Imaging Guidelines for Paediatric Brain Tumours 1

Response assessment in paediatric low-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group

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Paediatric low-grade gliomas (also known as pLGG) are the most common type of CNS tumours in children. In general, paediatric low-grade gliomas show clinical and biological features that are distinct from adult low-grade gliomas, and the developing paediatric brain is more susceptible to toxic late effects of the tumour and its treatment. Therefore, response assessment in children requires additional considerations compared with the adult Response Assessment in Neuro-Oncology criteria. There are no standardised response criteria in paediatric clinical trials, which makes it more difficult to compare responses across studies. 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. We established a subcommittee to develop consensus recommendations for response assessment in paediatric low-grade gliomas. Final recommendations were based on literature review, current practice, and expert opinion of working group members. Consensus recommendations include imaging response assessments, with additional guidelines for visual functional outcomes in patients with optic pathway tumours. As with previous consensus recommendations, these recommendations will need to be validated in prospective clinical trials.

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This is the first in a **Series** of three papers about imaging guidelines for paediatric brain tumours

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Introduction

Paediatric low-grade gliomas are the most common brain tumours in children, representing 40–50% of all paediatric CNS tumours.[1] Although overall survival for children with these tumours is excellent, event-free survival remains low, with many children requiring multiple therapies throughout childhood.[2] In addition, many children have functional deficits (such as visual dysfunction and sensorimotor deficits) as a consequence of their tumour, its treatments, or both. Because the majority of patients survive, a paradigm shift has occurred among paediatric low-grade glioma treatment experts, with a new focus on preserving functional outcomes and maintaining a good quality of life (QOL).[1,3,4]

Several molecularly targeted agents are being investigated in clinical trials, with early data showing their efficacy.[5] Comparing outcomes of these new agents with outcomes of previous therapies is crucial. However, historical studies used varied measures of outcome (with the majority based on imaging response assessment alone) so using standardised imaging sequences is of the utmost importance. The comparability of outcomes is complicated further, because the radiographic response of the tumour to therapy does not always correlate with functional outcome, especially in optic pathway gliomas associated with neurofibromatosis type 1.[6] It is essential to better standardise the response definitions for paediatric low-grade glioma clinical trials, not only to make comparisons of response outcome across multiple international studies more feasible, but also to incorporate functional outcomes when appropriate. We, therefore, established an international subcommittee of the Radiologic Assessment in Pediatric Neuro-Oncology (RAPNO) Working Group to develop consensus recommendations for response assessment in paediatric low-grade gliomas. The committee consisted of 25 international experts in the areas of paediatric neuro-oncology, neuroradiology, and neurosurgery.

The committee first met and developed a set of agreed assignments—ie, questions they deemed necessary to understand the controversies of imaging assessment in paediatric low-grade gliomas (panel 1). These assignments were then divided among the committee members, who researched, and then presented, all available literature to the entire RAPNO committee, who then discussed these data. The committee then developed consensus statements and recommendations, on the basis of available literature, committee expertise, and clinical experience. Each topic assignment was discussed until a consensus was reached.

Specific issues and challenges with response assessment in paediatric low-grade gliomas

Disease classification

The term paediatric low-grade glioma refers to paediatric WHO grade I and II tumours of glial origin, with

Panel 1: **Response Assessment in Pediatric Neuro-Oncology (RAPNO) consensus committee assignment questions regarding existing data in the medical literature on imaging assessment in paediatric low-grade gliomas**

- What are the data for perfusion and PET imaging?
- What are the data for T1-weighted and contrast MRI?
- What are the data on T2-weighted and T2-weighted-fluid-attenuated inversion recovery MRI and two-dimensional versus three-dimensional sequence acquisition imaging?
- What are the data on histology or tumour location and imaging?
- What are the data on molecular biology and imaging?
- What are the data on patients with neurofibromatosis type 1 and imaging?
- What are the data on cysts imaging?
- What are the data on timing and frequency of imaging?
- What are the data and what is the understanding regarding visual outcomes in relation to imaging and response?
- What are the data and what is the understanding for other functional outcomes (eg, motor, language, adaptive behaviour), and how are they associated with changes in imaging?
- Are there any data on focal areas of response as assessed by imaging within a large tumour and how does the focal area relate to responses and outcome?
- What is considered a measurable lesion?
- What should the standard sequences be in assessing a paediatric low-grade glioma?
- How should all these questions contribute to defining radiological response?

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pilocytic astrocytoma being the most frequent diagnosis.[3] It is now generally accepted that most paediatric low-grade gliomas are a single-pathway disease affecting the MAPK signal transduction pathway, despite varying histological appearances, with *BRAF–KIAA1549* fusion and *BRAF*^{V600E} (ie, Val600Glu) mutation events comprising the most frequent somatic molecular alterations (whereas alterations in *NTRK* genes, *FGFR* genes, and *MYB* are much less common).[4,7–9]

Characteristic subependymal giant cell astrocytoma occur in patients with tuberous sclerosis complex, constituting 1–2% of paediatric low-grade glioma cases, whereas 10–15% of patients with neurofibromatosis type 1 will develop paediatric low-grade gliomas, classically within the optic pathway and brainstem.[10–14]

Unique patient population

The median age at presentation of paediatric low-grade gliomas is between the ages of 6 and 8 years, although a small proportion of patients will present before age 1 year. In general, paediatric low-grade gliomas show clinical and biological features that are distinct from their adult counterparts, and how aggressive the tumours are in terms of growth and response to treatment can vary depending on whether they are sporadic or associated with a cancer predisposition syndrome, such as neurofibromatosis type 1 or tuberous sclerosis complex. Paediatric low-grade gliomas most frequently arise in the hypothalamic–chiasmatic region (40%), followed by the cerebellum (25%), cerebral hemispheres (17%), and brainstem (9%).[1,15] Tumours frequently involve the optic pathway, with extensive and diffuse disease rather than a discrete focal mass, making accurate measurement of these lesions quite difficult. Patients with paediatric low-grade gliomas frequently present with visual dysfunction, motor deficits, coordination difficulties, epilepsy, and endocrine dysfunction, in addition to non-specific symptoms (such as nausea, emesis, and increased head circumference), due to increased intracranial pressure.[1,7] Children younger than three years with hypothalamic paediatric low-grade gliomas can also present with diencephalic syndrome, which is a rare neurological disorder commonly characterised by failure to thrive, defined as severe emaciation despite normal or only slightly decreased caloric intake, and euphoria. Diencephalic syndrome as a cause of failure to thrive is exceedingly rare, and therefore often results in a delay in diagnosis of paediatric low-grade glioma.[16]

