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Response Assessment in Neuro-Oncology (RANO): more than imaging criteria for malignant glioma

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The introduction of antiangiogenic therapies for the treatment of malignant glioma and the effect of these agents on standard imaging studies were the stimuli for forming a small group of investigators to critically evaluate the limitations of the Macdonald criteria in assessing response to treatment. The initial goal of this group was to highlight the challenges in accurately determining the efficacy of therapeutic interventions for malignant glioma and to develop new criteria that could be implemented in clinical care as well as in the design and conduct of clinical trials. This initial Response Assessment in Neuro-Oncology (RANO) effort started in 2008 and over the last 7 years, it has expanded to include a critical review of response assessment across several tumor types as well as endpoint selection and trial design to improve outcome criteria for neuro-oncological trials. In this paper, we review the overarching principles of the RANO initiative and the efforts to date. We also highlight the diverse and expanding efforts of the multidisciplinary groups of investigators who have volunteered their time as part of this endeavor.

Keywords: malignant glioma, Response Assessment in Neuro-Oncology (RANO) criteria.

Recognizing the challenge in determining response to antiangiogenic agents in the treatment of malignant glioma, the initial RANO effort was focused on critically analyzing the strengths and shortcomings of the Macdonald criteria, with the additional goal of updating them to include new criteria specific to evaluating treatment with these agents.[1] Following the formation of a multidisciplinary and international working group, consensus was reached in developing updated criteria.[2] The new criteria recommended incorporating T2/fluid-attenuated inversion recovery (FLAIR) imaging to identify pseudoresponse to anti-angiogenic agents, and also addressed the difficulty of evaluating psuedoprogression following chemo-radiotherapy. There was also a clear acknowledgement of the difficulty in quantifying T2/FLAIR change and the evolving nature of the criteria, with the intent for future validation with clinical outcome, as well as the plan to ultimately incorporate validated imaging and image-analysis technologies that more accurately characterized tumor burden. As this initial RANO effort was formalized, it became clear that there was expanding interest in the critical evaluation of response assessment across other tumor types as well as a review of relevant topics that pertained to clinical trial design and conduct in neuro-oncology. It was therefore critical to establish overarching principles that could be applied to any RANO project to ensure a cohesive and coordinated end result that would benefit the neuro-oncology community. We present an overview of these principles as well as the wide scope of expanded efforts that have emerged as a result of the initial RANO effort.

Overarching Principles

Formation of a Steering Committee

The first action of the group was to formalize a RANO steering committee that comprised the 5 members of the initial effort. This group consisted of academic clinicians who recognized the challenges of assessing radiographic response to antiangiogenic agents and coordinated the first open meeting at the 2008 Society of Neuro-Oncology annual conference. Currently, the responsibilities of this group are to identify key issues in neuro-oncology trial design and conduct that may be challenging or problematic and to help standardize these efforts across projects. The vetting of these issues is performed twice per year and is based on

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consensus decision. An example of an issue that was not chosen to pursue was related to central nervous lymphoma. In this case, the international community of investigators in the field agreed that updating response criteria to new therapies was already being addressed and that a RANO effort would be redundant. One of the major goals of the steering committee is to ensure international, multidisciplinary collaboration to garner the strength of global expertise in neuro-oncology and to enhance consensus building. Working groups are led by group leaders who have expertise in the area of interest as demonstrated by their accomplishments in the target field through their publication portfolio and academic achievements. These leaders express interest in participating in the RANO effort and agree to volunteer their time and effort to coordinate the communication among the working group members through multiple conference calls. They are also responsible for reporting on the progress of the group and for the publication of any results. A member of the steering committee is an active participant of the individual working groups, allowing for synergy across efforts and avoiding redundancy in the generation of criteria. This is particularly critical in clinical scenarios of overlap; eg, the development of criteria for leptomeningeal disease and criteria for pediatric tumors with a propensity for cerebrospinal fluid spread.

RANO Recommendations

Another important principle of RANO is that the recommendations should be evidence-driven whenever possible, and if evidence is not available, the recommendations should be consensus driven. The major task of the working group is to perform a detailed and critical assessment of the criteria used in the area of interest and to assess the level of evidence available to generate the criteria. To date, the recommendations have been primarily consensus driven because of the lack of evidence available to support the criteria. The major goal of the RANO effort to date has therefore been to develop standardized criteria that can be implemented into clinical trials so comparison of results across studies is meaningful. A clear example of this is in metastatic brain tumor studies where multiple criteria have been used in the past. Once the criteria are implemented into prospective studies on a universal basis, subsequent validation and refinement can then be performed. This is an ongoing effort in the field.

