Response assessment in paediatric intracranial ependymoma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group

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Response criteria for paediatric intracranial ependymoma vary historically and across different international cooperative groups. The Response Assessment in the Pediatric Neuro-Oncology (RAPNO) working group, consisting of an international panel of paediatric and adult neuro-oncologists, neuro-radiologists, radiation oncologists, and neurosurgeons, was established to address both the issues and the unique challenges in assessing the response in children with CNS tumours. We established a subcommittee to develop response assessment criteria for paediatric ependymoma. Current practice and literature were reviewed to identify major challenges in assessing the response of paediatric ependymoma to clinical trial therapy. For areas in which data were scarce or unavailable, consensus was reached through an iterative process. RAPNO response assessment recommendations include assessing disease response on the basis of changes in tumour volume, and using event-free survival as a study endpoint for patients entering clinical trials without bulky disease. Our recommendations for response assessment include the use of brain and spine MRI, cerebral spinal fluid cytology, neurological examination, and steroid use. Baseline postoperative imaging to assess for residual tumour should be obtained 24–48 h after surgery. Our consensus recommendations and response definitions should be prospectively validated in clinical trials.

Introduction

Ependymomas remain a major cause of cancer-related death in childhood and adolescence. These tumours can occur throughout the CNS, most commonly occurring intracranially in paediatric patients. Two-thirds to three-quarters of paediatric intracranial ependymomas arise within the posterior fossa and the remaining are supratentorial.[1–11] Historically, ependymomas were classified by WHO solely on the basis of histopathology: grade I (subependymoma or myxopapillary), grade II (classic), and grade III (anaplastic), determined by the presence or absence of anaplasia, mitotic activity, necrosis, and vascular proliferation. Beginning with the 4th edition of the WHO Classification of Tumors of the Central Nervous System in 2016 and expanded in 2021 in the 5th edition, molecular characterisation has been incorporated into the WHO classification, stratifying ependymomas into clinically relevant biological groups.[1,2,6,12–16] Despite these advances, therapy for grade II and grade III paediatric ependymomas diagnosed in children older than 1 year and up to 21 years has not changed. The standard of care for all intracranial ependymomas begins with maximal safe surgical resection. Although some pathological groups of supratentorial ependymomas can be cured with resection alone (ie, tumours with *YAP1* fusions free of postoperative microscopic residual disease), the majority of intracranial ependymomas (excluding those in children diagnosed younger than 1 year of age) are treated with adjuvant radiation therapy (involved field for non-metastatic tumours, and craniospinal for metastatic tumours).[1,2,6,14,16–19] The effect of adjuvant chemotherapy remains incompletely defined; final results from randomised studies should better inform which patient populations benefit from post-chemoradiotherapy (NCT02265770).[20] Recurrence of ependymomas occurs in up to 50% of patients, with most cases recurring locally. 5-year event-free survival in paediatric intracranial ependymoma ranges from 50% to 71%, and 10-year event-free survival drops to 29% due to late disease recurrence; event-free survival is defined as the time to any local relapse or progression, dissemination, or death (whichever comes first) as evaluated by MRI.[1,4,14,16,19,21–24] In posterior fossa group A ependymoma, gain of chromosome 1q genomic aberration is associated with inferior event-free survival and overall survival, and more frequent metastatic recurrences than posterior fossa group A ependymomas without gain of 1q.[3,5,19,23,25–29] No curative therapy for recurrent ependymoma has been identified; surgical resection, when possible, remains the mainstay of treatment.

Radiologically, infratentorial ependymomas are more homogeneous than supratentorial ependymomas, although the amount and pattern of contrast enhancement varies. Similar to their supratentorial counterparts, infratentorial ependymomas often have cysts, punctate calcifications, haemorrhage, or necrosis. These tumours are typically soft, conforming to the fourth ventricle and extending through the fourth ventricular outlets into the cisterns.[1,7,30–32] Supratentorial ependymomas are classically large, complex-appearing tumours. They heterogeneously enhance, and are often associated with cysts, calcifications, haemorrhage, necrosis, or perilesional tumour oedema.[1,13,31,33]

Clinical trials currently being designed for both newly diagnosed and recurrent paediatric intracranial ependymoma will risk stratify not only on the basis of

