Imaging Criteria in Neuro-oncology

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Every year approximately 18 and 22 out of 100,000 people are diagnosed with a primary brain tumor in Europe1 and in the United States,2 respectively. Of these, 15 per 100,000 are diagnosed with a nonmalignant brain tumor, and 7 per 100,000 with a malignant brain tumor. The most common nonmalignant tumor is meningioma (53.2%), and glioblastoma is the most common malignant primary brain tumor (45.6%). In addition, it is estimated that the incidence of brain metastases is 3 to 10 times that of primary brain tumors.3,4 Although understanding of tumor biology has undergone remarkable evolution in recent years, the neuro-oncologic clinical trials landscape is dominated by negative phase III study results, and it is now 13 years since the standard of care for glioblastoma was established.5 Tumor heterogeneity, adaptive and intrinsic resistance, lack of predictive biomarkers, and the blood–brain barrier are some of the factors contributing to the lack of therapeutic progress. Magnetic resonance imaging (MRI) is the gold standard diagnostic tool to monitor brain tumors. As trials of novel agents are designed, the traditional methods of assessing tumor response are increasingly being questioned, and more accurate assessment of response and progression are needed.6,7 This has led to the development of updated criteria on response and progression based on new information provided by MRI and standardization of imaging definitions, with rules for measurements and clear guidelines for patients entering clinical studies.8,9

Abstract

The identification of more effective therapies for brain tumors has been limited in part by the lack of reliable criteria for determining response and progression. Since its introduction in 1990, the MacDonald criteria have been used in neuro-oncology clinical trials to determine response, but they fail to address issues such as pseudoprogression, pseudoresponse, and nonenhancing tumor progression that have arisen with more recent therapies. The Response Assessment in Neuro-Oncology (RANO) working group, a multidisciplinary international group consisting of neuro-oncologists, medical oncologists, neuroradiologists, neurosurgeons, radiation oncologists, and neuropsychologists, was formed to improve response assessment and clinical trial endpoints in neuro-oncology. Although it was initially focused on response assessment for gliomas, the scope of the RANO group has been broadened to include brain metastases, leptomeningeal metastases, spine tumors, pediatric brain tumors, and meningiomas. In addition, subgroups have focused on response assessment during immunotherapy and use of positron emission tomography, as well as determination of neurologic function, clinical outcomes assessment, and seizures. The RANO criteria are currently a collective work in progress, and refinements will be needed in the future based on data from clinical trials and improved imaging techniques.

Keywords
► response assessment
► RANO
► brain tumors
► glioma

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How Did the Response Criteria Evolve?

Initial efforts to systematically develop response assessment criteria on a large scale were made by the World Health Organization (WHO) in 1979, which resulted in the WHO handbook for reporting results of cancer treatments. Based on modern scanning and a fuller appreciation of the influence of steroids on neurologic findings and brain tumor images, the MacDonald criteria were introduced in 1990. These criteria provided an objective radiologic assessment of tumor response and were based primarily on contrast-enhanced computerized tomography (CT) and the two-dimensional WHO oncology response criteria using enhancing tumor area (the product of the maximal cross-sectional enhancing diameters) as the primary tumor measure. With the advent of surgery, radiation therapy, chemotherapy, targeted, and antiangiogenic treatment approaches, significant limitations of the MacDonald criteria became obvious. Consequently, the Response Assessment in Neuro-Oncology (RANO) working group was formed and updated the response assessment criteria for use in clinical trials in high-grade glioma (HGG) in 2010. Since then, several subgroups have been established that work on response assessment criteria for other nervous system tumors. The different RANO reports published to date are based on the best currently available evidence, and updates are to be expected as more data become available.

Which Challenges Are Addressed by RANO?