Early on in the process of criteria development by the various RANO groups, it is critical to facilitate discussion, obtain early feedback and buy-in, and gain consensus from the neuro-oncology community. This is achieved by hosting two open meetings per year at the respective annual meetings of the American Society of Clinical Oncology (May/June) and the Society of Neuro-Oncology (November). This enhances multi-sector participation that spans the academic, community, pharmaceutical, governmental, federal, regulatory, and advocacy entities. This dynamic and iterative process is key to the success of RANO. The open meetings also establish a concrete timeline for updating the efforts of the working groups and provide a venue for identifying future projects.

Wide Dissemination of Results Through Publications

Another important principle is the mandate to widely disseminate the results of the working group efforts through presentations at national scientific meetings and through publication in high-impact journals. To date, 15 RANO-related manuscripts accepted for publication[1–15] reflect the breadth and depth of the topics and issues related to clinical trial design and conduct in neuro-oncology.

Importance of Volunteerism Among Colleagues

It is important to note that the RANO group is inclusive and independent without sponsorship or specific affiliation with any commercial, nonprofit, or governmental entity. This effort is truly a result of volunteerism among colleagues who are dedicated to critically appraising current standards to ultimately improve the design and conduct of clinical trials to more accurately and efficiently evaluate novel treatments across many tumor types. Although this is an advantage in terms of flexibility, the challenge is to accomplish the work in addition to the ongoing academic and clinical responsibilities of the participants. More recently, collaboration with other groups, such as the National Brain Tumor Society, has been initiated with major efforts focused on standardizing imaging-parameter acquisition and the standardization and incorporation of clinical outcome assessments into clinical trials. These include patient-reported outcomes and functional assessments. Further refining the imaging criteria for progression through correlative retrospective and prospective studies remains the future emphasis of the RANO effort.

Overview of Current and Future RANO Efforts

Initial Efforts in Glioma

As previously mentioned, the changing landscape of therapies for high-grade glioma was the impetus to reassess the criteria for determining response. Following an initial paper highlighting the limitations of imaging criteria, revised criteria were proposed for both high-grade glioma and low-grade glioma.[1–3] It was clear that several aspects of clinical benefit spanning seizure control, cognition, and symptom burden needed to be incorporated into clinical trials of this disease and these are highlighted in the RANO report on assessing outcomes in clinical trials of low-grade glioma.[3] Additionally, the evaluation of surgically based therapies for glioma was reviewed.[4] These revised criteria have since been incorporated into prospective clinical trial protocols universally and many investigators have performed analyses comparing the Macdonald and RECIST criteria.[16–19] In addition, acknowledgement of the limitations of the RANO criteria and the need to continually improve the assessment of response has been the focus of ongoing and future efforts.[20]

Expanding the Effort to Include Issues in Neuro-Oncology Trial Design and Conduct

As the therapeutic landscape changes we need to address challenges in the rapid and efficient assessment of novel therapies. The other major effort across RANO is the selection of specific clinical trial endpoints and a critical review of phase II clinical trial design. These reviews are important to foster novel design methodology, especially in the era of neuroimmunological approaches and precision-based medicine approaches.[5,6]

The Need for Independent Criteria Based Upon Pathology and Clinical Situations

The steering committee recognized early on in the formation of the group that scenario-specific criteria tailored to pathology and clinical situation would be an advantage. Expanding beyond glioma in adults, the RANO effort now spans response assessment in several tumor types. Pediatric tumors have different histological, molecular cytogenetic, and clinical courses than adult tumors and the RANO group on pediatrics (Response Assessment in Pediatric Neuro-Oncology [RAPNO]) will define these differences and make decisions about adopting appropriate criteria as outlined in the adult tumor population and identifying new criteria that are relevant to the pediatric population.[7] An example is the formation of separate working groups related to pontine glioma and primitive neuroectodermal (PNET) tumors.

Brain metastases are the most common brain tumors and clinical trials evaluating novel drug, surgical, and radiation strategies are ongoing. The RANO group on these tumors has identified the challenges related to solid tumor brain metastases in clinical trials and identified key factors that need to be addressed such as the heterogeneity of the patient population and the difficulty of determining response to treatment and progression.[8] Many therapeutic trials in metastatic brain disease have not demonstrated an improvement in overall survival mainly because of the overwhelming effect of the extent of systemic disease control on survival. This highlights the priority of assessing neurocognitive, neurological, and quality-of-life outcomes in this patient population and was the focus of a publication on this disease entity.[9] This group subsequently published proposed criteria that can be incorporated into trials.[10]

Leptomeningeal disease remains a particularly challenging entity to create standardized clinical trials for, and a working group is building consensus on the criteria that should be considered for this disease.[11] Collaboration among the leptomeningeal and PNET working groups will ensure synergistic efforts. Cross talk with the brain metastases group ensures alignment with that disease area as well. As targeted agents are increasingly tested in the usually slow-growing meningioma tumors, standardization for these trials will also be critical.[12,13] A newly formed working group is dedicated to spinal tumors.[14] A review of the challenges in these tumor types followed by proposed new standards for response criteria is the paradigm undertaken by all of these groups. Input into the clinical trial design of studies incorporating these proposed criteria will be the next step for these disease types.