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clinical features such as patient age and extent of resection, but also on molecular features including the gain of chromosome 1q and molecular grouping (ie, posterior fossa group A, posterior fossa group B, *YAP1*, and *ZFTA* fusion-positive supratentorial ependymoma). MRI remains the mainstay for the assessment of objective response to therapy and duration of disease stability. As such, it is crucial to develop standardised response assessment criteria for paediatric intracranial ependymoma clinical trials to accurately compare results between studies. The Response Assessment in Pediatric Neuro-Oncology (RAPNO) paediatric intracranial ependymoma working group is composed of paediatric neuro-oncologists, neuroradiologists, and molecular biologists.[34] At the outset, the group identified specific challenges in assessing response to therapy in ependymoma. To that end, the expert members reviewed relevant published literature, assessed current clinical practice, and engaged in iterative discussions to provide consensus recommendations for objective response assessment in paediatric intracranial ependymoma for use in prospective clinical trials. Of note, these recommendations focus only on primary intracranial WHO grade II and III ependymomas.

Specific challenges in assessing response to therapy in ependymoma

Objective radiological response to therapy versus event-free survival as study endpoints

Maximal safe surgical resection is the first and most important step in the treatment of newly diagnosed ependymoma. Postoperatively many patients, with either no evidence of or minimal residual disease on imaging, will receive adjuvant therapy. Similarly, in the setting of localised (or isolated) recurrence, gross total resection of the recurrence is often done before any additional therapy is given. Overall, this surgical resection makes objective radiological response to therapy a difficult endpoint to evaluate in ependymoma. Furthermore, in the setting of bulky or mass disease, radiological disease response to therapy (ie, decreased tumour size) might not be as clinically meaningful an endpoint as event-free survival. Similar to assessment of therapeutic efficacy in diffuse intrinsic pontine glioma, a clinical trial of a therapeutic intervention in residual or relapsed ependymoma that shows prolongation of event-free survival (ie, prolonged stable disease), in the absence of objective radiological response, could be a better measure of therapeutic efficacy than radiologic disease response.[35]

The effect of postoperative residual disease before adjuvant therapy on survival

The most consistent prognostic factor for intracranial ependymoma, as repeatedly shown in clinical trials, is the extent of postoperative residual tumour.[1,3,4,17,18,19,22,29] To accurately interpret the results of clinical trials, be it assessment of radiological disease response or, more importantly, prolonged stable disease, it is crucial to define the extent of postoperative residual disease before the initiation of adjuvant therapy. Interpretation of the immediate postoperative imaging, however, can be complicated by postoperative artifact, bleeding, or inflammation.

Variable definitions of residual disease

Postoperative residual disease in ependymoma has not been consistently defined between studies.[3,21,22] In the second *Associazione Italiana di Ematologia e Oncologia Pediatrica* (AIEOP) study for paediatric intracranial ependymoma, patients with gross total resection were defined as having no radiologically visible tumour, and patients with near total resection had residual disease that was less than 5 mm at the greatest dimension.[23] In the St Jude Young Children 07 (SJYC07) trial, gross total resection was defined similarly to the AIEOP study, although near total resection included residual tumour of less than 1 cm^2.[3] The Children's Oncology Group (COG) ependymoma studies (ACNS0121 and ACNS0831) divided patients with no radiologically visible residual tumour into two groups: gross total resection 1 (no microscopic residual tumour identified by the neurosurgeon under the operating microscope), and gross total resection 2 (microscopically visible residual tumour identified under the operating microscope but no radiological evidence of disease).[19,20] In the current ongoing International Society of Paediatric Oncology (SIOP) Ependymoma Program II study, patients' postoperative residual intracranial disease is defined similarly to the COG studies: SIOP R0 corresponds to COG gross total resection 1, SIOP R1 to COG gross total resection 2, SIOP R2 to COG near total resection, and SIOP R3 and R4 to COG subtotal resection (residual tumour ≥5 mm; NCT02265770). Despite the differences in definition, studies have shown no difference in survival between patients with gross total resection and those with near total resection when the same postoperative adjuvant therapy is administered.[3,19,20,21]

Recurrence patterns

As previously mentioned, the most common site of recurrence for localised ependymoma is the primary site. However, metastatic recurrence can occur, even when the original tumour was localised, and is most common in posterior fossa group A ependymoma tumours with chromosome 1q gain.[1,3–5,14,16,19,21–29] The increased risk of metastatic recurrence in certain patient populations becomes an issue when clinical trials of intracranial ependymoma differ with regard to spine MRI frequency.

Late recurrences

Compared with other paediatric CNS malignancies, ependymoma is the most common tumour to have late recurrences (>5 years after completion of upfront therapy).[4,14,21] From a feasibility standpoint, however, we

acknowledge that it is difficult to conduct a clinical trial with an event-free survival or overall survival endpoint assessed more than 5 years after completion of treatment, especially with patients typically starting a new therapy at the time of tumour progression or relapse.

