



Response assessment in pediatric neurooncology (RAPNO) criteria revisited: a practical navigation guide for neuroradiologists

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Abstract

The Response Assessment in Pediatric Neuro-Oncology (RAPNO) Working Group is an international, collaborative network of experts dedicated to pediatric central nervous system (CNS) tumors that was created in 2011. Since then, six RAPNO articles with imaging guidelines for response assessment in diverse pediatric tumor subgroups have been published, namely: 1) medulloblastomas and leptomeningeal seeding tumors (2018), 2) pediatric high-grade gliomas (2020), 3) pediatric low-grade gliomas (2020), 4) diffuse intrinsic pontine gliomas (2020), 5) pediatric intracranial ependymomas (2022) and 6) pediatric craniopharyngiomas (2023). The purpose of this article is to review all current available RAPNO criteria using a systematized and comparative approach centered on the role of neuroradiologists and supported by neuroimaging examples. Special emphasis will be placed on clarification of core concepts as well as practical adoption aspects of the RAPNO guidelines, namely how and when to image the brain and/or the spine; how to interpret the imaging findings; which other clinical, therapeutic and laboratory variables to consider; and finally how to apply the information to attribute the final appropriate response assessment classification.

Keywords Central Nervous System Neoplasms · Neuroimaging · Pediatrics · Brain tumor · Spinal cord tumor

Keypoints

- Six different Response Assessment in Pediatric Neuro-Oncology (RAPNO) criteria guidelines have been published so far.
- Neuroimaging plays a fundamental role in the diagnosis and longitudinal assessment of CNS tumors in children and is incorporated in all available RAPNO guidelines.
- Specific instructions regarding how and when to image affected children as well as on how to interpret images are provided in each of the guidelines, with some being similar for all tumor subtypes.
- Radiological evaluation of tumor response assessment needs to be correlated with other non-radiological variables for final categorization.

Abbreviations

AFP	Alpha fetoprotein
CNS	Central nervous system
CP	Craniopharyngioma
CSF	Cerebrospinal fluid
CT	Computed tomography
DIPG	Diffuse intrinsic pontine glioma
EP	Ependymoma
βhCG	β-Human chorionic gonadotropin
HGG	High grade glioma
LGG	Low grade glioma

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MRI	Magnetic resonance imaging
NF1	Neurofibromatosis type 1
RANO	Response assessment in neuro-oncology
RAPNO	Response assessment in pediatric neuro-oncology
REiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis

Introduction

The Response Assessment in Pediatric Neuro-Oncology (RAPNO) Working Group is an international, collaborative network of experts dedicated to pediatric central nervous system (CNS) tumors that was created in 2011 and includes pediatric and adult neuro-oncologists, radiologists, radiation oncologists, neurosurgeons and other related clinicians [1]. The formation of this group was inspired by a similar multidisciplinary team established since 2008 but dedicated instead to adult neuro-oncology, the so called Response Assessment in Neuro-Oncology (RANO) working group [2].

Similarly to RANO, the aim of the RAPNO working group was to define objective, standardized radiological assessment and response criteria for neuro-oncology clinical trials, but specifically adjusted to the pediatric population [1]. Indeed, there are unique challenges and issues related to pediatric brain tumors when compared to their adult counterparts that must be considered and require a dedicated approach in clinical research.

CNS tumors are overall much less common in children than in adults, thereby limiting sample sizes and reducing overall statistical power in clinical studies in this area [1]. Despite the relative low numbers compared to adults, pediatric CNS tumors still represent the second most common

type of pediatric malignancy (after hematologic malignancies) and the leading cause of pediatric cancer mortality [3].

On the other hand, pediatric brain tumors are also a more heterogeneous group of pathologies when compared to their adult counterparts. Accordingly, different RAPNO subcommittees were subsequently formed to develop standard criteria that could be applicable to the diverse landscape of CNS neoplasms. Up to the present date, a total of 6 different standardized criteria have been developed and published by the RAPNO group, including the criteria for medulloblastomas (MB) and other leptomeningeal seeding tumors (2018) [4], pediatric low-grade gliomas (LGG) (2020) [5], pediatric high-grade gliomas (HGG) (2020) [6], diffuse intrinsic pontine glioma (DIPG) (2020) [7], ependymomas (EP) (2022) [8], and craniopharyngiomas (CP) (2023) [9]. The exact CNS tumor subtypes to which these criteria apply are presented in Table 1.

