Imaging Guidelines for Paediatric Brain Tumours 3

Response assessment in diffuse intrinsic pontine glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group

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Optimising the conduct of clinical trials for diffuse intrinsic pontine glioma involves use of consistent, objective disease assessments and standardised response criteria. The Response Assessment in Pediatric Neuro-Oncology working group, consisting of an international panel of paediatric and adult neuro-oncologists, clinicians, radiologists, radiation oncologists, and neurosurgeons, was established to address issues and unique challenges in assessing response in children with CNS tumours. A working group was formed specifically to address response assessment in children and young adults with diffuse intrinsic pontine glioma and to develop a consensus on recommendations for response assessment. Response should be assessed using MRI of brain and spine, neurological examination, and anti-inflammatory or antiangiogenic drugs. Clinical imaging standards are defined. As with previous consensus recommendations, these recommendations will need to be validated in prospective clinical trials.

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This is the third paper in a **Series** of three papers on imaging guidelines for paediatric brain tumours

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Introduction

Diffuse intrinsic pontine glioma (DIPG) is an aggressive brainstem tumour of childhood that carries a median overall survival of less than 1 year.[1,2] Although our understanding of DIPG biology continues to expand, a diagnosis can still be made on the basis of clinical and imaging features alone, without the acquisition of tissue. The characteristic findings on clinical examination include the triad of multiple cranial neuropathies, long tract signs (hyper-reflexia, clonus, increased tone, and presence of a Babinski reflex), and ataxia. Classic features on MRI are a homogeneous mass centred within the pons, encompassing at least 50% of the pons, and causing them to expand (figure). DIPGs are typically hypointense or isointense on T1-weighted MRI sequences, hyperintense on T2-weighted MRI sequences, and hyperintense on fluid attenuated inversion recovery (FLAIR) sequences. DIPGs can show little or no contrast enhancement at initial diagnosis, but enhancement patterns can vary considerably.[3–9] Often, involvement of the pons is ventral and encases the basilar artery (figure).[6,10,11] Treatment options for these children are scarce, and enrolment on clinical trials upfront or at relapse is common.

Optimising the conduct of clinical trials involves use of consistent, objective disease assessments and standardised response criteria. The Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group, consisting of an international panel of paediatric and adult neuro-oncologists, clinicians, radiologists, radiation oncologists, and neurosurgeons, was established to address issues and unique challenges in assessing response in children with CNS tumours.[12] Although the majority of DIPG tumours share biological similarities with other diffuse midline gliomas, DIPGs involve a unique set of challenges for diagnosis, treatment, and response assessment and the following recommendations pertain specifically to DIPGs. A RAPNO working group was formed specifically to address response assessment in children and young adults with DIPG, and to develop a consensus on recommendations for response assessment that can be prospectively evaluated in clinical trials. In generating these recommendations, major confounding issues were first identified, the literature and current practices were then reviewed, and recommendations were subsequently developed about which consensus was reached. These recommendations were based upon scientific evidence when available, common clinical practice, and the expertise of RAPNO working group members.

Specific issues and challenges with response assessment in DIPG

Defining DIPG

Although the use of brainstem biopsy has become increasingly common in the era of modern surgical technology and advanced techniques, diagnosis of DIPG is most commonly made on the basis of clinical and MRI criteria described earlier.[13–15] Misdiagnosis was recognised as a possibility in the absence of tissue acquisition, as has been documented in case reports, reported anecdotally by RAPNO working group members, and described as an issue by the 2019 International DIPG Symposium.[16,17]

Disease classification

Advances in the understanding of DIPG biology include the discovery of a mutation in the genes encoding histone H3.1 (*HIST1H3B* [*H3C2*] and *HIST1H3C* [*H3C3*]) and histone H3.3 (*H3F3A* [*H3-3A*]), now defined as "diffuse midline glioma, H3 K27M [Lys27Met]-mutant" in the