Radiation necrosis mimicking disease recurrence

Given the efficacy of radiotherapy in the treatment of intracranial ependymoma, both at diagnosis and recurrence, many clinical trials include radiotherapy.[1,14,17,19,21,36–40] However, the use of upfront radiotherapy, particularly proton beam radiotherapy in posterior fossa ependymomas adjacent to the brainstem, and re-irradiation carry a risk of radiation necrosis.[36,37,39,40] Radiation necrosis can be difficult to differentiate from tumour recurrence or progression when assessed radiologically at a single imaging timepoint, yet this distinction is crucial for the interpretation of study results related to treatment efficacy, response, and safety. Advanced imaging methods including diffusion-weighted imaging, spectroscopy, and perfusion imaging could help in some cases to differentiate post-radiation changes from residual or recurrent tumour.

Clinical differences in biological groups

The most common molecular group of paediatric posterior fossa intracranial ependymoma is posterior fossa group A ependymoma, which can be differentiated from posterior fossa group B ependymoma by methylation analysis. Posterior fossa group B tumours are seen most frequently in children older than 3 years. Supratentorially, *ZFTA*-fused (previously known as *RELA*-fused) ependymoma is the most common group, whereas *YAP1*-fused ependymoma is relatively rare. These four groups have distinct clinical characteristics and survival rates.[1–3,6,15] Additionally, as previously mentioned, gain of chromosome 1q in posterior fossa ependymoma also negatively effects survival.[3,5,19,23,25–29] It is much less clear if chromosome 1q gain has an effect on overall and event-free survival in supratentorial ependymoma. Imaging recommendations for patients enrolled in clinical trials, both on therapy and off treatment, do not differ on the basis of the molecular tumour features. Given the differences in sites, frequency, and rate of recurrence between ependymoma groups, it has been suggested that timing and extent (brain alone *vs* brain and spine) of radiological assessments for patients enrolled on clinical trials should be dictated by each tumour's specific molecular features. However, no large historical cohort based on molecular features exists, and randomised phase 2 studies would require many patients and a longer time to completion.

Radiological recommendations for assessing paediatric ependymoma response

The following recommendations apply to paediatric ependymomas arising intracranially, and do not apply to those originating in the spine.

Imaging standards for clinical trials for ependymoma

A brain tumour imaging protocol was established in 2015 by the Brain Tumour Imaging Standardisation Steering Committee to standardise neuroimaging acquisition and response assessment for adult patients with glioblastoma in clinical trials. The recommendations were generated with the goal of more accurately comparing disease responses and imaging endpoints across clinical trials. The protocol highlighted the need to balance feasibility of obtaining recommended imaging sequences (related to both equipment and scan time) with optimisation of image quality and accurate disease assessment.[41] In agreement with this protocol and previously published paediatric brain tumour-specific RAPNO guidelines, we recommend that clinical trials for paediatric intracranial ependymoma have prespecified imaging parameters that use the same magnet strength and consistent imaging protocol as those used for adult patients with glioblastoma for the duration of the study.[34,42,43] We also agree with the recommendation that imaging sequences used in clinical trials should be widely available across hospitals caring for paediatric patients to maximise compliance with study imaging standards and quality. More advanced imaging sequences, such as spectroscopy or perfusion imaging, can be used at sites with the capability to do so, although they are not part of the standardised protocol we recommend for assessment of response in clinical trials.[33,34,41,43]

Similar to recommendations made in the RAPNO tumour response guidelines for medulloblastoma and high-grade gliomas, we suggest that, at timepoints when both brain and spine imaging are required, these images be acquired during the same imaging session. This approach decreases the frequency of sedation and anaesthesia for patients who require such during imaging, but is ideal even in patients who do not require sedation if they are able to tolerate both scans in one setting.[33,43] We additionally concur with the recommendations of previous RAPNO guidelines and the global ependymoma consensus conference that centralised review of MRIs by paediatric neuroradiologists is optimal at the time of clinical trial eligibility assessment and throughout trial participation, to accurately assess imaging-based response to therapy.[15,33,34,42,43]

Brain and spine imaging

Standardised imaging to characterise intracranial ependymoma should include imaging done before and after intravenous gadolinium-based contrast administration T1-weighted imaging, T2-weighted imaging, contrast-enhanced fluid-attenuated inversion recovery (FLAIR) imaging, and diffusion-weighted imaging (table 1). We recommend that the primary sequences for detecting and measuring disease, including residual, recurrent, and metastatic disease, are the contrast-enhanced T1-weighted sequence or T2-weighted

sequence (T2 or T2-FLAIR), depending on which sequence the tumour is best visualised by (some ependymomas are poorly enhancing). If a heavily T2-weighted sequence is available and better delineates the tumour, this sequence should be used as an adjunct. The same sequence should be used throughout the disease course to assess tumour response.