In each RAPNO guideline, a review of the scientific literature including current practices was performed, followed by identification of major confounding issues, development and discussion of standard guidelines, and obtention of a final consensus [4–9].

In this paper we aim to review and compare the different RAPNO criteria published so far using a systematized and practical approach centered in the role of (pediatric) neuro-radiologists and with the support of neuroimaging examples.

Glossary

Before diving deep into the specific RAPNO criteria, it is prudent to clarify the essential concepts and terminology that apply to almost all RAPNO criteria:

Table 1 Tumor subtypes covered by the current RAPNO criteria

RAPNO criteria	TUMOR SUBTYPES
MB and leptomeningeal seeding tumors	All subtypes of pediatric and adult MB Other common CSF seeding tumors, including: All other embryonal tumors (including ATRT) Germ cell tumors Pineoblastoma Choroid plexus tumors
HGG	All subtypes of WHO grade 3 and 4 pediatric tumors of glial origin, except non-pontine diffuse midline gliomas and intracranial ependymomas
LGG	All subtypes of WHO grade 1 and 2 pediatric tumors of glial origin, except intracranial ependymomas
DIPG	All forms of diffuse intrinsic pontine glioma, regardless of molecular subtype (including H3 K27M-mutant and wildtype)
Ependymomas	All subtypes of intracranial ependymomas
Craniopharyngiomas	Adamantinomatous craniopharyngiomas

ATRT, Atypical teratoid rhabdoid tumor; *CSF*, Cerebrospinal fluid; *DIPG*, Diffuse intrinsic pontine glioma; *HGG*, High grade gliomas; *LGG*, Low grade gliomas; *MB*, Medulloblastoma; *WHO*, World Health Organization

- **Measurable disease:** Tumor lesions (either enhancing or non-enhancing) which are ≥ 10 mm or ≥ 2 times the MRI slice thickness plus the interslice gap in both perpendicular diameters;
- **Non-measurable disease:** Tumor lesions too small to be accurately measured (that is, < 10 mm in at least one perpendicular diameter, or < 2 times the MRI slice thickness plus the interslice gap times in at least one perpendicular diameter) and/or leptomeningeal disease;
- **Target lesions:** Include the primary “measurable” tumor and/or a few additionally selected “measurable” lesions present at distance (with the maximum number of selected lesions depending on the tumor subtype), and which will continue to be measured throughout the course of a clinical trial;
- **Non-target lesions:** Include both the “measurable tumoral lesions” that were not selected as target lesions due number constraints as per individual guidelines and all the “non-measurable disease”; these lesions are not measured but monitored qualitatively instead.

How to image?

General concepts regarding imaging technique

Imaging protocols

All RAPNO criteria published so far have emphasized the critical importance of uniform, standardized neuroimaging techniques and quality control for appropriate evaluation of response assessment in pediatric brain tumors clinical trials. Indeed, images should be always obtained using the recommended brain and/or spine MRI protocols with pre-defined imaging parameters. In turn, these protocols were selected by all subcommittees aiming to obtain a balance between feasibility, quality and compliance. Only routine clinical sequences were recommended across all RAPNO criteria, therefore allowing inclusion of a wide spectrum of imaging facilities, from small community centers to large, well-equipped institutions [4–9].

Images can be acquired for all tumor subtypes on either 1.5 or 3 Tesla magnets. Nevertheless, the magnetic field strength should ideally remain the same throughout the surveillance of a given patient on a given trial [4–9].

Although brain and spine MRI protocols vary according to the specific CNS tumor, special attention should be paid in all cases to avoid incomplete or poor-quality imaging, including acquisition of inadequate sequences, inappropriate resolution and/or slice thickness, motion or metal artifacts, lack of imaging in 2 planes, absence of full visualization of structures, and/or skipped regions [4–9].