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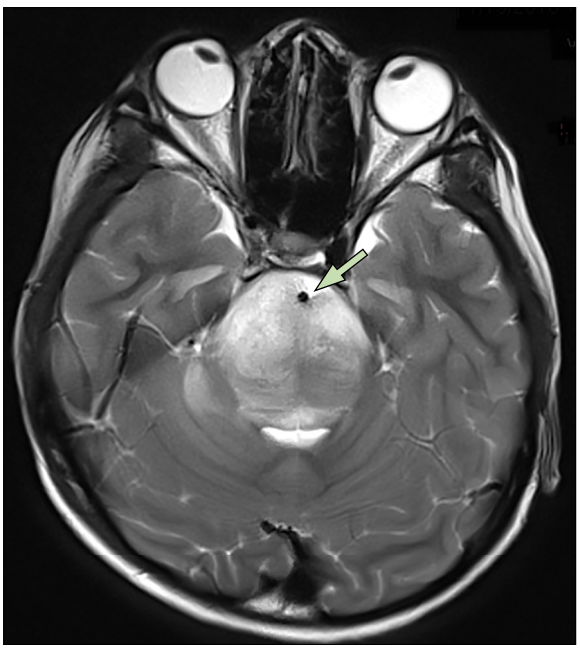

Figure: **MRI of diffuse intrinsic pontine glioma**
Axial T2-weighted MRI shows a homogeneous mass centred within the pons, encasing the basilar artery (arrow), and causing the pons to expand.

2016 revision of the WHO Classification of Tumors of the Central Nervous System.[18–20] DIPG largely represents the anatomical variant of diffuse midline glioma H3 K27M-mutant presenting in the pons, but can also include diffuse midline glioma H3 wild type.[21] As far as we know, to date no specific imaging criteria have been prospectively proven to delineate H3 wild type diffuse pontine glioma from H3 Lys27Met-mutated diffuse pontine glioma. Furthermore, how genetic heterogeneity corresponds to radiographic heterogeneity has yet to be explored.

Imaging response

Accurate, reproducible assessments that reflect potential clinical benefit are crucial to determine response to therapy and compare results across studies. DIPGs are infiltrative tumours with often indistinct borders, and tumour measurements are difficult to obtain reliably and consistently, even among experienced imaging readers.[22] Previous studies have shown poor inter-reader agreement in determining DIPG tumour size.[7,22–24] Furthermore, what constitutes a meaningful reduction in tumour size, to be applied as an objective response, has not been well documented, most likely owing to an absence of proven, effective therapies. In one study of 39 patients with DIPG, no standard change in size measured by MRI—whether measured by Response Evaluation Criteria in Solid Tumors (ie, the sum of the longest diameters of target lesions) or WHO criteria (ie, the sum of the products of the perpendicular diameters of target lesions) to either the baseline or post-treatment scans—had a statistically significant association with overall survival.[8] One retrospective series of 75 patients with DIPG reported lower inter-reader variability measuring the entirety of the pons, as opposed to presumed tumour boundaries, with changes in one-dimensional and two-dimensional pons size over time showing prognostic utility, but this method has not yet been validated prospectively.[25] In a subsequent report from the Pediatric Brain Tumor Consortium, the cohort of 106 children with DIPG who had a 25% decrease in either tumour volume (as measured by FLAIR sequences on MRI) or diffusion ratio values had longer progression-free survival (p=0·028) and overall survival (p=0·0009) than those who did not have a 25% decrease in tumour volume (overall survival at 6 months was 70% *vs* 20%).[7]

An additional challenge of defining response on the basis of change in tumour size on imaging is interpreting primary tumour volume changes after focal pontine drug delivery. A single-centre, phase 1 trial of radiolabelled antibody ^{124}I-8H9 given by convection-enhanced delivery for DIPG was published in 2018, showing promising results of safety and feasibility.[26] Several other phase 1 trials on convection-enhanced delivery for DIPG are ongoing (NCT03566199, NCT03086616, NCT01502917), and we anticipate seeing trial evaluations of efficacy in the near future. Tumour volume can increase because of infused drug volume and oedema, and might not reflect long term response. Also, extrapontine disease might be unaffected by direct drug delivery into the tumour, and needs to be assessed separately.

Steroid and angiogenic inhibitor use

Steroids and bevacizumab are used in the management of patients with DIPG, from diagnosis through to end-of-life care. There have been calls for the development of evidence-based guidelines for steroid prescription in DIPG.[27,28] Steroid use should be considered when interpreting imaging information, as steroids can contribute to tumour volume changes through reduction of oedema, which could lead to inaccuracies in response assessment and potential overestimation of therapeutic response.[29] Bevacizumab is often used for DIPG as an alternative to steroids, or as a means to reduce the dose of steroids.[27] Data are scarce regarding the effects of bevacizumab on imaging response, but the RAPNO working group agrees that bevacizumab use should also be considered when interpreting imaging information because, like steroids, it might contribute to tumour volume changes, as is consistent with paediatric high-grade glioma RAPNO guidelines presented in this Series.