Functional deficits: visual impairment, motor dysfunction, and epilepsy

Preserving neurological function is the key aspect of paediatric low-grade glioma management, and there is international agreement that some specific functional outcome measures should be incorporated into response assessments in paediatric low-grade gliomas along with imaging measurement.[3,4] Paediatric low-grade gliomas are frequently localised in the hypothalamic–chiasmatic region, especially in children with neurofibromatosis type 1-associated paediatric low-grade gliomas, so visual impairment, rather than radiographic tumour growth, is one of the most frequent clinical symptoms leading to initiation of adjuvant therapy in these patients.[14–17] Therefore, vision is considered to be a key outcome measure in optic pathway and hypothalamic paediatric low-grade gliomas. The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration has already defined criteria for measurement of visual function that are suitable for incorporation into the RAPNO paediatric low-grade glioma outcome assessments.[17,18]

Other common clinical symptoms leading to initiation of adjuvant therapy are related to motor pathway and brainstem dysfunction, such as weakness or dysmetria. There are initial data on quantitative assessment of motor dysfunction in paediatric low-grade gliomas, using the Vineland Adaptive Behavior Scale,[19] To date, these scales have not been formally included as a part of primary response assessment in paediatric low-grade gliomas.

Defining baseline scans

Classically, whether in or outside of a clinical trial, MRI scans are done before surgical resection or biopsy, and are typically repeated within 24–72 h postoperatively to assess the amount of residual disease before initiating a medical therapy, such as chemotherapy or radiotherapy. Paediatric low-grade glioma can present as a clinical

emergency with symptoms of acute increased intracranial pressure due to obstructive hydrocephalus. Such clinical emergencies can lead to patients not being imaged, or not being imaged with full protocol, because of required emergency procedures (such as extraventricular drain placement) before a definitive surgical resection. In a clinical emergency, a non-contrast head CT is often obtained first, because it is usually easily accessible, has a fast acquisition time, and typically does not require any sedation. If an MRI cannot be done before a surgical resection or biopsy, baseline CT imaging is often a less precise measure of tumour burden. Optic pathway paediatric low-grade gliomas might take an insidious course, with stochastic growth over long periods of imaging surveillance. Because of all these confounding factors, and the issue of whether a patient undergoes a biopsy versus a partial resection, definitions about what should be used as the postsurgical and baseline premedical treatment imaging scan have varied.

Refractory disease

For patients with paediatric CNS tumours, many early phase clinical trials allow patients to enrol with refractory disease, but these trials often do not clearly define refractory disease or indicate how potential residual active disease should be assessed. If refractory disease is defined as residual disease without radiographic progression, response results might be skewed, especially when the trial objective is to evaluate response. Of note, it is often difficult on imaging to distinguish between treatment effect and true refractory disease.

Absence of consensus about imaging and tumour measurement standards

There is no global consensus on imaging standards and the appropriate manner to measure tumour on MRI across paediatric low-grade glioma studies. This lack of agreement has led to a substantial difficulty in comparing international and historical studies in which tumours are assessed and measured in different ways. For example, the interpretation of changes in cystic, or solid components, or both, of a tumour has varied substantially across studies. There has been an absence of consensus among the International Society for Paediatric Oncology Europe (SIOPE), the Children's Oncology Group (COG), and other international groups about the best way to incorporate all of these variables into defining tumour measurement and response. These differences across studies further highlight the need for universal guidelines for both image acquisition and response evaluation, to better prospectively evaluate tumours and compare outcomes across international studies.

Recommendation

The RAPNO paediatric low-grade glioma committee recommends the combined use of imaging, clinical, and in some scenarios, functional evaluations to assess response in clinical trials, as discussed in detail later in this Series paper. Our goal is to establish a basic standardised protocol that is applied internationally and prospectively. With this recommendation, response results from international studies can be compared without substantial confounding factors. In line with the principle of maximising compliance and imaging quality across international imaging centres with varied capacity, the RAPNO committee recommends image acquisition using common sequences that are readily available at most centres, to assess clinical trial primary study endpoints as discussed in detail throughout this Series paper.

Radiological recommendations: imaging standards for clinical trials for paediatric low-grade glioma

Baseline brain or spine imaging and frequency of surveillance

If feasible and safe, all patients with paediatric low-grade glioma receiving treatment as an adjunct to surgery should have a presurgical baseline MRI scan to assess the tumour, and a postoperative MRI scan within 24–72 h after surgery to assess the amount of residual tumour. In situations for which surgery is not indicated, or only a small biopsy sample is taken, a postoperative MRI scan might not be clinically indicated or necessary to assess residual tumour, and the diagnostic or prebiopsy scan could serve as a baseline scan pretreatment. Based on historical study guidelines and committee expertise, 24–72 h postoperatively is, in general, the ideal time to obtain an MRI to prevent substantial postoperative changes from limiting tumour evaluation. If there are extensive parenchymal postoperative changes that obscure a residual tumour, a second MRI approximately 2–3 weeks after surgery might better define residual disease. Patients should be enrolled into clinical trials within 4 weeks following the baseline scan, or as delineated by a specific clinical trial. For surveillance evaluations while on a clinical trial, most published clinical studies use imaging once every 12 weeks (3 months) during therapy.[2,10,20]