Finally, although the recommended imaging protocol for each RAPNO tumor subtype may be upgraded or complemented according to local capabilities, preferences and practices, or to answer alternative research questions being addressed as secondary outcomes in a given clinical trial, additional sequences should not be used for primary assessment of tumor response [4–9].

Gadolinium injection

According to current RAPNO guidelines, injection of contrast agents is nearly always required at both baseline and follow-up brain and/or spine MRI examinations, and pre- and postcontrast imaging protocols should remain similar in terms of acquisition plane and sequence type [4–9]. The only exceptions are represented by the rare cases of completely non-enhancing pediatric LGG, in which follow-up MR studies without gadolinium injection can be considered [5], as well as fast brain MRI protocols for evaluation of CP cysts during radiotherapy [9].

In the context of Neurofibromatosis type I (NF1), injection of contrast can also be useful to detect NF1-related tumors, as presence of enhancement can help distinguishing them from non-neoplastic focal areas of signal abnormality [5].

To minimize the risk of nephrogenic systemic fibrosis and gadolinium deposition in the tissues, only macrocyclic gadolinium-based contrast agents must be used in pediatric clinical trials [5]. In addition, whenever possible, the same contrast agent should be consistently used throughout a specific clinical trial [5].

Quality control for imaging

According to the RAPNO criteria of MB [4], DIPG [7] and EP [8], reliance on local MRI interpretation is not considered adequate for clinical trials assessing efficacy of new therapies in pediatric neuro-oncology due to subjectivity of interpretation, misdiagnosis and interrater variability, potentially biasing clinical trials results, and impacting their interpretation.

Therefore, at least in those tumor subtypes, all neuroimaging data should be revised centrally by pediatric neuroradiologists with expertise in pediatric tumor imaging at the time of study entry for study eligibility as well as throughout the study for response assessment and/or risk assessment as well as quantification of postoperative residual tumor (whenever applicable) [4, 7, 8]. The MB RAPNO subcommittee further states that MRI analysis should be performed by more than one central rater, especially in case of disagreement between local center and central review [4].

Imaging recommendations

Computed tomography (CT)

For tumors presenting as a clinical emergency as well as in countries with less MR availability, a head CT scan is commonly the first examination performed in affected children, due to its accessibility, fast acquisition time, reduced costs and possibility to acquire images without the need of sedation. However, CT uses ionizing radiation and represents a less precise tool for CNS tumor measurement, limiting its utilization. Therefore, all currently published RAPNO criteria are based on brain and/or spine MR imaging evaluation and not CT [4–9].

Of note, the CP RAPNO subcommittee acknowledges that a CT may be useful at diagnosis in case the initial brain MRI shows a non-specific sellar/suprasellar mass since identification of calcifications within the lesion strongly suggests the correct diagnosis [9].

Brain MRI

Whole brain MRI The recommended protocols for whole brain MRI according to the currently available RAPNO guidelines are presented in Table 2. These protocols are similar for sporadic tumors and tumors arising in the setting of a tumor predisposition syndrome (including NF1 and non NF1-related LGG) [4–9]. However, in the specific context of NF1, the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria should also be applied, whenever appropriate [5, 10–12].

In addition, as previously mentioned, advanced structural and functional neuroimaging sequences are considered overall exploratory techniques across all RAPNO guidelines, due to lack of standardization and available data [4–8].

Focused brain MRI In addition to whole brain imaging, a more detailed imaging evaluation of the orbit and/or suprasellar region and adjacent structures is required for LGG arising from the optic pathway/hypothalamic region (NF1-related or not) [5] and also for CP [9]. The focused imaging protocol suggested for those tumor subtypes is presented in Table 3.

Fast brain MRI As per RAPNO guidelines, rapid (approximately 1 min duration) brain MRI acquisitions focused on the suprasellar region may be used for longitudinal evaluation of CP, but only for assessment of tumoral cysts and ventricular size [9]. In such cases, the suggested protocol

includes three orthogonal acquisitions of a single-shot fast or turbo spin echo sequences with up to 4 mm of slice thickness, 0% gap and in-plane resolution of 0.4×0.4 mm [9]. This approach is usually well-tolerated, especially in older children, therefore avoiding unnecessary sedation [9].