Pseudoprogression

Pseudoprogression because of inflammation caused by anti-tumour therapy can manifest as worsened imaging appearance with or without clinical symptoms, or as worsened clinical symptoms only; either manifestation is suggestive of disease progression, but each subsequently

resolves or stabilises without treatment. Interpretation of either steroid or bevacizumab use can be further complicated by pseudoprogression, a known occurrence in 21–44% of DIPG cases.[30–33] Appropriate recognition of pseudoprogression is necessary to prevent premature discontinuation of adjuvant treatment.

Recommendations for assessing DIPG response

The following methods should be used to assess DIPG response in clinical trials: MRI of brain and spine, neurological examination, and use of anti-inflammatory drugs (ie, steroids) or antiangiogenics (ie, bevacizumab). The following DIPG response criteria should be used for all forms of DIPG, regardless of molecular subtype. Of note, H3 Lys27Met-mutated diffuse midline gliomas arising outside of the pons are included within the RAPNO recommendations for paediatric high-grade glioma in this Series.

Imaging standards for clinical trials for DIPG

As recommended by the Brain Tumor Imaging Standardization Steering Committee, clinical trials should have prespecified imaging parameters, and patients should be assessed using the same imaging method and magnet strength throughout the trial.[34] In keeping with the principles of maximising compliance of standards and imaging quality across imaging centres with varied capacity, image acquisition should use common sequences that are readily available at most centres to address the primary study endpoints. Additional imaging sequences (eg, perfusion imaging, diffusion tensor imaging, spectroscopy, PET) could be added at sites with the capability, to address specific additional research objectives, but should not be used in the primary assessment of response. The following imaging techniques and sequences are recommended.

Brain imaging

Basic characterisation of the tumour is achieved with multiplanar sequences including T1-weighted, T2-weighted, and FLAIR sequences, and slice thickness should be 4 mm or less with a minimal gap or no gap (table 1). T1-weighted sequence (precontrast and postcontrast) is done as part of routine MRI procedures, but has restricted use in characterising the pontine tumour, as tumour delineation on T1-weighted sequencing without contrast can be difficult, and contrast enhancement in DIPG can vary, both interpatient and intrapatient.[5] Although diffusion-weighted sequences are commonly obtained in imaging these tumours, intratumoural heterogeneity can make diffusion-weighted MRI measurements challenging to interpret, and the role of diffusion imaging in DIPG response evaluation has yet to be established.[30,35–37] Although evidence suggests T2-weighted sequences show better discrimination of intratumoural heterogeneity than FLAIR sequences, either T2-weighted or FLAIR sequences can be used to measure tumour diameter.[38] FLAIR images should be obtained ideally after contrast administration. For imaging tumour protocol, see table 1.

Baseline scan timing for all patients should be no earlier than 4 weeks before entry onto a clinical trial. In newly diagnosed patients with pretreatment specified as the clinical trial baseline and who had a biopsy, prebiopsy imaging can be used as the baseline, if the imaging was done no earlier than 4 weeks before trial entry and perioperative complications from biopsy or changes in neurological status are not substantial.

If the postradiotherapy scan is specified as the clinical trial baseline, it should be done 4–6 weeks after radiotherapy is completed.

Subsequent imaging in trials that incorporate upfront focal radiation should be done 4–6 weeks after radiotherapy is completed. Thereafter, for all trials, brain MRI should be done every two cycles of therapy (assuming a cycle is ≤6 weeks in length), with possible exceptions depending on the timing of anticipated effects of therapy (eg, immunotherapy), but should be done at least once every 3 months. Pseudoprogression is not uncommon in patients with DIPG.[32] If it is unclear that the patient has disease progression, it might be a reasonable option to keep the patient in the study until subsequent assessments, done 4–8 weeks later, to clarify interpretation. If the subsequent assessment confirms disease progression, the date of progression should be backdated to the onset of imaging changes, if those changes preceded neurological deterioration.