Measurements should be performed in all three conventional orthogonal planes (transverse, anteroposterior, and craniocaudal), with the largest measurement for each plane recorded. When metastatic disease is present, only the three largest measurable lesions in the brain or spine should be followed, in addition to any residual disease at the primary tumour focus. Consistent with previous RAPNO guidelines, leptomeningeal disease is considered to be non-measurable.[33,34,42,43]

Defining postoperative residual intracranial disease

We recommend the following definitions for the assessment of postoperative disease on imaging to be used in future prospective trials of paediatric ependymoma: gross total resection, defined as no radiological evidence of disease; near total resection, defined as residual tumour with a maximum dimension in any plane measuring 5 mm or less; and subtotal resection, defined as residual tumour measuring more than 5 mm as the maximum dimension in any plane, or patients who underwent biopsy only rather than debulking or resection. We further suggest that patients with gross total resection and near total resection be risk-stratified and analysed together in clinical trials regarding their post-treatment outcomes (assuming their adjuvant therapy was the same). Lastly, we recommend that baseline imaging be centrally reviewed at the time of study entry by a paediatric neuroradiologist for accurate quantification of postoperative residual tumour.

Timing of imaging

A baseline postoperative brain MRI for assessment of residual disease should be obtained ideally within 24–48 h of surgery, but at maximum within 72 h postoperatively, to reduce the occurrence of non-neoplastic post-surgical contrast enhancement. Scanning at this timepoint should be irrespective of whether an intraoperative scanner is available at the time of surgical resection. This recommendation is to standardise the timing of postoperative scans, as has been done in the majority of ependymoma trials. We are aware that some scans are difficult to interpret in this immediate postoperative time period, but there is an absence of research defining a better imaging window. However, if the immediate postoperative scan is inconclusive for residual disease due to postoperative changes, a follow-up scan could be obtained 2–3 weeks after surgery to confirm the presence or absence of residual disease. If more than 4–6 weeks have elapsed between surgical resection and the start of adjuvant therapy, we recommend performing a pre-treatment brain MRI, to serve as a new baseline assessment of disease.[45,46]

Interpretation of baseline spine imaging obtained following primary tumour resection or biopsy is frequently complicated by the presence of intrathecal blood products and inflammation, making definitive identification of leptomeningeal tumour dissemination extremely challenging.[47,48] Consequently, we strongly recommend that baseline spine imaging for the detection of tumour dissemination be performed before any neurosurgical intervention. Assessment for intracranial tumour dissemination will ideally occur with imaging obtained preoperatively for similar reasons. If a spine MRI is not obtained preoperatively, we recommend waiting 10–14 days after surgical resection before pursuing spinal imaging, to allow for postoperative change to decrease or resolve. Again, this recommendation is pragmatic to allow for standardisation based on the timing of imaging used in the majority of ependymoma trials; given a lack of data showing a better timing window for postoperative spinal imaging, this time period has the advantage that MRI in sedated patients can be combined with a baseline spinal tap for assessment of cerebral spinal fluid (CSF) cytology after the imaging is completed.

For patients with non-metastatic disease enrolled on a clinical trial, spinal imaging should occur at minimum with every other brain MRI. However, patients with metastatic disease at diagnosis or chromosome 1q gain should have spinal imaging obtained with every brain MRI due to the increased risk of metastatic recurrence in these populations.[3,5,19,23,25–29]

Standards for assessing measurable versus non-measurable disease

We concur with the definitions and standards established in the RAPNO guidelines for high-grade gliomas regarding assessment of measurable versus non-measurable disease in paediatric intracranial ependymoma. Measurable disease is defined by RAPNO as a tumour, either enhancing or non-enhancing, which is at least 1 cm, or at least two times (in both perpendicular diameters) the MRI slice thickness plus the interslice gap. Non-measurable disease is defined as a tumour too small to be accurately measured (ie, less than 1 cm in at least one perpendicular dimension, or less than two times the MRI slice plus the interslice gap). Leptomeningeal disease is also considered to be non-measurable.[43]