A spine MRI is typically recommended for patients with a primary paediatric low-grade glioma in their brain when there is a concern for metastatic disease, such as a specific high-risk pathology (such as pleomorphic xanthoastrocytoma) or symptoms that can indicate spinal disease (such as back pain or urinary retention). Typically, it is best to obtain the baseline spine MRI either before a surgical resection or biopsy, or 10–14 days after a surgical resection or biopsy, to minimise postsurgical blood products and dural enhancement that might confound imaging interpretation. Among all paediatric low-grade gliomas, primary or secondary dissemination develops in only 5–10% of patients, making it a rare occurrence overall.[7] If spinal dissemination is identified, however, repeat surveillance spinal MRI is recommended at the same intervals as the

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primary intracranial lesion, as discussed later in this Series paper. In patients with a primary spinal cord low grade glioma, we recommend a baseline brain MRI, and if brain dissemination is identified, we recommend repeat surveillance brain MRI at the same interval as for the primary spine lesion.

The table lists the specific essential recommended MRI sequences for primary brain, spine, and optic pathway paediatric low-grade glioma tumours, adapted from both COG and SIOPE, and agreed upon by the RAPNO paediatric low-grade glioma committee. As a general rule, the minimum recommended sequences (table) should be implemented; however, they can be upgraded or complemented according to local scanner capabilities, local radiologist preferences, local protocol, or research questions being addressed in a specific clinical trial. Intraoperative MRI can be considered as a substitute for the baseline postsurgical brain MRI when it is done on a 3 T MRI scanner (as these data have only been validated on 3 T MRI).[21] Data on intraoperative MRI are still emerging, however, and continued prospective studies are necessary.

Recommendation

If feasible and safe, baseline brain MRI (or baseline spine MRI, or both, depending upon the primary lesion location and risk of metastases, as detailed earlier) should be done preoperatively, and 24–72 h postoperatively. The postoperative scan should be used as the new baseline scan for future comparisons of response assessment. A baseline scan should be done at a maximum of 4 weeks before treatment start, or as required by a specific trial. This scan can be the postoperative imaging if there is an absence of postoperative artifacts, such as massive intratumoural bleeding, which might require a repeat scan 2–3 weeks postoperatively to better assess residual disease.

MRI to evaluate metastases (a spine MRI for primary brain lesions and a brain MRI for primary spinal lesions) should be done either preoperatively or 10–14 days postoperatively.

Routine imaging for children with paediatric low-grade gliomas enrolled on a clinical trial should be done once every 12 weeks (3 months) while on therapy. Specific clinical trials might require more frequent imaging because of the unique intervention or study-specific imaging objectives.

Role of T1-weighted contrast-enhanced imaging, T2-weighted, and T2-fluid attenuated inversion recovery imaging and image acquisition

Although contrast-enhanced T1-weighted (T1) imaging is a mainstay for assessment of brain tumours, in general the use of contrast agents in paediatric low-grade glioma is controversial, given the spontaneous change in contrast uptake behaviour in residual tumours without clinical progression, and data concerning potential long-term toxic effects of contrast agents.[22,23] The literature does not have a substantial amount of data discussing the specific use of T1 and postcontrast imaging for response assessment for paediatric low-grade glioma. Some historical trials have used contrast alone in defining response, but trials in the past 5–10 years recognised that contrast enhancement is variable and does not appear to be the most effective sequence for measuring response in paediatric low-grade gliomas.[24] For anterior optic glioma, however, clinical experience suggests that contrast sequences are useful to assess response, because many of these lesions enhance completely. In addition, contrast might help to distinguish between neurofibromatosis type 1-associated focal areas of signal intensity (formerly known as unidentified bright objects), and neurofibromatosis type 1-associated low-grade gliomas.[25–27] Contrast might also be important in evaluating leptomeningeal disease and spinal tumours, and is therefore considered to be a standard required sequence.[28,29] Given the known risk of gadolinium deposition and renal toxicity, most European and US medical centres are now using macrocyclic agents that are considered to be safer than other types of contrast agents.[30] Some preliminary clinical experience suggests a rapid decrease in contrast enhancement with the use of some molecularly-targeted agents, such as MEK inhibitors and BRAF inhibitors, further supporting the idea that a change in contrast enhancement alone should not be the sole measure of imaging response.[22] In general, T2-weighted and T2-weighted-fluid-attenuated inversion recovery (FLAIR) imaging appear to be the best measures of tumour size, on the basis of the small amount of literature available, clinical expertise, and experience of the committee.

Two-dimensional (2D) image acquisition is better studied, with more robust data and clinical experience, compared with three dimensional (3D) image acquisition. However, 3D scans are often preferred to 2D scans if volumetric analysis is intended, and also better match the planes of measurement. 3D scans might also help to distinguish focal vascularity from subtle enhancement. For these reasons, in the table, 3D scanning is listed under optional sequences, and as an addition to 2D scanning, which is listed under recommended required sequences.

The role of postcontrast T2-FLAIR sequence in evaluation of paediatric low-grade gliomas has not been systematically reviewed, and its use is limited to a handful of institutional practices. Most of these practices acquire T2-FLAIR sequence before contrast administration. Finally, although we acknowledge that some institutions do T1-FLAIR for spinal imaging, on the basis of consensus this type of imaging is not included under the recommended sequences in the table. Additional sequences (including T1-FLAIR) can be used to