Spine imaging

There is little information in the literature regarding standards for screening for tumour metastases in DIPG. Distant leptomeningeal spread has been reported in as many as 20% of DIPG cases and is likely to be under-detected.[39–43] Furthermore, screening practices and experience differ among individual institutions. Recommendations for assessment of leptomeningeal disease in patients with DIPG include radiographic assessment only, as cerebrospinal fluid acquisition might entail risk to some patients and the risk–benefit ratio of obtaining cerebrospinal fluid should be assessed by the treating physicians. However, standards for uniform imaging and quality control should be incorporated into clinical trials, and the following recommendations are made, consistent with RAPNO spine imaging guidelines for high-grade glioma.

Imaging of the spine should be done immediately after brain MRI, with a postcontrast T1-weighted series acquired first, followed by a steady-state acquisition (either, constructive interference steady-state or fast imaging employing steady-state acquisition) sequence in the sagittal plane. An additional injection of intravenous contrast is not recommended, because all T1-weighted spine imaging can usually be acquired within 45 min of initial contrast administration using the recommended

	Sequence	Slice thickness	Gap percentage	In-plane resolution	Comment
Brain					
1	Axial T2-weighted turbo spin echo or fast spin echo	≤4 mm	0	≤1·0 × 1·0 mm	None
2	(a) 3D T1-weighted MPRAGE, SPGR, fast field echo, or turbo field echo; or (b) axial T1-weighted spin echo, turbo spin echo, or fast spin echo	(a) 1–1·5 mm; (b) ≤4 mm	(a) 0; (b) 0–10%	(a) 1·0 × 1·0 mm; (b) 1·0 × 1·0 mm	Sagittal, coronal, or axial plane
Gadolinium contrast administration					
3	Axial T2-weighted FLAIR plus contrast	≤4 mm	0	≤1·0 × 1·0 mm	Can acquire as first postcontrast sequence
4	Axial T1-weighted spin echo, turbo spin echo, or fast spin echo, plus contrast	≤4 mm	0–10%	≤1·0 × 1·0 mm	Avoid flow compensation and fat saturation
5	(a) 3D T1-weighted SPACE, Cube, or VISTA, plus contrast; or (b) coronal T1-weighted spin echo, plus contrast	1 mm	0	1·0 × 1·0 mm	Sagittal or coronal plane; avoid flow compensation and acquire images in consecutive order
Spine					
1 and 2	Sagittal T1-weighted spin echo, upper or lower, plus contrast	3 mm	0–10%	≤1·0 × 1·0 mm	Use anterior saturation band
3 and 4	(a) Axial T1-weighted VIBE, FAME, LAVA, or THRIVE, plus contrast upper or lower; or (b) axial spin echo T1-weighted, upper or lower, plus contrast; or (c) axial T1-weighted FLAIR (propeller), upper or lower, plus contrast	(a) 3 mm; (b) 4–5 mm; (c) 4–5 mm	(a) 0; (b) 10%; (c) 10%	(a) ≤1·0 × 1·0 mm; (b) ≤1·0 × 1·0 mm; (c) ≤1·0 × 1·0 mm	Acquire images in consecutive order
5 and 6	Sagittal CISS or FIESTA, upper or lower	1 mm	0	≤1·0 × 1·0 mm	Can replace with T2-weighted sagittal imaging with SPACE, Cube, or VISTA

3D=three dimensional. CISS=constructive interference in the steady state. FAME=fast acquisition with multiphase enhanced fast gradient echo. FIESTA=fast imaging using steady-state acquisition. FLAIR=fluid-attenuated inversion recovery. LAVA= liver acquisition with volume acquisition. MPRAGE=magnetisation-prepared rapid acquisition with gradient echo. SPACE=sampling perfection with application optimised contrasts using different flip angle evolution. SPGR= spoiled gradient recalled. THRIVE=T1-weighted high-resolution isotropic volume examination. VIBE=volumetric interpolated breath-hold sequence. VISTA=volume isotropic turbo spin echo acquisition.

Table 1: **Recommended imaging sequences and parameters for assessment of diffuse intrinsic pontine gliomas**

sequences. For postcontrast sagittal T1-weighted sequencing, slice thickness should be 3 mm or less with a minimal gap or no gap. To minimise motion artifacts from the chest and abdomen, anterior saturation pulses should be placed close to the anterior margin of the spinal column.[44]

For patients without spinal metastasis at baseline, repeat spine imaging is required only at the onset of clinically suspicious signs or symptoms, or in the rare case of complete response in the brain, to confirm complete absence of radiographic disease. Patients with spinal metastasis should have follow-up spine MRI for assessment of response done with brain imaging every two cycles, with possible exceptions depending on the timing of anticipated effects of therapy (eg, immunotherapy), but at least once every 3 months.