Assessment of CSF cytology

Similar to recommendations made in the medulloblastoma RAPNO guidelines, intraoperative CSF should not be used for staging purposes due to the risk of false positives from tumour cells circulating in the CSF.[8,33,42,49,50] Cytology should be sent on lumbar CSF obtained at least 10–14 days postoperatively and obtained after postoperative spinal

	Slice thickness (mm)	Gap percentage	In-plane resolution (mm)	Utility	Comments
Brain (pre-gadolinium contrast administration)					
3D T1-weighted gradient echo, acquired in sagittal plane	1·0–1·5	0%	1·0 × 1·0	Depicts T1 characteristics, and serves as a comparator for the post-gadolinium T1-weighted images	NA
Axial T1-weighted spin echo, TSE, or FSE*	≤4	0–10%	≤1·0 × 1·0	Depicts T1 characteristics, and serves as a comparator for the post-gadolinium T1-weighted images	NA
Axial T2-weighted TSE or FSE	<4	0%	≤1·0 × 1·0	Identifies tumour margins, and aids in detection of recurrent disease	NA
Axial DWI (b=0 and 1000) with ADC	<4	0%	2·0 × 2·0	Identifies hypercellularity (lower ADC values correspond to higher grade and cellularity)	NA
Axial bSSFP[44] (CISS, bFFE, or FIESTA; can be replaced with sagittal T2-weighted Cube, SPACE, or VISTA)	1	0%	<1·0 × 1·0	Highlights small metastatic deposits that are not well visualised on T1-weighted post-contrast images	Perform through posterior fossa for posterior fossa ependymomas, or through region of interest for supratentorial ependymomas
Brain (post-gadolinium contrast administration)					
3D T1-weighted gradient echo, acquired in sagittal plane	1·0–1·5	0%	1·0 × 1·0	Identifies enhancement characteristics (enhancement can correspond to higher grade components), and metastatic disease	Sagittal plane acquisition for 3D T1-gradient echo; avoid flow compensation, acquire images in consecutive order (reconstructed into axial and coronal planes)
Axial T1-weighted spin echo, TSE, or FSE*	≤4	0–10%	≤1·0 × 1·0	Identifies enhancement characteristics (enhancement can correspond to higher grade components), and metastatic disease	Sagittal plane acquisition for 3D T1-GRE; avoid flow compensation, acquire images in consecutive order (reconstructed into axial and coronal planes)
Axial or coronal T2-weighted FLAIR	<4	0%	≤1·0 × 1·0	Identifies tumour margins, and aids in detection of metastatic and recurrent disease	Can perform before contrast, after contrast, or both, although after contrast is recommended
3D FLAIR acquired in sagittal plane†	1·0–1·5	0%	<1·0 × 1·0	Identifies tumour margins, and aids in detection of metastatic and recurrent disease	Can perform before contrast, after contrast, or both, although after contrast is recommended
Spine (post-gadolinium contrast administration)					
Sagittal T1-weighted spin echo	3	0–10%	<1·0 × 1·0	Identifies spinal leptomeningeal metastases	Acquired as two sweeps (upper and lower spine); use anterior saturation band
Axial T1-weighted VIBE, FAME, LAVA, or THRIVE	3	0–10%	<1·0 × 1·0	Identifies spinal leptomeningeal metastases	Acquired as two sweeps (upper and lower spine); acquire in consecutive order
Axial T1-weighted spin echo‡	4–5	0–10%	<1·0 × 1·0	Identifies spinal leptomeningeal metastases	Acquired as two sweeps (upper and lower spine); acquire in consecutive order
Axial T1-weighted FLAIR (propeller)§	4–5	0–10%	<1·0 × 1·0	Identifies spinal leptomeningeal metastases	Acquired as two sweeps (upper and lower spine); acquire in consecutive order
Sagittal bSSFP[44] (CISS, bFFE, or FIESTA; can be replaced with sagittal T2-weighted Cube, SPACE, or VISTA)	1	0%	<1·0 × 1·0	Highlights small metastatic deposits that are not well visualised on T1-weighted post-contrast images	NA