	Sequence	Slice thickness	Gap percentage	In-plane resolution	Comments
Brain imaging for primary brain paediatric low-grade glioma (for both 1·5 T and 3 T magnets)					
Recommended sequences					
T1-weighted	2D spin echo, turbo spin echo, or fast spin echo†	≤4 mm; for very small lesions consider ≤3 mm	0*	230 mm (range 220–250 mm, depending on head size) image resolution field of view; matrix frequency is a minimum of 256 voxels (512 voxels is desirable for better resolution)	Axial plane (along anterior commissure–posterior commissure axis); for posterior fossa tumours, 2D gradient echo T1 is recommended to avoid phase encoding artifacts from the transverse or sigmoid sinus
T2-weighted	2D spin echo, turbo spin echo, or fast spin echo	≤4 mm; for very small lesions consider ≤3 mm	0*	230 mm (range 220–250 mm, depending on head size) image resolution field of view; matrix frequency is a minimum of 256 voxels (512 voxels is desirable for better resolution)	Axial plane; if measuring in three planes or dimensions (per a clinical trial or in cases in which the tumour location dictates), T2-weighted coronal or sagittal imaging can be added as necessary
T2-weighted FLAIR	2D turbo spin echo, or fast spin echo	≤4 mm; for very small lesions consider ≤3 mm	0*	230 mm (range 220–250 mm, depending on head size) image resolution field of view; matrix frequency is a minimum of 256 voxels (512 voxels is desirable for better resolution)	Axial or coronal plane
T1-weighted plus contrast	2D spin echo, turbo spin echo, or fast spin echo†	≤4 mm; for very small lesions consider ≤3 mm	0*	230 mm (range 220–250 mm, depending on head size) image resolution field of view; matrix frequency is a minimum of 256 voxels (512 voxels is desirable for better resolution)	Axial, coronal, or sagittal plane; for posterior fossa tumours, 2D gradient echo T1 is recommended to avoid phase encoding artifacts from the transverse or sigmoid sinus
Diffusion-weighted imaging with apparent diffusion coefficient	2D echo-planar imaging	≤4 mm; for very small lesions consider ≤3 mm	0*	230 mm (range 220–250 mm, depending on head size) image resolution field of view; matrix frequency is a minimum of 96–128 voxels	Axial plane (along anterior commissure–posterior commissure axis)
Optional sequences					
T1-weighted	3D	1·0–1·2 mm isotropic acquisition (if 3D sequence is obtained, and only in addition to 2D sequences)	0*	1 mm × 1 mm × 1 mm isotropic voxel resolution is desirable, depending on scanner capability	Sagittal plane acquisition, axial and coronal reformats
T1-weighted plus contrast	3D	1·0–1·2 mm isotropic acquisition (if 3D sequence is obtained, and only in addition to 2D sequences)	0*	1 mm × 1 mm × 1 mm isotropic voxel resolution is desirable, depending on scanner capability	Sagittal plane acquisition, axial and coronal reformats
T2-weighted FLAIR plus contrast	3D	1·0–1·2 mm isotropic acquisition (if 3D sequence is obtained, and only in addition to 2D sequences)	0*	1 mm × 1 mm × 1 mm isotropic voxel resolution is desirable, depending on scanner capability	Sagittal plane acquisition, axial and coronal reformats
Orbital imaging for primary optic pathway or hypothalamic paediatric low-grade glioma					
Recommended sequences					
T1-weighted	2D spin echo, turbo spin echo, or fast spin echo	≤3 mm	0*	180–200 mm image resolution field of view; matrix frequency is a minimum of 256 voxels (if feasible, 512 matrix frequency is recommended for better resolution)	Coronal plane; orbital imaging should be added to MRI brain in patients with optic pathway or hypothalamic lesions
T2-weighted	2D spin echo, turbo spin echo, or fast spin echo with fat saturation or short inversion time inversion recovery	≤3 mm	0*	180–200 mm image resolution field of view; matrix frequency is a minimum of 256 voxels (if feasible, 512 matrix frequency is recommended for better resolution)	Axial plane; orbital imaging should be added to MRI brain in patients with optic pathway or hypothalamic lesions
T2-weighted	2D spin echo, turbo spin echo, or fast spin echo with fat saturation or short inversion time inversion recovery	≤3 mm	0*	180–200 mm image resolution field of view; matrix frequency is a minimum of 256 voxels (if feasible, 512 matrix frequency is recommended for better resolution)	Coronal plane; orbital imaging should be added to MRI brain in patients with optic pathway or hypothalamic lesions
T1-weighted plus contrast	2D spin echo, turbo spin echo, or fast spin echo with fat saturation	≤3 mm	0*	180–200 mm image resolution field of view; matrix frequency is a minimum of 256 voxels (if feasible, 512 matrix frequency is recommended for better resolution)	Coronal plane; orbital imaging should be added to MRI brain in patients with optic pathway or hypothalamic lesions

(Table continues on next page)

	Sequence	Slice thickness	Gap percentage	In-plane resolution	Comments
(Table continued from previous page)					
T1-weighted plus contrast	2D spin echo, turbo spin echo, or fast spin echo with fat saturation	≤3 mm	0*	180–200 mm image resolution field of view; matrix frequency is a minimum of 256 voxels (if feasible, 512 matrix frequency is recommended for better resolution)	Axial plane; orbital imaging should be added to MRI brain in patients with optic pathway or hypothalamic lesions
Spine imaging for patients with primary spinal cord tumours					
Recommended sequences					
T1-weighted	2D spin echo or turbo spin echo	≤3 mm	0*	Matrix frequency is a minimum of 256 voxels (if feasible, 512 matrix frequency is recommended for better resolution)	Sagittal plane whole spine (entire dural sac), use anterior saturation band
T2-weighted	2D spin echo or turbo spin echo	≤3 mm	0*	Matrix frequency is a minimum of 256 voxels (if feasible, 512 matrix frequency is recommended for better resolution)	Sagittal plane whole spine (entire dural sac), use anterior saturation band
T2-weighted	2D spin echo or turbo spin echo	4–5 mm	0*	Matrix frequency is a minimum of 256 voxels (if feasible, 512 matrix frequency is recommended for better resolution)	Axial plane but only through the intramedullary tumour; not needed for evaluation of leptomeningeal metastases
T1-weighted plus contrast	2D spin echo or turbo spin echo	≤3 mm	0*	Matrix frequency is a minimum of 256 voxels (if feasible, 512 matrix frequency is recommended for better resolution)	Sagittal whole spine (entire dural sac), use anterior saturation band
T1-weighted plus contrast	2D spin echo or turbo spin echo or 3D gradient	4–5 mm (for spin echo) and 3 mm (for 3D gradient)	0*	Matrix frequency is a minimum of 256 voxels (if feasible, 512 matrix frequency is recommended for better resolution)	Axial plane (for spin echo; physiological veins over the surface of the cord can be mistaken for nodules of dissemination and therefore axial slices are essential for all suspected areas; as fat suppression often leads to artifacts and is not necessary for the delineation of meningeal disease, it should not be used routinely); sagittal plane acquisition, reformats (for 3D gradient)

2D=two-dimensional. 3D=three-dimensional. FLAIR=fluid-attenuated inversion recovery. NA=not applicable. *No gap is preferred whenever possible.