Quality control for imaging

As stated earlier, the use of clinical and imaging criteria alone for DIPG leaves room for subjectivity of interpretation and misdiagnosis.[16,17] Furthermore, inter-reader variability has been well described for measurements of DIPG, which is understandable when considering the invasive nature, ill-defined borders, and hazy patterns of enhancement of tumours.[22,45] The small amount of published data available, and the experience of RAPNO working group members, show that MRI results as interpreted by local radiologists, and not by central neuroradiology reviewers, are not adequate for assessment of response on clinical trials. Discordant results from different centres have an effect on the interpretation of clinical trial results and are also of relevance in determining optimal treatment for an individual patient. The following recommendations are made for determining acceptable imaging for use in clinical trials.

Centralised MRI review, for confirmation of DIPG by neuroradiologists with expertise in paediatric CNS imaging, should be done before patient inclusion in a treatment cohort. Substantial motion artifacts or metal artifacts (eg, orthodontics, Ommaya reservoirs) should be absent. To minimise motion artifacts from the chest and abdomen, anterior saturation pulses should be placed close to the anterior margin of the spinal column. Baseline spinal MRI should include full visualisation of the entire spine.

Neurological examination

Evaluation of neurological functioning has yet to be regularly included as an endpoint in clinical trials for patients with paediatric brain tumours. Furthermore, there are no published data regarding neurological assessments specifically for patients with DIPG. As such,

	Complete response	Partial response		Stable disease	Progressive disease	
		Pons	Extrapontine*		Pons	Extrapontine*
Brain MRI	No evidence of disease (enhancing or non-enhancing, measurable or non-measurable) maintained for ≥8 weeks; no new lesions	≥25% decrease (compared with baseline) in the 2D product of the largest perpendicular diameters (using T2-weighted or FLAIR sequences) maintained for ≥8 weeks.	≥50% decrease (compared with baseline) in the 2D product of the largest perpendicular diameters of all (up to three measurable lesions, using T2-weighted or FLAIR sequences) measurable lesions maintained for a ≥8 weeks	Does not meet criteria for complete response, partial response, or progressive disease	≥25% increase (compared with smallest measurement at any timepoint from trial baseline) in the 2D product of the perpendicular diameters (using T2-weighted or FLAIR sequences)†	≥25% increase (compared with smallest measurement at any timepoint from trial baseline) in the 2D product of perpendicular diameters (using T2-weighted or FLAIR sequences) of any measurable lesion†; any new sites of disease
Spine MRI‡	No evidence of disease (enhancing or non-enhancing, measurable or non-measurable) maintained for ≥8 weeks; no new lesions	Not applicable	≥50% decrease (compared with baseline) in the 2D product of perpendicular diameters of all measurable lesions maintained for ≥8 weeks	Does not meet criteria for complete response, partial response, or progressive disease	Not applicable	≥25% increase (compared with smallest measurement at any timepoint) in the 2D product of perpendicular diameters of any measurable lesion; any new tumour
Neurological examination	Stable or improving	Stable or improving	Stable or improving	Stable or improving	Clinical deterioration not attributable to other causes	Not applicable
Steroid and antiangiogenic drugs dose	Off steroids or physiological replacement doses and off antiangiogenics	Stable or on less than the baseline dose of steroids and off antiangiogenics	Stable or on less than the baseline dose of steroids and off antiangiogenics	Stable or on less than the baseline dose of steroids and off antiangiogenics	Not applicable	Not applicable

All criteria must be met to define a complete response, partial response, or stable disease; however, to define progressive disease, only one criterion must be met. 2D=two-dimensional. FLAIR=fluid-attenuated inversion recovery. RAPNO=Response Assessment in Pediatric Neuro-Oncology. *Extrapontine refers to lesions non-contiguous to the primary pontine lesion. †Measurements meeting the criteria for progressive disease that, in the opinion of the investigator, might reflect treatment effect (eg, pseudoprogression) should be coded as indeterminate. If subsequent imaging done 4–8 weeks later confirms progressive disease, the timepoint at which progressive disease is declared should be backdated to the time of the indeterminate scan. ‡For patients without spinal metastasis at baseline, repeat spine imaging is required only at the onset of clinically suspicious signs or symptoms, or in the rare case of complete response in the brain to confirm complete absence of radiographic disease.