When interpreting brain tumor MR images, one has to recall that the various imaging features are the result of pathophysiologic processes, and tumor burden is depicted only indirectly. Contrast enhancement is the result of blood–brain barrier breakdown, and can be influenced by non-tumor-related conditions such as ischemia and epileptic seizures, as well as iatrogenic factors such as surgery, radiation, chemotherapy, steroids, and antiangiogenic drugs. MacDonald criteria take only the contrast-enhancing tumor component into account; therefore, nonenhancing tumor progression and therapy-related phenomena such as pseudoprogression and pseudoresponse pose challenges for these criteria, and were the driving force to develop the RANO criteria. Pseudoprogression is defined as a transient increase in contrast enhancement, with or without associated T2/fluid-attenuated inversion recovery (FLAIR) changes, in the absence of true tumor progression. It is observed in approximately 10 to 30% of patients with glioblastoma who receive radiation with temozolomide, and methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter may enhance the risk to develop pseudoprogression. Clinically, pseudoprogression may be associated with neurologic decline and a requirement for steroids; however, it typically resolves spontaneously within 3 to 6 months, even if treatment is continued.

Pseudoresponse is defined as a decrease in contrast enhancement without a true antitumor effect, observed in approximately 20 to 60% of patients receiving antiangiogenic therapy (i.e., bevacizumab, cediranib), which is attributed to a normalization of abnormally permeable blood vessels within the tumor. An instructive example highlighting the importance of reliable imaging response parameters in the clinical trial setting was experienced with bevacizumab, a monoclonal antibody targeting vascular

Fig. 1 Pseudoprogression. MRI course of a 58-year-old patient undergoing biopsy for a contrast-enhancing lesion in the right parietal lobe. Histology revealed a glioblastoma, isocitrate dehydrogenase 1 (IDH1) wild type, with MGMT promoter methylation. The patient received radiation (60 Gy) with concomitant and adjuvant temozolomide chemotherapy for six cycles. The MRI 12 weeks after biopsy showed an increase in the contrast-enhancing lesion in T1-weighted sequences, with an increase in the T2 hyperintense signal. Clinically, the patient did not demonstrate any decrease in neurologic function, and therefore temozolomide therapy was continued. At 20 weeks, the contrast-enhancing lesion increased further and additionally demonstrated a necrotic core, but on subsequent MRI scans a regression of the contrast-enhancing lesion as well as the T2 hyperintensity was noted—an example of pseudoprogression.
endothelial growth factor (VEGF) ligand. Despite an increase in progression-free survival in the treatment of primary \cite{29,30} and recurrent \cite{31,32} glioblastoma patients, pseudoresponses, possibly resulting in inaccurate tumor size determination during treatment with bevacizumab, together with the lack of a significant effect on overall survival, were factors contributing to the failure of bevacizumab to receive approval by the European Medicines Agency.

In addition, nonenhancing tumor progression constitutes a further imaging challenge not fully captured by the MacDonald criteria, and can be observed in approximately 10 to 40\% of patients with glioblastoma.\cite{33,34} Nonenhancing tumor progression can develop independently from the use of antiangiogenic agents.\cite{35-37} and is radiologically characterized by an increase in T2/FLAIR hyperintense signals, usually accompanied by clinical deterioration.\cite{33,38} Therefore, the RANO criteria for HGG have incorporated the assessment of T2/FLAIR changes to more accurately assess response and progression during treatment.\cite{66}