Intraoperative brain MRI The RAPNO criteria of pediatric LGG consider that intraoperative 3 Tesla MRI can be employed as a substitute for the baseline postsurgical brain MRI [5]. Inversely, the RAPNO guidelines of MB and other leptomeningeal seeding tumors specifically mention that MRI acquired during surgery should not be used as an alternative to baseline postoperative imaging [4]. On the other side, the EP RAPNO criteria state that “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” and that scanning at that time point should be “irrespective of whether an intraoperative scanner is available at the time of surgical resection” [8].

Finally, the HGG RAPNO criteria mention that although this approach might be useful in the future, it still requires validation and remains unavailable in multiple centers [5] and the RAPNO guidelines of DIPG and CP do not specifically address this topic [7].

Spine MRI

Spine MRI for detection of leptomeningeal spread

The RAPNO guidelines concerning the recommended protocols for spine MRI evaluation in the context of leptomeningeal spread screening at baseline and follow-up are systematized in Table 4. Spinal leptomeningeal deposits are usually seen as nodular or plaque-like, single or multiple, enhancing lesions or present with a “sugar-coating” appearance, and their likelihood depends on the nature of the primary brain tumor (being higher for MB and other leptomeningeal seeding tumors followed by EP and HGG).

As per RAPNO guidelines, when imaging the entire neural-axis is needed in the context of a primary brain tumor, images should be obtained in a single session to avoid multiple appointments and reduce sedation risk and gadolinium-based contrast utilization [4–8]. In addition, spinal images should be acquired as a minimum of two stations (upper and lower segments) and include visualization of the entire spinal canal (including the *cul-du-sac*) without skipped regions. For sagittal post-gad T1WI, an anterior saturation band should be placed close to the anterior wall of the vertebral bodies and fat suppression techniques avoided, aiming to obtain a homogeneous signal within the spinal CSF and eliminating both pulsation and physiologic motion artifacts,

Table 2 Review of the imaging recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) subcommittees concerning whole brain MRI protocols

PROTOCOL	MB	DIPG	LGG	HGG	EP	CP	
PRE-GAD	T1	X Ax 2D SE/TSE/FSE OR Sag/Cor/Ax 3D MPRAGE/ SPGR/FFE/ TFE	X Ax 2D SE/TSE/FSE OR Sag/Cor/Ax 3D MPRAGE/ SPGR/FFE/ TFE	X Ax 2D SE/TSE/FSE (GE if post fossa tumor) OPTIONAL Sag 3D	X Sag 3D Gradient/ SE-based technique OR Ax 2D SE/TSE/FSE	X Sag 3D Gradient- based technique OR Ax 2D SE/TSE/FSE	X Sag/Cor/Ax 3D MPRAGE/ SPGR/FFE/ TSE
	T2	X Ax 2D TSE/FSE	X Ax 2D TSE/FSE	X Axial 2D SE/TSE/FSE OPTIONAL Cor/Sag 2D SE/TSE/FSE	X Ax 2D TSE/FSE	X Ax 2D TSE/FSE	X Ax 2D TSE/FSE
	T2-FLAIR	-	-	X Ax/Cor 2D TSE/FSE OPTIONAL Sag 3D	X Ax 2D	OPTIONAL ¹ Sag 3D OR Ax/Cor 2D	X ¹ Ax 2D TSE/FSE
	DWI with ADC	X ^b	-	X	X	X	X
	SWI	-	-	-	-	-	OPTIONAL Ax (in cases without concurrent CT)
	bSSF	-	-	-	-	X CISS/bFFE/ FIESTA OR Sag Cube/ SPACE/ VISTA	OPTIONAL Add CISS/ FIESTA OR Sag Cube/SPACE/ VISTA
POST-GAD	T1	X Ax 2D SE/TSE/FSE AND Sag/Cor 3D SPACE/Cube/ VISTA OR Cor 2D SE (in case 3D Post- GAD images are unavailable or have motion)	X Ax 2D SE/TSE/FSE AND Sag/Cor 3D SPACE/Cube/ VISTAOR Cor 2D SE	X Ax/Cor/Sag 2D SE/TSE/FSE (GE instead if post fossa tumor) OPTIONAL Sag 3D	X Sag 3D Gradient or SE-based techniques OR Ax 2D SE/TSE/FSE AND Cor/Sag 2D SE	X Sag 3D Gradient- based technique OR Ax 2D SE/TSE/FSE	X Ax 2D TSE/FSE OR Sag/Cor/Ax 3D MPRAGE/ SPGR/FFE/ TSE
	FLAIR	X Ax 2D (may be the 1st post-contrast sequence)	X Ax 2D	OPTIONAL Ass sag 3D	-	X ^a Sag 3D OR Ax/Cor 2D	OPTIONAL ^a Ax 2D TSE/FSE