New Imaging Modalities and Therapies and Other Challenges

Novel imaging biomarkers in neuro-oncology provide another challenge in determining how these techniques should be implemented to assess tumor burden and response to therapy. The PET-RANO group is charged with providing an overview of metabolic imaging in neuro-oncology as well as establishing parameters for standard acquisition across institutions. As new therapeutic strategies are clinically tested in neuro-oncology, prospectively evaluating response assessment is a critical step in terms of standardizing the criteria for determining response. This is particularly important if the mechanism of action is likely to result in an inflammatory response that could confound the imaging changes and result in high rates of pseudoprogression. The immunotherapy (i-RANO) group is an example of a working group charged with developing criteria in this area.[15] Recognizing the time it takes to validate criteria for a relatively new clinical area of interest, at least standardizing the criteria that could be incorporated across early immunotherapy trials will provide a database for evaluation and optimization. Future efforts will address the incorporation of volumetric-based tumor assessment as advanced image analysis tools become more widely available to support neuro-oncologists in clinical practice.

Other challenges of interest include the incorporation of standardized clinical measures such as the neurological examination, the use of corticosteroids, seizure characterization, and clinical outcome assessments that span patient-reported outcomes, neurocognitive function, and health-related quality-of-life measures. All of these topics are being explored in newly formed working groups within RANO and validation of the measures will be the priority. The impetus to focus on the neurological assessment was based on the importance of this metric in the response assessment criteria but lack of standardization across studies. As part of the RANO effort, a prospective interobserver and intraobserver variability study was initiated to assess the feasibility and ease of incorporating a scale based on various neurological domains. Several clinical trials are currently piloting this scale.

Synergistic efforts across other groups such as the Jumpstarting Brain Tumor Drug Development Coalition supported by the National Brain Tumor Society, Society For Neuro-Oncology, Musella Foundation, and Accelerated Brain Cancer Cure have resulted in the development of imaging acquisition standardization to facilitate the interpretation of imaging results across studies[21,22] This is viewed as a major priority among pharmaceutical members and regulatory representatives at the U.S. Food and Drug Administration (FDA). In the first FDA workshop focused on imaging endpoints in neuro-oncology, there was clear acceptance by the agency of the high-grade glioma criteria generated by the RANO group. There was, however, a firm mandate to standardize the acquisition of imaging parameters. With the

Table 1. Summary of RANO working groups, the respective leaders, and relevant publications

Working group	Leaders	Reference(s)
High-grade glioma	Patrick Wen	2
Low-grade glioma	Martin Van den Bent	3
Phase 2 design	Eva Galanis	6
Endpoints	David Reardon	5
Surgical trials	Michael Vogelbaum	4
Brain metastases	Nancy Lin	8–10
Leptomeningeal disease	Marc Chamberlain	11
Pediatrics	Mark Kieran	7
Meningioma	Michael Vogelbaum	12,13
Neurological assessment	David Reardon	
PET	Joerg Tonn	
Seizures	Edward Avila	
Steroids	Patrick Wen	
Immunotherapy	Hideho Okada, David Reardon	14
Spinal tumors	Arjun Sagal	15

collaboration between the Brain Tumor Group of the European Organization for Research and Therapy of Cancer and under the leadership of neuro-radiologists, recommendations for a Brain Tumor Imaging Protocol has been proposed, along with the scientific and practical aspects and challenges of incorporating these recommendations.[22] Internationally comprised working groups have been formed and are focused on the standardization of diffusion and perfusion imaging techniques that can be implemented into the early evaluation of novel agents in clinical trials to assess their role as biomarkers of response. Future efforts include integrating standardized clinical outcome assessments into neuro-oncology trials.

Summary of Current Working Groups, Leaders, and Respective Publication References

Table 1 outlines the current working groups and leaders, as well as publications that have arisen out of the respective working groups.

Conclusion

We provide an overview of the international and multidisciplinary RANO efforts to date. The initiative started with the identification of a single clinical challenge and has garnered support to address many other important issues in our field. The overarching goal is for a collaborative network to generate consensus criteria that is made accessible to the neuro-oncology community through communications at open national meetings and publications in high-impact journals. One of the important tenets of RANO is the validation and ongoing optimization of criteria. All of this work is volunteer-driven and would not be possible without the dedication and commitment of the members. We urge our colleagues who may be interested in participating in a working group to contact the respective group leaders.

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