Oncology (RANO) Working Group is an international multidisciplinary group whose goal is to improve response criteria and define endpoints for neuro-oncology trials.
- The RANO criteria for high-grade gliomas attempt to address the issues of pseudoprogression, pseudoresponse, and nonenhancing tumor progression but remain a work in progress.
- RANO criteria have been developed for brain metastases and are in progress for meningiomas, leptomeningeal disease, spinal tumors, and pediatric tumors.
- The RANO group has also developed criteria for neurologic response (Neurologic Assessment in Neuro-Oncology [NANO]) and immunologic therapies (Immunotherapy RANO [iRANO]), and criteria for seizures and steroid use are in progress.

BACKGROUND AND SUMMARY OF CURRENT RESPONSE ASSESSMENT IN NEURO-ONCOLOGY CRITERIA

Progress in improving therapies for patients with brain tumors has been limited not only by the lack of effective treatments but also by the limitations and variability of the available response criteria used in clinical trials. The RANO Working Group was established in 2008 to address some of these limitations. The work of the RANO group has recently been summarized.[1]

After its introduction in 1990, the Macdonald criteria,[2] which used the product of the maximal cross-sectional enhancing diameters as the primary measure of tumor size, were widely adopted in neuro-oncology clinical trials. It gradually became clear, however, that the Macdonald criteria had several important limitations.[3,4] They included the failure account for pseudoprogression after chemoradiotherapy, a lack of definitions of measurable and nonmeasurable disease, and failure to assess nonenhancing tumor and pseudoresponse in patients who received antiangiogenic therapies, such as bevacizumab that reduced vascular permeability and contrast enhancement.[3,4] In 2010 the RANO criteria for

Disclosures: Dr R.Y. Huang is a consultant for Celldex Therapeutics and Agios Pharmaceuticas. Dr P.Y. Wen provides research support to Angiochem, Agios, AstraZeneca, Exelixis, Genentech/Roche, GlaxoSmithKline, Karyopharm, Merck, Novartis, Sanofi-Aventis, and Vascular Biogenics; he serves on the advisory board for Agios, Cavion, Cortice Bioscience, Genentech/Roche, Monteris, Novartis, Novocure, Regeneron, and Vascular Biogenic; he is a speaker at Merck and is on the data safety committee at Monteris and Tocagen.

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Magn Reson Imaging Clin N Am ■ (2016) ■–■

http://dx.doi.org/10.1016/j.mric.2016.06.003

high-grade gliomas were published to address some of the limitations of the Macdonald criteria[4] (**Box 1**, **Table 1**). As with the Macdonald criteria, the RANO criteria continued to use the product of the maximal cross-sectional enhancing diameters as the primary measure of tumor size and also took into account corticosteroid use and clinical status. The key features of the RANO criteria included

1. Definition of measurable disease as contrast-enhancing lesions with clearly defined margins by CT or MR imaging scan, with 2 perpendicular diameters of at least 10 mm, visible on 2 or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip. Nonmeasurable disease was defined as either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm.
2. Allowing up to 5 measurable lesions
3. Introducing a minimum requirement for entry into clinical trials for recurrent gliomas by requiring a 25% increase in the sum of the products of perpendicular diameters of the contrast-enhancing lesions while on stable or increasing doses of corticosteroids
4. Addressing pseudoprogression by excluding patients within the first 12 weeks after completion of radiotherapy from clinical trials for recurrent disease unless the progression is clearly outside the radiation field (eg, beyond the high-dose region or 80% isodose line) or if there is pathologic confirmation of disease progression
5. Addressing "pseudoresponse" by requiring a repeat scan at 4 weeks or later to confirm the response
6. Introducing the concept of nonenhancing tumor progression. For patients to achieve a partial or complete response, in addition to 50% reduction or disappearance of the contrast-enhancing disease, respectively, there could not be an increase in the amount of nonenhancing tumor. For progression, in addition to a 25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline or best response, on stable or increasing doses of corticosteroids, a significant increase in T2/fluid-attenuated inversion recovery (FLAIR) nonenhancing lesion not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects) could constitute progression. Given the difficulty in measuring nonenhancing disease, no specific criteria were recommended to determine progression of nonenhancing disease. This subjective assessment of nonenhancing disease remains an important limitation, allowing patients in cases of uncertainty regarding whether there is progression, to continue on treatment and remain under close observation (eg, evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression is backdated to the time point at which this issue was first raised.

CURRENT ADOPTION OF RESPONSE ASSESSMENT IN NEURO-ONCOLOGY AND CHALLENGES

The RANO criteria have been increasingly adopted to assess response endpoints in recent high-grade glioma clinical trials.[5–12] To date it is not clear whether the new criteria have adequately addressed the challenges arising from pseudoprogression, pseudoresponse, and nonenhancing tumor progression. Although the 12-week cutoff in the RANO criteria seem to help reduce pseudoprogression, there is concern that pseudoprogression can occur beyond the 12-week cutoff. In a prospective series of 56 patients with glioblastoma who demonstrated conventional findings concerning for progression of disease post–radiation treatment, pseudoprogression occurred in 27 of 56 patients as determined by perfusion MR imaging technique, and 8 of these 27 patients (39%) developed pseudoprogression 3 months post–radiation therapy.[13] In this series, the overall survival (OS) was significantly longer in patients with pseudoprogression (35.2 months) compared with those who never experienced pseudoprogression (14.3 months, $P<.001$). These results highlight both the benefit and limitation of the RANO criteria in the assessment of pseudoprogression and modification of the current criteria to more accurately identify the patients with delayed pseudoprogression is necessary.

The impact of the inclusion of T2/FLAIR assessment in the RANO criteria has been examined in several retrospective studies. Radbruch and colleagues[14] evaluated serial MR imaging studies of 144 patients with glioblastoma and reported that 62% of the scans with progression on T2-weighted imaging alone were followed by progression of enhancing lesion during the next follow-up scan, in contrast to 32% of the those showing stable disease. In this study, a 15% threshold of tumor increment on T2-weighted