2D, two-dimensional; 3D, three-dimensional; ADC, apparent diffusion coefficient; Ax, Axial; bFFE, balanced fast field echo; bSSFP, balanced steady-state free precession; CISS, constructive interference in the steady state; Cor, Coronal; CT, Computed tomography; DIPG, Diffuse intrinsic pontine glioma; DWI, diffusion-weighted imaging; EPI, Echo planar imaging; FIESTA, fast imaging using steady-state acquisition; FLAIR, fluid-attenuated inversion recovery; FFE, Fast field echo; FSE, fast spin echo; GAD, Gadolinium; GE, Gradient echo; GRE, gradient-recalled echo; HGG, High grade glioma; LGG, Low grade glioma; MB, Medulloblastoma; Sag, Sagittal; SE, Spin echo; SPACE, sampling perfection with application optimised contrast using different flip angle evolution; MPRAGE, Magnetization-prepared rapid acquisition with gradient echo; SPGR, SPOiled Gradient-Recalled; TSE, turbo spin echo; VISTA, volume isotropic turbo spin echo acquisition

^aAt least one FLAIR sequence must be obtained, either before or after gadolinium injection

^bOr axial Diffusion Tensor Imaging

Table 3 Review of the imaging recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) subcommittees concerning focused brain MRI protocols

MRI PROTOCOL	LGG ^a ORBITS/SELLA	CP ^b SELLA
PRE-GAD	T1 2D Cor SE/TSE/FSE	Cor + Sag TSE/FSE
	T2 2D Ax + Cor SE/TSE/FSE with FAT SAT or STIR	Sag <u>OR</u> Cor TSE/FSE
POST-GAD	T1 2D Ax + Cor SE/TSE/FSE FAT SAT	Cor + Sag TSE/FSE

2D, Two-dimensional; Ax, Axial; CP, Craniopharyngioma; Cor, Coronal; FSE, Fast spin echo; GAD, Gadolinium; LGG, Low-grade glioma; Sag, Sagittal; SE, Spin echo; STIR, Short inversion time inversion recovery; TSE, Turbo spin echo

^aAll sequences: ≤3 mm slice thickness; 0% gap percentage; 0.4 × 0.4 mm in-plane resolution

^bAll sequences: ≤3 mm slice thickness; 0% gap percentage; 180–200 mm image resolution field of view; 512 matrix frequency (minimum 256)

which in turn are more intense in the pediatric age group. On the other hand, for axial T1 contrast-enhanced images, acquisition should be performed in a consecutive (that is, not interleaved) order [4–8].

Addition of sagittal T2 myelographic sequences (ideally 3D T2WI FSE/TSE sequences, such as CUBE/SPACE/VISTA or alternatively FIESTA/FISP/balanced FFE) can highlight minimal metastatic deposits that are not well detected on post-contrast T1WI and help to exclude possible mimickers, namely pulsation artifacts or physiologic veins along the surface of the spinal cord. Importantly, false positive lesions are more commonly seen in only one plane and/or acquisition and therefore confirmation of imaging abnormalities in multiple planes/sequences supports any suspicious finding [4–8].

Spine MRI for primary spinal cord tumors

The LGG and HGG RAPNO criteria also apply to tumors originating primarily from the spinal cord [5, 6] and a dedicated spine MRI protocol has been suggested by the LGG subcommittee [5] (Table 4).