**How Do RANO Criteria for High-Grade Glioma Work?**

Considering the earlier-mentioned imaging challenges, the RANO criteria evaluate four MR categories for the assessment of the tumor response: (1) measurable contrast-enhancing disease of a minimum size (>10 × 10 mm), (2) the presence of new lesions, (3) nonmeasurable enhancing disease below a minimum size (<10 × 10 mm), and (4) T2/FLAIR hyperintense, nonenhancing disease. As a fifth, non-MRI criteria, steroid dose is included as a variable. In enhancing lesions, a bidimensional measurement of the individual lesions’ greatest perpendicular diameters is recommended (not including a central cavity or nonenhancing tumor area), and if there are multiple lesions, two to five lesions should be measured. Due to difficulties measuring nonenhancing lesions, solely a “significant increase in T2/FLAIR hyperintense signal” is required to qualify for progression. Tumor response is graded as complete response, partial response, stable disease, or progressive disease on follow-up, with specific cut-off values.\cite{66} Grading of tumor response is performed in relation to a baseline MRI, which in general is the pre-study MRI. Exceptions to this rule are patients with pseudoprogression and patients with response, where the baseline MRI is the MRI at best response. Because of pseudoprogression, tumor progression within the first 12 weeks of completion of radiotherapy can only be determined if the majority of the new enhancement is outside of the radiation field or if there is pathologic confirmation of progressive disease by a surgical procedure.\cite{68} To prevent clinical study patients from being withdrawn prematurely from studies and incorrectly being assessed as nonresponders, the RANO criteria furthermore do not allow the enrollment of patients into clinical trials within the first 12 weeks following radiotherapy unless progression is evident by histological
confirmation or again with the appearance of new lesions outside the radiation field.8

RANO Criteria in Other CNS Tumors

Because of the diversity of neuro-oncologic entities and the advent of new therapy concepts that challenge the current RANO criteria, it became evident that response to treatment cannot be accurately assessed by one response guideline only. Therefore, several subgroups were established to work on response assessment criteria for other nervous system tumors. Each working group is an international, multidisciplinary effort consisting of neuro-oncologists, medical oncologists, neurosurgeons, radiation oncologists,

Fig. 3 Nonenhancing tumor progression. MRI of a recurrent glioblastoma patient receiving bevacizumab treatment. Six weeks after start of treatment, a decrease of the contrast-enhancing lesion and the T2 hyperintensity is noted. At 12 weeks, no contrast enhancement is detected on T1-weighted imaging; however, a significant increase of the T2 hyperintense tumor is noted, demonstrating progressive disease according to the RANO criteria.

Fig. 4 Difficulties in assessing nonenhancing tumor progression. MRI of a 47-year-old patient who underwent surgery for tumor recurrence. Four weeks after surgery, lomustine was started and MRI scans were performed at 12-week intervals. No contrast enhancement can be detected during the course of treatment; the patient, however, demonstrated steady cognitive decline. Of note, from week 12 forward, an increase of the T2 hyperintense signal is noted near the resection cavity in the left frontal lobe, with subsequent signal extension into the basal ganglia. According to the RANO criteria, a “significant T2/FLAIR signal increase” qualifies for tumor progression, but this example illustrates the difficulties associated with this terminology and may result in contrary opinions among neuroradiologists as to which time point tumor progression is defined.
Table 1 RANO criteria

<table>
<thead>
<tr>
<th></th>
<th>Complete response</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast-enhanced T1-weighted lesion</td>
<td>Complete decrease</td>
<td>≥50% decrease</td>
<td>&lt;50% decrease</td>
<td>≤25% decrease</td>
</tr>
<tr>
<td>T2/FLAIR hyperintense lesion</td>
<td>Stable or decrease</td>
<td>Stable or decrease</td>
<td>Stable or decrease</td>
<td>Significant increase</td>
</tr>
<tr>
<td>New lesion</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>No</td>
<td>Stable or decreased dose</td>
<td>Stable or decreased dose</td>
<td>–</td>
</tr>
<tr>
<td>Clinical status</td>
<td>Stable or increased</td>
<td>Stable or increased</td>
<td>Stable or increased</td>
<td>Significant decline</td>
</tr>
<tr>
<td>Requirements for response</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>Any</td>
</tr>
</tbody>
</table>

Abbreviations: FLAIR, fluid-attenuated inversion recovery; RANO, Response Assessment in Neuro-oncology. Source: Adapted with permission from Wen et al.8

Are Imaging Criteria Most Important to Judge Successful Treatment?