3D=three-dimensional. ADC=apparent diffusion coefficient. bFFE=balanced fast field echo. bSSFP=balanced steady-state free precession. CISS=constructive interference in the steady state. DWI=diffusion-weighted imaging. FAME=fast acquisition with multiphase enhanced fast gradient echo. FIESTA=fast imaging using steady-state acquisition. FLAIR=fluid-attenuated inversion recovery. FSE=fast spin echo. GRE=gradient-recalled echo. LAVA=liver acquisition with volume acquisition. NA=not applicable. SPACE=sampling perfection with application optimised contrast using different flip angle evolution. THRIVE=T1-weighted high-resolution isotropic volume examination. TSE=turbo spin echo. VIBE=volumetric interpolated breath-hold sequence. VISTA=volume isotropic turbo spin echo acquisition. *An alternative to 3D T1-weighted gradient echo. †An alternative to axial or coronal T2-weighted FLAIR. ‡An alternative to axial T1-weighted VIBE, FAME, LAVA, or THRIVE, and axial T1-weighted FLAIR (propeller). §An alternative to axial T1-weighted VIBE, FAME, LAVA, or THRIVE, and axial T1-weighted spin echo.

Table 1: **Recommended brain and spine MRI protocol for paediatric patients with intracranial ependymoma, by sequence**

imaging (if it is being done). Of note, the role of CSF cytology in the assessment of metastatic disease in intracranial ependymoma is less well defined than in medulloblastoma and other embryonal tumours.

Overall, the incidence of isolated CSF metastases (M1 disease) in ependymoma is quite low. A retrospective study of 61 newly diagnosed paediatric patients did not identify a single patient with M1 disease.[8] In the much larger HIT-2000 and the HIT-2000 Interim Registry studies for paediatric patients with newly diagnosed intracranial ependymoma, only three (1%) of 402 patients had M1 disease.[51] A meta-analysis of seven studies (two single-institution retrospective studies and five multicentre prospective studies) of 392 paediatric patients with newly diagnosed ependymoma identified only 11 (3%) with isolated CSF metastases (M1 disease).[49] In the SJYC07 study of children younger than 3 years at diagnosis, only one (2%) of 41 patients had M1 disease.[3] Despite the low

incidence of M1 disease, however, 5-year event-free survival and overall survival is worse in patients with positive CSF cytology than in those with negative cytology, and similar between patients with M1 versus M3 disease (radiologically identified spinal metastases).[49,52]

We recommend assessing the CSF of newly diagnosed patients; however, the evidence does not support serial testing of CSF if it is originally showing negative cytology. Similar to the recommendations made in the RAPNO medulloblastoma guidelines, if the CSF testing shows that cytology is positive at the time of study entry, it must be reassessed and found to be negative at least twice, sampled at least 2 weeks apart, to meet the criteria for complete response to therapy.[43] There could be a benefit to measuring ependymoma biomarkers in CSF as a more accurate reflection of minimal residual disease than imaging, but the utility of this approach is still under evaluation.

In a study of 16 patients with relapsed ependymoma (non-metastatic at diagnosis), treated at diagnosis with focal radiotherapy, no patients had positive CSF cytology at the time of relapse despite ten patients having distant failure.[53] Because this study was small, we do recommend reassessing CSF cytology at the time of recurrence, but acknowledge that future larger prospective studies might show this method to be of low yield.

Definitions of treatment response

To assess radiological response to therapy in ependymoma, we recommend consistently using the same imaging sequence that best represents the tumour, either contrast-enhanced T1-weighted or T2-weighted sequence (T2 or T2-FLAIR), and using the same MRI magnet strength if possible. The same imaging sequences and parameters should be used at baseline and at all subsequent timepoints for assessment of response if possible.[33,34,43] However, as previously mentioned, radiological response to therapy is of little value in clinical trials of patients with ependymoma, since most patients enrol on clinical trials with either no evidence of disease (ie, following total resection of the tumour), or with only minimal disease. In recurrent or progressive disease that cannot be resected, true radiological disease response to therapy is less clinically meaningful as a study endpoint than event-free survival (representing prolonged stable disease) or overall survival, but could provide a signal of efficacy worthy of future exploration in patients with complete to near complete resections.