Moreover, in both cases a baseline screening brain MRI is recommended to exclude intracranial leptomeningeal dissemination [5, 6]. However, for spinal HGG, the brain MRI should be repeated at the same time point as the follow-up spine MRI irrespectively of the results of the screening brain examination [6], while for spinal LGG a follow-up brain MRI should only be obtained in case

Table 4 Review of the imaging recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) subcommittees concerning spine MRI protocols

MRI PROTOCOL	Leptomeningeal screening ^a	Primary spinal tumor ^b
PRE-GAD	T1	- X Sag 2D SE/TSE
	T2	- X Sag + Ax* 2D SE/TSE
POST-GAD	T1	X Sag 2D SE <u>AND</u> Ax 3D VIBE/FAME/LAVA/ THRIVE <u>OR</u> Ax 2D SE <u>OR</u> Ax 2D FLAIR (propeller)
		X Sag 2D SE/TSE <u>AND</u> Ax 2D SE/TSE <u>OR</u> Sag 3D gradient
	T2 myelographic sequences	X Sag CISS/FIESTA <u>OR</u> Sag CUBE/SPACE/VISTA

2D, Two-dimensional; Ax, Axial; Cor, Coronal; FAME, Fast acquisition with multiphase enhanced fast gradient echo; FSE, Fast spin echo; GAD, Gadolinium; Sag, Sagittal; SE, Spin echo; TSE, Turbo spin echo

*Pre-contrast axial T2 images acquired only through the tumor

^aApplies to medulloblastomas and other leptomeningeal seeding tumors, ependymomas, diffuse infiltrating pontine gliomas and high-grade gliomas. No specific spine MRI protocol for leptomeningeal screening was provided by the pediatric low-grade glioma RAPNO criteria. As per RAPNO, craniopharyngiomas do not require spine MRI screening

^bApplies to pediatric low-grade gliomas; may be also considered for high-grade gliomas although no specific protocol provided in the corresponding guidelines

Table 5 Review of the imaging recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) subcommittees concerning whole brain MRI protocols

	MB	DIPG	HGG*	LGG**	EP	CP
Definition of baseline brain MRI	<72 h post-cx MRI OR 2-3W delayed post-cx MRI (in case of extensive post-cx changes)	If biopsy only: Pre-biopsy diagnostic MRI ^a If post-RT baseline: 4-6W post-RT	<72 h (ideally <24 h) post-cx MRI ^b OR 2-3W delayed post-cx MRI ^b (in case of extensive post-cx changes) If post-RT baseline: 4-8W post-RT	If Cx: 24-72 h post-cx MRI ^a OR 3 T intraOP MRI ^b OR 2-3W delayed post-cx MRI ^b (in case of extensive post-cx changes) If biopsy only: Pre-biopsy diagnostic MRI ^b	<72 h (ideally <24-48 h) post-cx MRI ^c OR 2-3W delayed post-cx MRI ^c (in case of extensive post-cx changes)	If Cx: <2W post-cx MRI ^c If biopsy solid portion only: Pre-biopsy diagnostic MRI ^c
Timing of FU brain MRI	At least once every 3 M	At least once every 3 M	If new dx: At least once every 3 M within the 1st Y (slow increase in the intervals may be considered thereafter) If relapse: At least once every 2 M	At least once every 3 M	If negative baseline AND absence of crIq gain⁵: <3Y: every 3-4 M 3-5Y: every 6 M 5-10Y: every 12 M If positive baseline OR crIq gain⁵: At least every 2 M	Once every 3 M
Need of baseline spine MRI	Yes	Yes	Yes	Only in special cases (symptoms suggestive of spinal disease/specific high-risk pathology)	Yes	No
Baseline spine MRI	Pre-cx MRI OR <72 h post-cx MRI* (if pre-cx spine MRI not available/ with low quality) OR 14-21D post-cx MRI* (if large subdural collections in early post-cx MRI)	Pre-biopsy MRI	Pre-cx MRI OR <72 h (ideally <24 h) post-cx MRI	Pre-cx/biopsy MRI OR 10-14D post-cx/biopsy MRI	Pre-cx MRI OR 10-14D post-cx MRI	-
Timing FU spine MRI	If negative baseline: Repeat only in case of new spinal signs/symptoms or to confirm complete radiologic response If positive baseline: FU concurrently with brain MRI	If negative baseline: Repeat only in case of new spinal signs/symptoms or to confirm complete radiologic response If positive baseline: FU concurrently with brain MRI	If negative baseline: Repeat only in case of new spinal signs/symptoms or to confirm complete radiologic response If positive baseline: FU concurrently with brain MRI	If negative baseline: Repeat only in case of new spinal signs/symptoms or to confirm complete radiologic response If positive baseline: FU concurrently with brain MRI	If negative baseline AND absence of crIq gain⁵: Minimum with every other brain MRI If positive baseline OR crIq gain⁵: FU concurrently with brain MRI	-