When kept in perspective, the shared goal of all parties developing therapies against brain tumors is to positively impact the lives of people affected by these cancers.45

Table 2 Summary of other RANO guidelines

<table>
<thead>
<tr>
<th>RANO guideline</th>
<th>Unique feature</th>
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<tbody>
<tr>
<td>RANO HGG8</td>
<td>A “significant increase” of T2/FLAIR hyperintense signal qualifies for tumor progression. Attaches importance on pseudoprogression and gives guidelines on clinical study entry</td>
</tr>
<tr>
<td>RANO LGG41</td>
<td>New or increased contrast-enhancement is recognized as an indicator of transformation to a higher tumor grade. Category “minor response” describes a 25–49% decrease in size of the T2/FLAIR hyperintense lesion.</td>
</tr>
<tr>
<td>RANO BM40</td>
<td>Differentiates between the intra- and extracranial compartments and recommends a bicompartimental assessment of treatment response and the formulation of separate study endpoints (PFS or RR) for each compartment</td>
</tr>
<tr>
<td>RANO LM39</td>
<td>Three basic elements are recommended to be used in assessing response in LM: 1. a standardized neurological examination 2. cerebrospinal fluid cytology in all cancers; flow cytometry in hematologic cancers 3. and radiographic evaluation consisting of a complete contrast-enhanced neuraxis MRI, and in instances of planned intra-CSF therapy, radioisotope CSF flow studies; to reliably describe imaging features, a novel radiological LM response scorecard is presented</td>
</tr>
<tr>
<td>iRANO27</td>
<td>They follow the recommendations of the previously published RANO-HGG, RANO-LGG, and RANO-BM criteria but provide additional guidance in the case of disease progression in patients receiving immunotherapies. As these therapies may induce differential responses,73 namely immediate response, response after stable disease, response after tumor burden increase, and response in the presence of new lesions, iRANO criteria determine that not every new lesion automatically signifies tumor progression and that response assessment is dependent on the duration of the immunologic treatment (≥ or &lt; than 6 mo). In addition, the minimization of corticosteroid which may result in a negative impact on the efficiency of immunotherapies is recommended</td>
</tr>
<tr>
<td>RAPNO42</td>
<td>In development, guidelines will be formulated for pediatric high-grade glioma, low-grade glioma, and diffuse intrinsic pontine glioma</td>
</tr>
<tr>
<td>Meningioma44</td>
<td>In development, guidelines will take into account the unique imaging properties and the prolonged course of (benign) meningiomas</td>
</tr>
<tr>
<td>SPINO43</td>
<td>In development, as spine metastases are associated with significant morbidity due to pain, guidelines will incorporate radiologic as well as pain assessment tools</td>
</tr>
</tbody>
</table>

Abbreviations: BM, brain metastases; CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; HGG, high-grade glioma; IRANO, immunologic RANO; LGG, low-grade glioma; LM, leptomeningeal metastases; MRI, magnetic resonance imaging; PFS, progression-free survival; RANO, Response Assessment in Neuro-oncology; RAPNO, Response Assessment in Pediatric Neuro-oncology; RR, relative response; SPINO, SPine response assessment in Neuro-Oncology.
Delayed radiographic responses to treatment are reported, especially for LGGs, and patients may be kept unnecessarily on toxic treatments—a hot topic in view of the latest positive survival data for combined chemoradiation in LGGs that are currently changing treatment paradigms. Therefore, reliable quantification of quality of life, neurologic function, and seizure activity as markers for therapy response are desired. The RANO scale (Neurological Assessment in Neuro-Oncology) provides a quantifiable clinician-reported outcome of nine neurologic function domains with high interobserver agreement. It is designed to be combined with radiographic assessment and replaced with subjective clinician assessment of clinical deterioration. Seizure frequency is also a quantifiable metric and is also being investigated as a surrogate marker of clinical benefit. Guidelines on assessment of seizures and the influence on health-related quality-of-life outcomes in patients enrolled in LGG therapeutic trials were recently published. Quality-of-life measures can be captured by different test batteries and are excellently reviewed in detail elsewhere.