Table: **Recommended imaging sequences and parameters for assessment of paediatric low-grade gliomas**

complement the recommended essential sequences, depending on local institutional practices.

Classic appearances of paediatric low-grade gliomas in the posterior fossa, optic pathway, hypothalamic region, and tectal region are seen in the appendix (pp 1–3).

See Online for appendix

Recommendation

Specific recommended sequences for brain, spine, and optic pathway tumours can be seen in the table. T2 and T2-FLAIR are necessary sequences and are, in general, considered the best sequences for assessing tumour changes in paediatric low-grade gliomas. Postcontrast imaging (T1-weighted) is necessary for paediatric low-grade glioma assessment and as part of evaluating response. The safest available contrast agents (currently, macrocyclic gadolinium-based contrast agents) should be used, if possible, to reduce risk of nephrogenic systemic fibrosis and to minimise tissue deposition (ie, brain deposition). Also, if possible, the same contrast agent should be used in the patient throughout their surveillance on a specific clinical trial. In the rare situation that a paediatric low-grade glioma is completely non-enhancing, imaging without contrast can be considered in follow-up surveillance. Finally, 2D scan acquisition should be considered as standard, with 3D scan acquisition considered as exploratory, or as an addition to 2D scan acquisition.

Advanced imaging, histology, and molecular subgroups

Preliminary literature on perfusion MRI, PET, and magnetic resonance spectroscopy indicates that these modalities and techniques can help to distinguish high-grade from low-grade gliomas, but these modalities are still considered exploratory at this point, are not standardised, and available data are insufficient to consider them in standard assessment of response in paediatric low-grade gliomas.[31–34] In addition, although there has been a great increase in the histological and molecular classification of paediatric low-grade gliomas, as well as advancements in various imaging techniques, there is no evidence to date that separate response criteria should apply to different paediatric low-grade glioma molecular subgroups or histologies.

Recommendation

Perfusion MRI, PET, and magnetic resonance spectroscopy should not currently be used as standard measures of response. All histological subtypes of paediatric low-grade gliomas (eg, pleomorphic xanthoastrocytoma, pilocytic astrocytoma, ganglioglioma, diffuse astrocytoma) and all molecular subtypes of paediatric low-grade gliomas (eg, *BRAF*^{V6000E}, *BRAF–KIAA1549* fusion) should be assessed similarly, with the same measures of response. Assessment of responses, as related to specific

histologies or molecular signatures, could be incorporated as research questions into prospective clinical trials.

Neurofibromatosis type 1-associated paediatric low-grade gliomas

Current data do not suggest that different imaging techniques or sequences should be used for neurofibromatosis type 1-associated paediatric low-grade gliomas versus non-neurofibromatosis type 1-associated paediatric low-grade gliomas. However, experts from the RAPNO working group agree that specific imaging should be part of any optic pathway or hypothalamic lesion, as discussed later in this Series paper. Currently, standard MRI sequences are the best way to determine focal areas of signal intensity or T2 hyperintense lesions versus paediatric low-grade gliomas in patients with neurofibromatosis type 1.[35,36] The current literature and data show that lesions with T2 hyperintensity are defined as a probable tumour if associated with T1 hypointensity relative to white matter, and the lesions have mass effect, or enhancement, or both.[37,38] The use of advanced imaging (eg, diffusion, magnetic resonance spectroscopy) for distinguishing a tumour from focal areas of signal intensity lesions is still exploratory and an ongoing research question. Also, the REiNS committee is establishing guidelines on specific functional outcomes and criteria for treatment initiation in the neurofibromatosis type 1 paediatric low-grade glioma population (ie, visual and motor dysfunction).

Recommendation

Standard sequences should be used in assessing neurofibromatosis type 1-associated low-grade gliomas and the REiNS criteria should be incorporated whenever appropriate, as published.[17,18,39] Specific imaging sequences to evaluate the anterior optic pathways and neighbouring structures, in addition to brain MRI, should be obtained in patients with primary optic pathway or hypothalamic tumours. The details of specific orbital sequences are shown in the table.

Assessment of cysts

There are minimal prospective data evaluating how a cyst should be incorporated into paediatric low-grade glioma tumour measurement and response. Clinical experiences and guidelines from historical and ongoing protocols from the COG, Pediatric Brain Tumor Consortium, and SIOPE, as well as some guidance for adult imaging from Response Assessment in Neuro-Oncology, help to inform this topic.[40] The following recommendations are based on the RAPNO international expert consensus and require further prospective evaluation in clinical trials.

Recommendation

If the cyst in question is a cystic component of a mixed solid-cystic tumour or a true tumour cyst, it should be included in the measurement of a target lesion. A tumour cyst can be considered measurable if the cyst meets one of the following criteria: is integrated within the solid component (soap bubble appearance); is not readily separable from the solid component, or there is the presence of thick cyst wall enhancement, or both; or there is a cluster of small microcysts within a tumour. Although tumour cysts are included in size measurements, imaging features indicating progression differ for cystic versus solid portions of the tumour, as discussed in detail in panel 2. Examples of a tumour cyst and a non-tumour cyst can be seen in figures 1 and 2.