Table 5 (continued)

CP, Craniopharyngioma; Cr, Chromosome; Cx, Surgery; D, Days; DIPG, Diffuse intrinsic pontine glioma; Dx, Diagnosis; EP, Ependymoma; FU, Follow-up; h, Hours; HGG, High grade glioma; *intraOP*, intraoperative; LGG, Low grade glioma; M, Months; MB, Medulloblastoma and other leptomeningeal seeding tumors; FU, Follow-up; RT, Radiotherapy; T, Tesla; Y, Year, W, Weeks

^aNeed to be completed no earlier than 4 weeks before clinical trial entry

^bIn case of relapsed disease, need to be completed no earlier than 3 weeks before clinical trial entry

^cNeed to be completed no earlier than 4–6 weeks before clinical trial entry

^dIn case of posterior fossa type A ependymomas

^eIn case of a primary spinal cord (instead of brain) HGG, a baseline brain MRI should always be obtained pre-cx and repeated with every follow-up spine MRI

^{**}In case of a primary spinal (instead of brain) LGG, a baseline brain MRI should be always obtained pre-cx and 24–72 h post-cx and if brain dissemination identified, FU brain MRI should be performed at the same time intervals as for the primary spinal lesion

of positive intracranial leptomeningeal dissemination at presentation [5].

When to image?

The recommended timing of baseline brain and/or spine MRI and frequency of routine surveillance imaging assessment according to the different RAPNO subcommittees is presented in Table 5.

In some instances, namely after a substantial tumor resection (rather than biopsy) at follow-up, the postsurgical MRI will become the new baseline. In addition, in the setting of a CP treated with radiotherapy, a new baseline brain MRI scan should be obtained 12 months after treatment completion [9].

Conversely, there are situations in which a shorter follow-up MRI is recommended by the RAPNO subcommittees, namely in case of indeterminate classification/suspicion of treatment-related effects including pseudo-response and pseudo-progression.

How to interpret images?

Besides the specific instructions provided below for evaluation of the neuroimaging component of RAPNO tumor response assessment criteria (namely performance of tumor measurements of target disease and evaluation of non-target disease), integrated imaging evaluation should be routinely performed at each time point, considering all radiographic determinants and available sequences as well as non-radiological variables [4–9].

Which sequence(s) should be used for tumor measurement?

The MB RAPNO provide only general recommendations concerning this task, referring that measurements should be made in the sequence(s) that best allow visualization of the lesion(s) [4], while the CP RAPNO guidelines do not specifically address this issue [9].

The HGG [6] and EP [8] RAPNO guidelines explicitly instruct to use either T2/FLAIR sequences or contrast-enhanced T1WI for detection and measurement of disease (depending on the degree of tumoral enhancement of the tumor at the initial MRI/baseline scan). In the setting of an EP, evaluation can also be complemented with dedicated heavily T2-weighted images [8].

On the other hand, the LGG [5] and DIPG [7] RAPNO subcommittees recommend performing tumor

measurements using either T2WI or T2/FLAIR sequences, but not contrast-enhanced T1WI.

As a general rule, once the selection of the measurement sequence is made for each patient amongst the recommended ones for each tumor subtype, it should be used systematically throughout the trial to assess tumor response.

On some occasions it may be difficult to delineate the margins of the tumor (due to difficult differentiation of tumor infiltration from vasogenic edema or treatment related changes), especially using T2/FLAIR sequences only. In such cases, the HGG RAPNO suggests that concurrent involvement of deep gray matter structures as well as presence of restricted diffusion and associated enhancement supports tumor involvement [6].