RANO—A Work in Progress

There is significant interest in increasing the robustness of the current response criteria in neuro-oncology. These efforts can be summarized by the term "quantification." As bidimensional measurements can be challenging when contrast-enhancing tumors have ill-defined margins and/or irregular shapes, volumetric measurement of tumor burden may be a solution. Changes in tumor volume correlate with clinical response as well as with changes in uni- or two-dimensional measurements with an acceptable intra- and interobserver variability. Unfortunately, volumetric measurements are not readily available at most institutions, and the current data are not strong enough to justify the mandatory inclusion in the RANO criteria. However, not only assessment of contrast-enhancing tumor components would profit from tumor volumetrics. The exact time point to decide on a nonenhancing tumor progression is difficult to assess, as the term "significant increase of T2/FLAIR hyperintensity" leaves room for subjective interpretation. Volumetric measurement may also potentially help in assessing nonenhancing tumor progression more accurately. According to the RANO criteria, tumor volumetric measurement is recommended as a secondary study endpoint in clinical trials to improve the understanding of its utility and enable the inclusion of volumetric assessments in future updates of the criteria.

Functional MRI sequences validated by neuronavigated tissue biopsy studies have been shown to refine information on tumor cellularity, aggressiveness, and vascularity. These techniques include the quantification of apparent diffusion coefficient ratios in diffusion-weighted MRI as a surrogate marker for cell density; choline, creatine, and N-acetylaspartate ratios from MR spectroscopy as a display of tissue metabolite ratios; and perfusion imaging, which utilizes changes in the relative cerebral blood volume to provide information on tumor vascularity, grading, and differentiation of therapy-associated changes. However, none of these techniques have currently been incorporated into current response criteria, as they are not universally available, are difficult to reproduce, and unlikely to gain widespread acceptance until they have been validated in clinical trials.

Positron emission tomography (PET)-based imaging, especially with amino acid tracers, provides information on tumor metabolism and is currently under intense investigation to address problems with differentiating neoplastic tissue from nonspecific, treatment-related changes after surgery, radiotherapy, chemotherapy, or immunotherapy. Recommendations on the clinical use of PET in neuro-oncology have been presented recently.

Further efforts complementing the evolving landscape of "image quantification" can be summarized under the term "radiomics"—which is the extraction of a large number of quantitative imaging features from tumors and recognition of imaging phenotypes/patterns by automated data characterization. The ultimate goal of this technique is not to replace the radiologists in charge of monitoring treatment response, but rather to serve as a decision support tool in this crucial mission. The great advantage is that radiomic features can be generated from standard of care clinical images, and accuracy as well as performance can be increased by sample size. Therefore, a harmonization of MRI protocols in neuro-oncology is required—a goal that was brought one step further during the "Jumpstarting Brain Tumor Drug Development Coalition" workshop held with the Food and Drug Administration in 2014, where a consensus brain tumor imaging protocol was proposed that has been widely adopted in Europe and the United States.

As a final point on future developments of response assessment in neuro-oncology, it is interesting to question whether all tumors follow the same mechanisms of response and progression. Assessment of radiologic phenotypes at progression in recurrent and primary glioblastoma patients has revealed two types of nonenhancing tumor progression, and has shown that complete resolution of contrast enhancement is associated with improved outcome compared with mere decrease of the contrast-enhancing tumor area (unpublished data). Whether these radiologic phenotypes can contribute to response assessment is currently being investigated.

Summary

Standardized early response assessment criteria are crucial in precision oncology. RANO criteria are currently a work in progress, and refinements will be needed in the future based on data from clinical trials and improved imaging techniques. Incorporation of functional MRI and PET parameters in clinical trials are urgently needed to establish reproducibility and applicability to optimize patient management, and ultimately, patient outcome.

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