If the cyst is a reactive cyst at the interface of the solid component of the tumour and healthy brain, intermingled with the resection cavity, or the tumour is predominantly cystic with a solid enhancing mural nodule but without substantial cyst wall enhancement, the cystic component is not included in the measurement for response assessment. The resection cavity should be excluded from the measurement. Importantly, substantial distortion of the solid component secondary to cyst compression should be taken into account during size comparison of the solid tumour on subsequent imaging to evaluate response.

Panel 2: Definition of responses for cysts using either two dimensional measurements or measurement in three perpendicular planes

- If the solid component has enlarged by more than 25% from baseline, regardless of the cyst size, the response should be considered to be progressive disease.
- If the solid component remains stable or has enlarged by less than 25% from baseline, but a tumour-associated cyst is progressing, a short-term follow-up (approximately 4–6 weeks, or as clinically indicated) MRI scan should be considered.
  - If, in the short-term follow-up, the cyst wall enhancement shows worsening, or there is solid tumor progression between imaging timepoints, or both, progressive disease should be considered and the date of actual tumour progression should be backdated to the date when cyst wall enhancement was initially identified.
  - Additionally, if in short-term follow-up the cyst wall enhancement is stable and the solid component is stable, the response should be considered to be stable disease and followed up at a routine surveillance interval.
- If the solid component remains stable or has enlarged by less than 25% from baseline, but the cyst is enlarging, mass effect from the cyst and the patient's clinical situation need to be considered.
  - If a cyst is not causing substantial mass effect and the patient is clinically stable, follow-up at regular intervals is sufficient. If a cyst is causing substantial mass effect, or symptoms, or both, and the cyst can be decompressed, a short-term follow-up MRI scan should be obtained after decompression.
    - If the solid component of a cyst remains stable on short-term follow-up, consider the overall response to be stable disease and follow up at routine intervals.
    - If the solid component shows progression on short-term follow-up, the overall response should be considered to be progressive disease. The date of actual tumour progression should be backdated to the date when cyst enlargement was initially identified.

Visual outcomes

A substantial proportion of sporadic and neurofibromatosis type 1-related paediatric low-grade gliomas

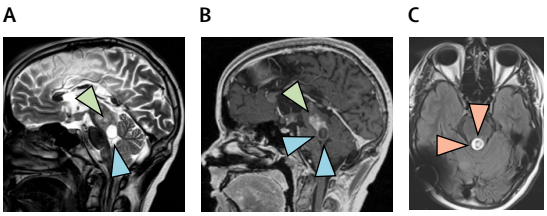

Figure 1: **Example of tumour cyst**
Sagittal T2-weighted image (A), off-midline, shows a large ill-defined tumour of the tectal plate, also invading the tegmentum, with a well defined cyst at the inferior aspect of the tumour (blue arrow). Postcontrast sagittal T1-weighted image through the same plane (B) shows heterogeneous enhancement of most of the solid component of the tumour (outlined by the arrows). The image also shows circumferential enhancement of the cyst wall (blue arrows). Postcontrast T2-weighted-fluid-attenuated inversion recovery image (C) also shows circumferential enhancement of the cyst wall (red arrows). There is heterogeneous enhancement of the cyst content as well, probably due to leakage of contrast into the cyst.

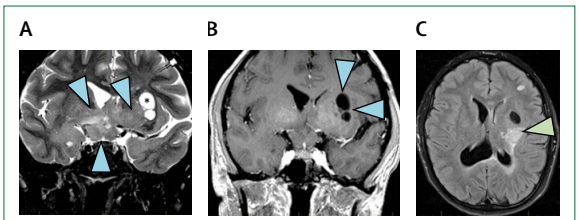

Figure 2: **Example of non-tumour cyst**
Coronal T2-weighted image (A) through the optic chiasm shows an ill-defined, infiltrating optic pathway glioma involving the optic chiasm, bilateral hypothalamic regions, left basal ganglia, and right medial temporal lobe. The cysts (largest one marked with an asterisk in the middle of the white area) are at the interface of the lateral margin of the basal ganglia component of the tumour and healthy brain. The cysts are not surrounded by the tumour. On postcontrast coronal T1-weighted image (B), there is no cyst wall enhancement (blue arrows). Axial T2-weighted-fluid-attenuated inversion recovery sequence through the largest cyst (C) shows no abnormal signal in the wall and at the interface of the cyst and healthy brain. The green arrow shows the location of the cyst is at the interface of tumour and healthy brain.

arises in the optic pathway and hypothalamic region affecting visual function and QOL of patients with paediatric low-grade gliomas. The prospect of stopping or potentially slowing a decline in visual acuity is an indication to initiate treatment in patients with paediatric low-grade gliomas.[41,42] There is consensus in the RAPNO group that assessment of visual function should be done in any patient with optic pathway or hypothalamic-related paediatric low-grade gliomas, both with and without a diagnosis of neurofibromatosis type 1.[41–43] Experts agree that modest worsening of visual acuity early in the treatment might not be a reason to discontinue therapy, as this worsening might represent previous damage, as opposed to ongoing visual worsening and therapy failure. The REiNS group recommendations, and outcomes from retrospective and ongoing prospective studies, are the basis for the following recommendations.[6,39] Current prospective trials, and some retrospective analyses, have defined changes based on Teller Acuity Cards and HOTV testing.[39]

Recommendation

The current recommendations used and published by the REiNS and paediatric low-grade gliomas International Consensus paper should be followed when assessing visual outcomes.[4,39] Teller Acuity Cards and HOTV testing (using a standardised testing protocol) should be the primary modes of assessing visual outcomes if possible, because together they can accommodate the widest range of developmental abilities. With small children, or children with developmental delays, testing can sometimes be unreliable. If it is unclear whether a noted vision change is due to true decline or poor patient cooperation, it is recommended that testing be repeated 1–2 weeks later to verify the change as best as possible. Visual responses are detailed (consistent with REiNS publication) in the appendix (p 3). Because of the challenge of achieving a reliable measurement in young children, visual fields are not currently standard measures to define response, and should only be incorporated as research questions at this point. In situations when visual acuity and imaging assessments differ (eg, stable or improved vison with progressive tumour on imaging), a clinical decision regarding what is best for the patient must be made. Typically, increased frequency of imaging and ophthalmological assessment is recommended to both assess trends and verify overall response.[42] A future clinical trial could be helpful for developing guidelines for these situations.