With this caveat, the recommended criteria for defining response or progression for paediatric patients with intracranial ependymoma enrolled on clinical trials are detailed in table 2. As with similar RAPNO guidelines, all criteria must be met to classify a patient as having an objective response or stable disease, although only one criterion is needed to meet the definition of progression. Additionally, if criteria for progression are not clearly met, the investigator's discretion should be used to decide whether to keep the patient in the study until the progression is more definitive; however, once progression is clear on the basis of subsequent assessments, the date of progression should be listed as the initial questionable progression timepoint.[33,34,42,43]

Consistent with previously published RAPNO guidelines, we recommend assessing for disease response in ependymoma by obtaining two-dimensional measurements (the largest diameter and its largest perpendicular) in the axial plane of any residual primary tumour, and up to three of the largest measurable metastatic lesions in the brain or spine, if present.[43] We accept that there is no data validating the measurement of three target lesions as

	Complete response*	Partial response*	Stable disease	Progressive disease
Requirement for response	All complete response criteria below must be met	All partial response criteria below must be met	All stable disease criteria below must be met	Any progressive disease criteria below may be met
MRI brain	No evidence of disease (measurable or non-measurable) maintained on subsequent imaging at the next study-required timepoint (minimum of 8 weeks required between imaging); no new lesions	≥50% decrease from baseline of the sum of the products of two perpendicular diameters in the axial plane of any residual primary tumour, and up to three of the largest measurable metastatic lesions maintained on subsequent imaging at the next study-required timepoint (minimum of 8 weeks required between imaging); no progression of non-measurable disease; no new lesions	Does not meet criteria for complete response, partial response, or progressive disease	≥25% increase (compared with best response) in the sum of the products of two perpendicular diameters in the axial plane of any residual primary tumour and up to three of the largest metastatic lesions; clear progression of non-measurable disease; new lesions
MRI spine	Same as MRI brain	Same as MRI brain; if negative at baseline, must remain negative	Same as MRI brain	Same as MRI brain
CSF cytology	If positive at study entry, must be negative twice at least 2 weeks apart	If positive at study entry, can be positive or negative; if negative at study entry, must remain negative	If positive at study entry, can be positive or negative; if negative at study entry, must remain negative	If negative at study entry, now positive
Neurological exam	Stable or improving	Stable or improving	Stable or improving	Clinical deterioration not attributable to other causes
Steroid use	Off non-physiological doses of steroids	Stable or reduced dose from time of study entry	Stable or reduced dose from time of study entry	Not applicable

CSF=cerebral spinal fluid. *Only applicable if disease is present at the time of study entry.

Table 2: **The Response Assessment in Pediatric Neuro-Oncology working group's response assessment for paediatric intracranial ependymoma**

opposed to another number of lesions; the recommendation to choose up to three of the largest measurable metastatic lesions in the brain or spine is our current suggestion based on iterative discussions with all authors. These target lesions, as well as residual disease at the primary tumour focus, should be measured at all imaging timepoints. Response will be determined as described in table 2, by comparing the sum of the products of these perpendicular diameters at study-defined timepoints. To confirm responses (other than progression), tumours must meet the response criteria in full over two serial study-mandated imaging timepoints (table 2).[34,43]

As described in the RAPNO high-grade glioma guidelines, there are no current standards to differentiate between quiescent post-treatment tumour and refractory disease. Consequently, we do not recommend using the term refractory disease in clinical trials for either eligibility or response assessment.[43]

Discussion

The consistent prognostic implication of postoperative residual tumour burden in children with ependymoma suggests a benefit for designing trials that are restricted to newly diagnosed patients, or those with a first relapse that are able to undergo a gross total resection or near total resection and have no substantial metastatic disease burden, despite the inability to follow up these patients for radiological response.[1,3,4,17–19,22,29] In these situations, we suggest using event-free survival as a study endpoint. Data currently under analysis from the COG study NCT01096368 should identify specific patient populations that might benefit from the use of chemotherapy as part of upfront treatment. Additional considerations for clinical trial design could include the type of radiotherapy (proton *vs* photon) to use upfront and at the time of re-irradiation if applicable, and the potential addition of a maintenance phase to treatment.

Most patients enrolled in clinical trials after diagnosis, or at first or even second relapse, will undergo tumour-reductive surgery and have minimal if any disease burden at the time of initiating study therapy. This lack of radiologically-detectable disease at baseline limits the ability to detect a radiological response to treatment other than progressive disease. Consequently, despite the fact that the majority of clinical trials in ependymoma have not shown positive results in patients with substantial postoperative residual disease (above a near total resection), there is certainly a role for investigation of novel therapies in patients with bulky tumour.[3,19,22,24,29,36,54] As an example, a phase 1 single-agent study of fluorouracil for paediatric and young adult patients with recurrent ependymoma noted that 22% (five of 23 evaluable patients) had a partial response. The results of this study have since become the rationale for an upcoming multi-institutional clinical trial further assessing the role of fluorouracil in patients with ependymoma.[55]

