

RAPNO efforts in Brain Tumour Outcomes

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Abstract

Assessing treatment efficacy for brain tumours has evolved since its inception with the introduction of MacDonald's criteria, which pioneered the utility of imaging to determine an objective and quantifiable response to treatment. This criterion failed to distinguish pseudo response or progression from progression and did not account for non-enhancing disease therefore; the response assessment in neuro-oncology (RANO) working group was established to account for these limitations. Since, its commencement it has worked to determine response assessment for multiple tumours. As paediatric tumours exhibit heterogeneous and variable-enhancing characteristics, the response assessment in paediatric neuro-oncology (RAPNO) working group was formed to create separate criteria. Six response criteria have been published to date, and the article summarizes them.

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Introduction

In neurooncology, assessing treatment response is particularly complicated. For this reason, Macdonald et al., established criteria that considered changes in 2-dimensional contrast enhancing measurements on CT/MRI, clinical status, and steroid use to define tumour response or progression.¹ However, it had two major limitations, it failed to account for non-enhancing tumours, and it was not able to distinguish true response or progression from pseudo-response/progression. To address these limitations, the RANO working group was established to redefine response assessments of brain tumours.² Since, its inception it has worked to produce response criteria for several adult brain tumours.

Although RANO criteria proved valuable for assessing adult brain tumour outcomes, there were many challenges unique to paediatric brain tumours.³ Childhood brain tumours are heterogeneous with variable enhancement on imaging and no standard definitions of response or progression. This called for the establishment of the Response Assessment in Paediatric Neurooncology.
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(RAPNO) working group to define response assessment in paediatric brain tumours. In this article, we present an overview of all these efforts to date.

Review of Evidence

Warren et. al recommended RAPNO guidelines for medulloblastoma (MBL) and leptomeningeal seeding tumours.⁴ These applied to all medulloblastoma subtypes and both children and adults. It was recommended that a post-operative brain MRI for residual tumour analysis should be obtained within 72 hours of surgery and if post-surgical changes obscure detection, then a second MRI should be obtained within 2-3 weeks of surgery. Moreover, follow-up MRI should be obtained every 2 cycles except for therapy-related effects but should occur at least every 3 months. For spinal metastases, preoperative MRI, or if not available then post-operative MRI within 72 hours of surgery should be used as a baseline.⁴

Furthermore, surveillance spinal imaging should be obtained with brain imaging in patients with initial leptomeningeal metastasis or positive CSF cytology at baseline and repeat spine imaging should be performed in patients with new spine symptoms. To assess treatment efficacy, the MRI sequence that best shows tumour extent should be used for measuring both enhancing and non-enhancing lesions and the largest tumour diameter and perpendicular to be used for 2D measurements of lesions. Moreover, specific recommendations for response, stable and progressive disease were made, but no recommendations were made on quantitative measurement of extra-CNS disease, incorporation of quality of life, and neurocognitive outcomes which is a potential limitation to be addressed in the future.⁴

Fangusaro et al., developed the RAPNO criteria to assess paediatric low-grade glioma (pLGG), which differs from adult LGG due to its cystic components and variable enhancement, necessitating unique evaluation methods.⁵ RAPNO emphasizes the assessment of non-enhancing infiltrative disease using T2/FLAIR imaging and recommends incorporating cystic components, particularly tumour cysts, into tumour measurements. It defines measurable lesions as those present in all three planes with a diameter of at least 10mm and introduces a minor response criterion to address the slow growth of pLGG. The criteria also suggest correlating changes in visual status with radiographic changes for response evaluation, given

the common involvement of the optic pathway in pLGG. While pLGG often leads to neurological and functional decline, as observed on functional MRI, additional research is needed to incorporate this information into response assessment protocols.⁵

Erker et al., suggested guidelines for paediatric high-grade gliomas (PHGG). They are diffusely infiltrative, with ill-defined margins and heterogeneous contrast enhancement that makes their identification difficult.⁶ RAPNO recommended a brain and spine imaging protocol that included the measurement of necrotic tissue and cystic components that are within a tumour. Moreover, T2/FLAIR was recommended to be used for non-enhancing or minimally-enhancing tumours. Moreover, diffusion-weighted imaging was suggested to be used as a qualitative measurement of response. Baseline post-operative imaging was recommended between 24-72 hours post-operatively with post-therapy imaging at a minimum of 8 weeks to determine initial treatment response. Future recommendations included the use of advanced imaging, volumetric analysis, and the utility of biomarkers in response assessment.⁶