Modest visual acuity worsening early in therapy should be considered carefully, because it might indicate previous damage as opposed to ongoing visual worsening. Although a decline from baseline of 0·2 logMAR is the criterion for visual worsening, it is recommended that such a drop in acuity not be considered to be visual progressive disease at the first on-therapy staging evaluation (at approximately 12 weeks) if the tumour is stable or responsive on MRI. In such cases, it is recommended that repeat visual acuity assessment should be completed within 4 weeks to confirm that further decline in visual acuity is not occurring. If the repeat visual acuity is stable (≤0·2 logMAR decline from pretreatment baseline), the patient should be classified as having stable vision (appendix p 3). If, however, the repeat visual acuity testing reveals additional visual loss (>0·2 logMAR decline from pretreatment baseline), the patient should be classified as having visual worsening (appendix p 3).

Monitoring of vision should occur on the same schedule as imaging outcomes, which is typically every 12 weeks while on treatment (consistent with REiNS recommendations).

Motor, neuropsychological, and patient-reported outcomes

In addition to impairment of visual function, a substantial proportion of patients with paediatric low-grade glioma have motor, cognitive, behavioural, and other neurological function deficits (such as epilepsy), resulting in

reduced quality of survival.[44] Pilot studies that evaluated various domains of neurological function in patients with paediatric low-grade gliomas using the Vineland Adaptive Behavioral Scale show substantial deficits in scores for various subdomains, including motor skills.[19,45] Loss of visual, motor, and cognitive function in survivors of paediatric low-grade gliomas were associated with damage to white and grey matter structures. This association was identified by use of advanced structural and functional imaging, such as voxel-based morphometry and diffusion tensor imaging.[46,47] Further research of these outcomes in paediatric low-grade gliomas is needed before these advanced and structural imaging techniques can be recommended as part of the routine response assessment of paediatric low-grade gliomas.[44,48]

Recommendation

Quantitative neurological function (including motor function and language assessment), neuropsychological outcomes, patient-reported outcomes (eg, QOL), and advanced structural and functional MRI data are valuable and important but not yet ready for routine inclusion in the response assessment of paediatric low-grade gliomas. We suggest that these measures be included as research aims in prospective clinical trials, or in separate trials that continue for longer periods of time that can also assess late treatment effects.

Defining radiological response

Clinical trial consortia (including COG, Pediatric Brain Tumor Consortium, and SIOPE) have generated a large number of response datasets in paediatric low-grade gliomas, using measurements in two or three perpendicular planes. Although prospective data comparing endpoints for measurements in two or three perpendicular planes are missing, there is wide experience of using both measures for clinical trials internationally. The RAPNO low grade glioma committee therefore proposes using both measurement systems in response assessment of paediatric low-grade gliomas, to allow comparison with available large historical datasets.

To compare changes from scan to scan, the product of the perpendicular measurements is used, both for two and three perpendicular planes Classical response definitions, and ones agreed upon by the RAPNO committee, have been as follows for both two and three perpendicular measurements. Complete response is defined as the complete disappearance of all T2, T2-FLAIR, and contrast, and complete disappearance of the lesion, using the baseline MRI or best recorded response for comparison. Partial response is defined as a 50% or greater reduction in the size of the target lesion on T2 and T2-FLAIR, and variable changes in enhancement (both an increase and a decrease in enhancement do not contribute overall) using the baseline MRI or best recorded response for comparison. Minor response is used in some studies and defined as between a 25% and 49% reduction in tumour measurement, usually on T2 and T2-FLAIR (both an increase and a decrease in enhancement do not contribute overall), using the baseline MRI or best recorded response for comparison.[49] Stable disease: is defined as a neither a decrease nor an increase in tumour size sufficient to qualify as progressive disease or a partial response. Of note, depending on whether the minor response category is used in a specific protocol, stable disease can also represent patients with 0–49% tumour shrinkage, and up to 24% enlargement, using the baseline MRI or best recorded response for comparison. Progressive disease is defined as a 25% or greater increase in tumour measurement, usually on T2 and T2-FLAIR (both an increase and a decrease in enhancement do not contribute overall), or the development of new or metastatic lesions, using the baseline MRI or best recorded response for comparison. All stable and responsive disease classifications (complete response, partial response, minor response, and stable disease) require that the patient be clinically stable overall or improved on physical examination and functional or neurological assessment. Of note, some specific clinical trials might have unique response definitions that vary from the definitions above.

Lesions visible in three standard planes, with a diameter of at least 10 mm in each plane, are considered to be measurable lesions. Typically, there will be only one target residual lesion to follow, although there are rare situations when there is more than one target residual lesion, and guidelines must be in place to quantify disease response in these rare occurrences. If there are multiple lesions or there is multifocal disease, based on the clinical experience of RAPNO committee members a maximum of five lesions should be measured (the largest and most symptomatic lesions or those actively progressing at the time of treatment initiation are preferred; appendix p 3). Studies evaluating neurofibromatosis type 1 optic pathway tumours have used magnetic resonance volumetric imaging as a measure of tumour volume and response. However, there are insufficient prospective data on paediatric low-grade gliomas to use magnetic resonance volumetric imaging as standard.[50–52]

Recommendation

The most reproducible way to measure two perpendicular planes consists of the longest measurement (width) of the tumour and the longest measurement perpendicular to the width. These same two planes should consistently be measured to compare subsequent imaging with previous imaging to estimate response. The most reproducible way to determine measurements for three perpendicular planes consists of determining the maximum diameters in the standard anterior–posterior, transverse, and caudocranial dimensions obtained on multiplanar imaging. It is recommended that future clinical trials incorporate measurements in both two and three perpendicular planes so that these two strategies can be prospectively

Panel 3: RAPNO response criteria for assessment of paediatric low-grade gliomas

The definitions below apply to lesion measurement in both two and three perpendicular planes. Volumetric MRI response criteria have not been validated and are not included.

