Evolution of RANO in Assessing Brain Tumour Outcomes

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Abstract

Assessing treatment response is extremely important in management of brain tumours. Response assessment in neuro-oncology (RANO) was introduced in 2008 for the purpose of making recommendations for it by addressing and countering the limitations in previously reported response criteriae. Subsequently, multiple RANO working groups have been formed to cater to different tumour types and to update their previous recommendations to counter the limitations in their criteria. Herein we have a summarized list of RANO criteria for adult brain tumours.

Keywords: RANO, neuro-oncology, brain tumour, outcome

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Introduction

The effectiveness of treatment of brain tumours requires techniques to assess treatment response or progression. To cater to this need, Macdonald et al., published a criteria in 1990, to assess response to therapy in high-grade glioma.[1] This criteria provided an objective radiologic assessment of tumour response which was based on the change in the maximal cross-sectional area of contrast-enhanced tumours on CT imaging. However, it did not differentiate true response/progression from pseudo-response or pseudo-progression. Moreover, it failed to account for infiltrative disease beyond areas of enhancement, or non-enhancing tumours.

To mitigate these limitations, the Response Assessment in Neuro-Oncology (RANO) Working Group was formed and published criteria to assess treatment response in high-grade glioma in 2010.[2] However, it became clear that separate criteria were needed to assess other tumour subtypes hence, RANO has worked to develop criteria to determine the response criteria of different tumours. In this article, we present an overview of the RANO efforts in adult tumours.

Review of Evidence

RANO working group first developed criteria to define treatment response in patients with high-grade glioma (HGG).[2] They categorized diseases as either measurable, or non-measurable. Measurable disease was any lesion diagnosed on T1-post-contrast with well-defined margins measuring ≥10mm in 2 perpendicular dimensions. On the other hand, non-measurable disease was defined as any T1 post-contrast lesion with maximal dimension < 10mm or cystic/necrotic regions of a tumour or surgical cavity. The authors also addressed pseudo-progression by recommending that post-radiation enhancement within 12 weeks of therapy should be considered pseudo-progression unless confirmed by histopathology; or if enhancement is clearly outside the radiation field. In addition to this, to counter pseudo-progression, they recommended that post-surgical MRI should be performed within 24-48 hours of surgery. Furthermore, they considered non-enhancing T2-FLAIR changes, corticosteroid use, and clinical status to classify an individual's treatment response. True progression was considered in an individual having enlarging areas of non-enhancing T2/FLAIR signals. However, no objective quantifiable measurement was proposed for non-enhancing lesions, which is a limitation of these criteria.

Low-grade glioma (LGG) is usually non-enhancing and slow growing therefore Bent et al., developed RANO criteria specifically for LGG in 2011.[3] These criteria had a similar definition of measurable and non-measurable disease, but it was measured on T2/FLAIR imaging as opposed to T1-contrast. A minor response criterion was also introduced to cater to the small changes in T2/FLAIR. A frequent challenge in LGGs is determining whether T2/FLAIR changes are due to tumour or post-surgical changes, post-radiation changes, demyelination, ischaemia, or other co-morbidities. To address this, RANO-LGG emphasized on integration of clinical outcome assessments, such as seizure control, quality of life, and neurocognitive status, with radiographic assessments, to determine treatment response.

Lin et al., proposed recommendations for therapy response in brain metastasis by forming a RANO-BM working group.[4] This group defined measurable disease as any contrast-enhancing lesion with the longest diameter > 10mm and a perpendicular diameter ≥5mm. Whereas a non-measurable lesion was defined as any lesion < 10mm, with borders that are non-reproducible or lesions in dura, bone, or leptomeninges, or lesions that only have cystic

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component. Moreover, they defined target lesions as 5 measurable lesions after accounting for their size, reliability of measurement, and recurrence following local treatment. Non-target lesions were all other lesions. Overall CNS response was defined as a combination of quantitative change in 2-dimensional measurements of target lesions, qualitative change in non-target lesions, corticosteroid use, and clinical status. RANO-BM used a bi-compartmental approach to define therapy responses in CNS and non-CNS diseases. However, these criteria use one-dimensional measurement and do not offer guidance for investigators who want to use volumetric assessment.