Cooney et al., formed the RAPNO group for diffuse intrinsic pontine glioma (DIPG) separately from HGG as it is an aggressive brainstem tumour with a median overall survival of less than a year. T2 or T2/FLAIR was recommended for tumour measurements with a baseline scan no earlier than 4 weeks before starting therapy or 4-6 weeks after therapy for new baseline imaging.⁷ Response assessment was determined using imaging, neurological assessment, and anti-inflammatory or antiangiogenic agents.⁷

Hoffman et al., formulated RAPNO recommendations for craniopharyngioma. It was recommended to obtain an MRI pre-operatively and within 2 weeks of surgery with follow-ups every 3 months on treatment.⁸ A radiologic response includes a measurement of both solid and cystic components however they can be approached separately in certain situations. Response definitions include endocrine and visual assessment. Moreover, cystic disease associated with functional impairment was considered as tumour progression.⁸

Lindsay et al., established the RAPNO group to address intracranial ependymoma. Their recommendations include pre- and post-contrast T1-weighted, T2-weighted, post-contrast T2 FLAIR, and diffusion-weighted brain imaging.⁹ Residual disease is defined as a tumour with a maximum diameter of 5mm or less in any plane, while subtotal resection entails a residual tumour with a diameter of 5mm or more. They propose conducting a baseline MRI within 24-72 hours post-surgery. Additionally, response assessment should involve brain and spine MRI, CSF

cytology, neurological examination, and monitoring steroid use.⁹

Conclusion

This review delineates the RAPNO efforts of different types of paediatric brain tumours, including low-grade gliomas, high-grade gliomas, diffuse intrinsic pontine gliomas, craniopharyngiomas, and intracranial ependymomas, each offering specific recommendations for imaging protocols and response assessment methods. Overall, these efforts represent significant progress in standardizing response assessment in Paediatric neuro-oncology, enhancing clinical decision-making and patient care. As they all are new, these needs to be validated in clinical trials. Future directions include the use of advanced imaging and volumetric analysis to better determine the effect of therapy.

References

1. Macdonald DR, Cascino TL, Schold Jr SC, 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. Warren KE, Poussaint TY, Vezina G, Hargrave D, Packer RJ, Goldman S, et.al. Challenges with defining response to antitumor agents in pediatric neuro-oncology: A report from the response assessment in pediatric neuro-oncology (RAPNO) working group. *Pediatr Blood Cancer.* 2013;60:1397-401.
4. Warren KE, Vezina G, Poussaint TY, Warmuth-Metz M, Chamberlain MC, Packer RJ, et.al. Response assessment in medulloblastoma and leptomeningeal seeding tumours: recommendations from the Response Assessment in Pediatric Neuro-Oncology committee. *Neuro Oncol.* 2018;20:13-23.
5. Fangusaro J, Witt O, Driever PH, Bag AK, de Blank P, Kadom N, et.al. Response assessment in paediatric low-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *The Lancet Oncol.* 2020;21:e305-16.
6. Erker C, Tamrazi B, Poussaint TY, Mueller S, Mata-Mbemba D, Franceschi E, et.al. Response assessment in paediatric high-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *The Lancet Oncol.* 2020;21:e317-29.
7. Cooney TM, Cohen KJ, Guimaraes CV, Dhall G, Leach J, Massimino M, et.al. Response assessment in diffuse intrinsic pontine glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *The Lancet Oncol.* 2020;21:e330-6.
8. Hoffman LM, Jaimes C, Mankad K, Mirsky DM, Tamrazi B, Tinkle CL, et.al. Response assessment in pediatric craniopharyngioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) Working Group. *Neuro-oncol.* 2023 ;25:224-33.
9. Lindsay HB, Massimino M, Avula S, Stivaros S, Grundy R, Metrock K, et.al. Response assessment in paediatric intracranial ependymoma: Recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *The Lancet Oncol.* 2022;23:e393-401.