Table 2: **RAPNO response criteria for assessment of diffuse intrinsic pontine glioma**

the RAPNO working group recommends response criteria for neurological examination consistent with previously published RAPNO response criteria. For medulloblastoma and leptomeningeal seeding tumours, RAPNO recommends doing the neurological examination, using a standardised method if available, at baseline and concurrent with imaging done during the trial.[46] If it is unclear whether the patient has disease progression, it would be a reasonable option to keep the patient in the study until subsequent assessments confirm disease progression. If subsequent assessment confirms progression, the date of progression should be backdated to the onset of neurological deterioration, if deterioration preceded radiological changes.

Definitions of response

The recommended criteria for defining response or progression for patients with DIPG enrolled on clinical trials, based on the available literature, existing clinical practice, and RAPNO working group clinical experience, are shown in table 2. Importantly, all of the criteria must be met to determine either an objective response or stable disease, whereas progression is defined when any of the listed criteria are met. If any criterion for disease progression is not clearly met (eg, unclear worsening on neurological examination, or increase in tumour measurements but pseudoprogression is suspected), the investigator's discretion can be used to retain a patient in the study until disease progression is definitive, but the date of disease progression should be backdated to the initial questionable progression timepoint, if progression is ultimately confirmed on subsequent assessments.

RAPNO defines measurable disease as a tumour, enhancing or non-enhancing, which is either (1) at least 1 cm, or (2) at least two times (in both perpendicular diameters) the MRI slice thickness, plus the interslice gap. Non-measurable is defined as a tumour too small to be accurately measured, being either less than 1 cm in both perpendicular dimensions, or less than two times the MRI slice thickness, plus the interslice gap. Leptomeningeal disease is considered as non-measurable. Cystic lesions are generally considered as non-measurable, unless they are not readily separable from the solid tumour component. Our definitions are consistent with the RAPNO recommendations for paediatric high-grade gliomas in this Series.[47]

For imaging studies, the lesion should be measurable at baseline (ie, either at least 1 cm, or at least two times the MRI slice thickness, plus the interslice gap). Patients should be assessed using the same imaging sequences, parameters, and magnet strength throughout the study. If multiple measurable lesions are present, up to three target lesions should be selected to follow up for response assessment.[48,49] Standard two-dimensional measurements (ie, the product of the largest tumour diameter and its largest perpendicular dimension) should be used, unless

Search strategy and selection criteria

Literature for diffuse intrinsic pontine gliomas published from Jan 1, 1994, to June 1, 2019, in the English language was reviewed by searching PubMed using the terms "diffuse intrinsic pontine glioma", "pontine glioma", or "brainstem glioma". The final references list was generated on the basis of originality and relevance to the broad scope of our recommendations.

otherwise defined in a specific study protocol. Note, the distinction between pontine and extrapontine response is incorporated (table 2), because it is prudent to determine incongruencies in response between pontine and extrapontine disease. Extrapontine progression might not reflect pontine response or, ultimately, the efficacy of focal pontine therapies.

Conclusions

DIPG involves distinct issues and challenges for baseline characterisation and response assessment. Accurately and adequately determining the efficacy of new drugs, particularly for a disease without known effective therapies, is crucial. It is important that all clinical trials assessing efficacy do so in a consistent and reliable manner.

Quality of life (QOL) is crucially important in assessing treatment effects. To date, there are no standard, validated, multilanguage paediatric QOL tests, so problems could occur when applying different measures across age groups and international sites. Consistent with other contemporary RAPNO recommendations,[46] the working group suggests that future studies should prospectively include a QOL test appropriate for the patient's age and development, available in multiple languages, for validation. Once such validation occurs, the incorporation of QOL into response criteria will be valuable in more fully assessing the risk–benefit ratio of therapy.

The recommendations shown represent an initial effort to uniformly collect and evaluate DIPG response assessment criteria. We recognise the absence of an evaluable retrospective cohort of paediatric patients with DIPG, and as such, propose to assess our recommendations prospectively in well defined patient cohorts. We advise immediate incorporation of our recommendations into clinical trials internationally, to assess their feasibility and corroboration with patient outcomes.

Contributors

All authors contributed to the analysis and interpretation of reviewed data, contributed to the writing of the manuscript, and reviewed and approved the final version.

Declaration of interests

We declare no competing interests.

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