Immunotherapy-RANO criteria were developed by Okada et al., to evaluate treatment response specifically for immunotherapy agents against immune checkpoint molecules like PD-L1 and CTLA-4, which cause therapy-related radiographic changes that are difficult to distinguish from the true progression.[5] To evaluate true radiographic progression, I-RANO proposed a repeat scan 3 months after contrast-enhancement is detected on a scan taken less than 6 months after immunotherapy in the absence of clinical deterioration. However, delaying therapy may be harmful in tumour types in which pseudo-progression is unlikely.

Chamberlain et al., published RANO-leptomeninges (LM) response criteria. This contained 3 aspects: neurological assessment, radiographic assessment, and CSF cytology or flow cytometry (FC).[6] They defined disease progression as either worsened radiographic or neurological assessment. However, they lacked consensus on defining disease progression based on CSF cytology/ FC. They suggested that progressive disease is considered in patients with persistently positive cytology or those with conversion of cytology from negative to positive. However, in cases where patients are persistently positive but are clinically and radiologically stable, it is difficult to determine refractory disease.

Ellingson et al., published a modified RANO approach to overcome challenges in the original RANO recommendations.[7] They recommended the use of post-radiotherapy MRI instead of post-surgical MRI for newly diagnosed glioblastoma as a baseline, and a repeat MRI to confirm progression. Moreover, they recommended considering only enhancing disease to determine tumour response/progression as opposed to previously employed qualitative assessment using T2/FLAIR.

Wen et al., published the RANO 2.0 criteria which was used as a standard for both high-grade and low-grade gliomas.[8] It reiterated the use of post-radiotherapy scans as a baseline in newly diagnosed settings. Moreover, they recommended confirmation of progression within 3 months of radiotherapy with repeat MRI or histopathology. However, beyond 3 months of radiotherapy, scans are not required to determine tumour progression or to evaluate the treatment response of recurrent tumours. Treatments with a likelihood of pseudo-progression mandate the use of a repeat MRI. Furthermore, they recommended that for IDH-wild glioblastoma, non-enhancing disease will not be evaluated and in IDH-mutated tumours, both enhancing and non-enhancing components of the tumour will be evaluated for response assessment.

Conclusion

RANO has paved the path to quantify response assessment in neuro-oncology. With the advent of advanced imaging techniques such as diffusion and perfusion imaging, magnetic resonance spectroscopy and amino acid positron emission tomography, that can more accurately determine tumour burden, RANO will not only require regular upgrades, but will also require validation studies to incorporate these advances.

References

1. Macdonald DR, Cascino TL, Schold SC, Jr., Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol. 1990;8:1277-80.
2. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010;28:1963-72.
3. van den Bent MJ, Wefel JS, Schiff D, Taphoorn MJ, Jaeckle K, Junck L, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. Lancet Oncol. 2011;12:583-93.
4. Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol. 2015;16:e270-8.
5. Okada H, Weller M, Huang R, Finocchiaro G, Gilbert MR, Wick W, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol. 2015;16:e534-e42.
6. Chamberlain M, Junck L, Brandsma D, Soffietti R, Rudà R, Raizer J, et al. Leptomeningeal metastases: a RANO proposal for response criteria. Neuro Oncol. 2017;19:484-92.
7. Ellingson BM, Wen PY, Cloughesy TF. Modified criteria for radiographic response assessment in glioblastoma clinical trials. Neurotherapeutics. 2017;14:307-20.
8. Wen PY, van den Bent M, Vogelbaum MA, Chang SM. RANO 2.0: The revised Response Assessment in Neuro-Oncology (RANO) criteria for high- and low-grade glial tumours in adults designed for the future. Neuro Oncol. 2023. doi: 10.1093/neuonc/noad189. Epub ahead of print. PMID: 37774741.