Complete response
Complete disappearance of the target lesion and all areas of metastatic disease on T2-weighted and T2-weighted fluid-attenuated inversion recovery imaging and contrast imaging using the baseline MRI or best recorded response for comparison. Overall, the patient should be clinically stable or have improved on physical examination and functional or neurological assessment.

Major response*
A 50% or greater reduction in the target lesion but insufficient response to qualify as a complete response (both an increase and a decrease in enhancement do not contribute overall). Overall the patient should be clinically stable or have improved on physical examination and functional or neurological assessment.

Partial response
A 50% or greater reduction in the target lesion, typically on T2-weighted and T2-weighted-fluid-attenuated inversion recovery imaging, and variable changes in enhancement (both an increase and a decrease in enhancement do not contribute overall) using the baseline MRI or best recorded response for comparison. Overall the patient should be clinically stable or have improved on physical examination and functional or neurological assessment.

Minor response*
A 25–49% reduction in the target lesion, usually assessed by T2-weighted and T2-weighted fluid-attenuated inversion recovery imaging (both an increase and a decrease in enhancement do not contribute overall) using the baseline MRI or best recorded response for comparison. Overall the patient should be clinically stable or have improved on physical examination and functional or neurological assessment.

Stable disease
An increase or a decrease in the target lesion that is not sufficient to qualify as progressive disease or responsive disease (major response, partial response, or minor response), respectively. Overall the patient should be clinically stable or have improved on physical examination and functional or neurological assessment.

Progressive disease
A greater than 25% increase in the target lesion, usually assessed on T2-weighted and T2-weighted fluid-attenuated inversion recovery imaging (both an increase and a decrease in enhancement do not contribute overall), or the development or substantial growth (>25%) of new or metastatic lesions using the baseline MRI or best recorded response for comparison, or worsening seen at physical examination or after clinical and functional assessment (or both) thought to be directly related to tumour progression.

RAPNO=Response Assessment in Pediatric Neuro-Oncology. *Major response and minor response guidelines are included above as recommendations if they were part of the response definition used within a specific clinical trial.

compared, to best define which is most useful and accurate.

In patients with diffuse or multifocal disease, a target lesion should be chosen to follow up as representative of disease burden. Typically, the lesion would be the largest measurable lesion or lesions, or the most actively growing or symptomatic lesion; however, detailed guidelines for tumours with multiple lesions are provided (appendix p 3).

In rare situations in which patients have diffuse leptomeningeal disease without a specific measurable target lesion, it can be difficult to measure tumour burden on MRI. Leptomeningeal disease, therefore, should be initially assessed in a binary fashion (present *vs* absent). The inclusion of these patients in a clinical trial will be trial specific, and sometimes assessment of response will have to be qualitative rather than quantitative, meaning that instead of using the definitions of response as shown in panel 3, the disease will simply be classified as improved, stable, or worsening. Changes in enhancement alone can make diffuse leptomeningeal disease difficult to assess for response. MRI volumetric assessment (ie, assessment using dedicated analysis software) is currently recommended as a research question in prospective trials and only in addition to measurement of lesions in two and three perpendicular planes on standard MRI. Panel 3 indicates the recommended definitions of response for clinical trials. Note that these definitions apply to measurements in either two or three perpendicular planes. It is recommended that to qualify as a response, the radiographic finding is maintained for two consecutive surveillance MRI scans, and the patient is clinically stable or improved on physical examination and functional assessment.

Search strategy and selection criteria

References for this Series paper were identified through searches of PubMed using the search terms "low-grade glioma", "pediatric", "radiologic assessment", "pilocytic astrocytoma", "response", "neurofibromatosis", "functional outcomes", "visual outcomes", "REiNS", and "RANO", for articles published from Jan 1, 2000, until June 30, 2019. Articles were also identified through searches of our own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Series paper.

Conclusions

Paediatric low-grade glioma tumours have unique characteristics compared with adult low-grade gliomas, which must be taken into consideration when defining radiological response. Also, given that most children with paediatric low-grade gliomas will not succumb to their disease, a focus on functional outcomes has moved to the forefront of the goals of treatment for these patients.[53] Although late effects are crucially important for these patients, these parameters are difficult to interpret in the acute setting while patients are enrolled and assessed on a clinical trial. Given that paediatric low-grade glioma is the most common paediatric CNS tumour, it is essential that all clinical trials assess response similarly, so that outcomes can be compared across trials internationally. The recommendations presented here by the RAPNO Low-Grade Gliomas committee represent an initial effort to uniformly collect and assess response. These recommendations should

now be evaluated in prospective clinical trials internationally in an effort to validate, assess, and modify the recommendations as appropriate.

Contributors

JF, OW, and KEW led the consensus panel and organised all discussions and meetings. JF and OW were the main writers of the manuscript. All authors participated in the literature search, data collection, consensus panel, data analyses, and final manuscript review and approval.

Declaration of interests

BB reports fees from Deutsche Kinderkrebsstiftung (German Pediatric Cancer Foundation), during the conduct, but outside the scope, of the submitted work. EB reports grants from Roche and Bristol-Myers Squibb, outside the scope of the submitted work. LK reports personal fees and funds from Roche, outside the scope of the submitted work. TYP reports grants from the Pediatric Brain Tumour Consortium Neuroimaging Center, outside the scope of the submitted work. MvdB reports personal fees from Abbvie, Celgene, Bristol-Myers Squibb, Bayer, Boehringer, Carthera, Agios, Genenta, and Nerviano, all outside the scope of the submitted work. OW reports non-financial support from Bristol-Myers Squibb, Syndax, Novartis, and Roche during the conduct of the study, but outside the scope of the submitted work. The other authors declare no competing interests.

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