As mentioned previously, for patients entering clinical trials without bulk disease (ie, having undergone a gross total resection or a near total resection, and not having measurable metastatic disease), we recommend using event-free survival as a study endpoint. 40% of relapses occur within 2 years of diagnosis, and median time to relapse is less than 2 years, with the majority of relapses being asymptomatic and detected only on surveillance imaging.[21,56,57] Relapse rates in ependymoma, however, generally do not plateau, and can be seen much later than in other paediatric brain tumours, especially in posterior fossa ependymoma.[4,21,56,58,59] For both paediatric and adult patients with a history of ependymoma, the European Association of Neuro-Oncology guidelines recommend long-term imaging given the risks of asymptomatic or late relapses.[60]

For trials enrolling patients at presentation or first relapse without residual postoperative disease, as mentioned earlier, we recommend obtaining brain imaging every 3–4 months for 3 years after completion of radiotherapy, and then imaging every 6 months for the following 2 years to measure 5-year event-free survival. For patients enrolled in such clinical trials with an endpoint of overall survival, we recommend continuing yearly surveillance brain imaging for an additional 5 years to complete 10 years of post-treatment radiological follow-up. We acknowledge that these long time periods might limit feasibility but feel that they are necessary given the known pattern of late relapses in this tumour.

In clinical trials for patients with recurrent or progressive metastatic ependymoma or ependymoma with chromosome 1q gain followed up for survival endpoints, the interval between scans can be shortened to every 8 weeks due to the increased propensity for progression. For the event-free survival endpoint, such patients can be followed up for 3 years (rather than 5 years), with all brain imaging accompanied by spine MRI. Other than our recommendation to obtain surveillance spine imaging at the same frequency as brain imaging for patients with chromosome 1q gain, there is insufficient data at present to differentiate the frequency and duration of surveillance imaging on the basis of molecular groups. However, as more group-stratified outcome and survival data are prospectively obtained, we expect imaging recommendations to become more specific to molecular groups.

Trials using response assessment to novel agents in patients with measurable disease could include early scanning after the first and second courses of the novel therapy and subsequent scans every 3 months, as done in many trial consortiums. However, we caution that in ependymoma, this type of trial using novel agents at the time of recurrence, although done multiple times, has not resulted in a positive outcome, and should be reserved to situations in which the preclinical data are compelling and novel.[61]

Search strategy and selection criteria

References for this Policy Review were identified through searches of PubMed with the search terms "ependymoma", "molecular group", "p(a)ediatric", "radiologic assessment", "residual disease", and "response" for articles published from Jan 1, 1999, until Nov 30, 2021. 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 Policy Review.

Similar to the discussion from the RAPNO low-grade glioma guidelines, we suggest that future ependymoma clinical trials evaluate the use and reproducibility of measuring tumours in three standard planes (transverse, anteroposterior, and craniocaudal) rather than two dimensions, to assess response to therapy to more accurately characterise the extent of disease.[62] We hypothesise that three plane measurements will allow better characterisation of the extent of disease over time, with changes in tumour size and shape, but acknowledge two versus three plane measurements for assessment of ependymoma treatment response needs to be prospectively compared.

In conclusion, intracranial ependymoma is a common type of CNS malignancy in the paediatric population, with a propensity for later recurrences than other CNS tumours. To accurately access the efficacy of therapies in clinical trials and compare results of studies, an initial standardised response assessment for ependymomas is presented here based on the available literature and recommendations from an international panel of experts. As future advances in our biological understanding of the tumor occur, and lead to biomarker-based treatment stratifications, these recommendations will be revised and updated. With the incorporation of these response assessment guidelines into clinical trials worldwide, our recommendations can be prospectively evaluated and further refined within well defined patient cohorts.

Contributors

HBL, KEW, NKF, and DMM led the RAPNO ependymoma working group, organised all discussions and meetings, and were the main writers of the manuscript. All authors contributed equally to the literature search, consensus panel participation, data collection and verification, and final manuscript review and approval. All authors had full access to all data and accept responsibility for the publication.

Declaration of interests

AB received a consulting fee from Guerbet for presentation, was paid for expert testimony in legal cases related to child abuse and hypoxic-ischaemic injury, and is a board member of the American Society of Pediatric Neuroradiology. LMH received payment from AstraZeneca for participation in an advisory board, and is on two data safety monitoring boards. KWP holds a grant from the German Childhood Cancer Foundation, the German Federal Ministry of Education and Research, and the German Research Foundation. TYP holds a grant from the Pediatric Brain Tumor Consortium Neuroimaging Center. All other authors declare no competing interests.

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