How to perform measurements in “measurable” tumoral lesions?

2D measurements

Two-dimensional measurements represent the current standard approach for response assessment according to all RAPNO guidelines [4–9].

When dealing with a **single measurable tumoral lesion** (see definitions provided above), the 2D measurements should be performed in the axial plane, consisting of the longest measurement of the tumor and its largest perpendicular diameter, as exemplified in Fig. 2 [4–9]. Measurements should be systematically performed in the same plane over time for a more accurate comparison [4–9].

In the setting of **multiple measurable tumoral lesions (multifocal or disseminated disease)**, measurement of additional lesions is indicated according to all RAPNO guidelines, although the maximum of total target lesions varies according to the tumor subtype (up to three in EP, DIPG and HGG [6–8], up to four in MB [4] and up to five in LGG [5]).

Selection of those additional lesions up to the maximum limit should be made based on the size (with the largest ones preferred) and/or presence of associated symptoms and signs active growth. The selected measurable lesions will be considered “target lesions” during longitudinal evaluation while the remainder measurable ones together with non-measurable disease become “non-target lesions” [4–9].

3D measurements and volumetric assessment using a dedicated software

So far, 3D tumoral measurements have only been included as an alternative and/or additional method to 2D approach for response assessment by the LGG RAPNO guidelines

[5]. For that purpose, it has been recommended to obtain the longest perpendicular diameters of the lesion in the orthogonal planes using multiplanar imaging [5].

Although the other RAPNO committees have not yet adopted the 3D methodology for response assessment categorization, supplementary obtention of 3D measurements has been highly encouraged by all of them for future comparison between the two approaches and definition of the most accurate one [4–9]. Similarly, volumetric assessment is not considered as a routine tool for response assessment by any of the current RAPNO guidelines, although its evaluation as a secondary endpoint in prospective trials has been recommended by most of them [4–9].

How to calculate the total dimensions of the target measurable disease?

As a general rule, after applying the 2D measurement guidelines described above, the product of the perpendicular measurements (in case of a single target lesion) or the sum of the product of the perpendicular measurements (in case of multiple target measurable lesions) should be calculated at each time point of the longitudinal neuroimaging assessment (Fig. 1) and the corresponding values should be compared with previous examinations (baseline study or best response, whichever applies) [4–9].

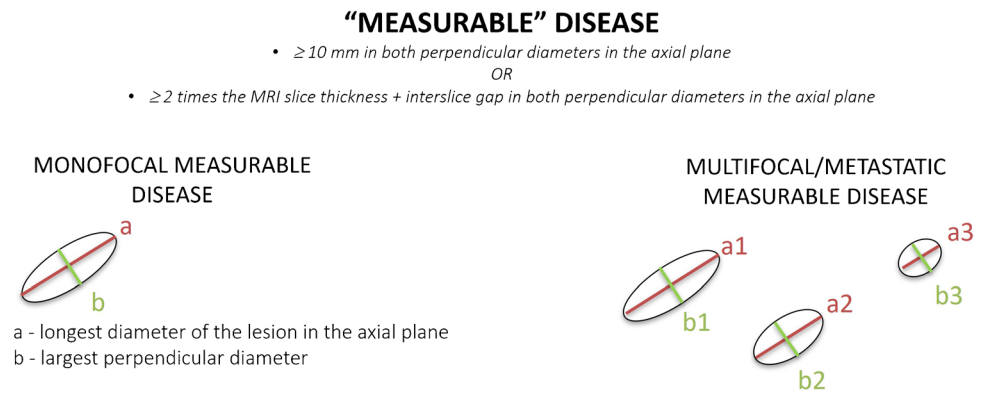
Importantly, the DIPG and CP RAPNO guidelines require additional steps for radiological assessment of measurable disease [7, 9]. Indeed, separated evaluation (and subsequent cut-offs for comparison) of pontine and extra-pontine (ie, non-contiguous with the primary pontine lesion) disease measurements and of total tumor (solid + cystic components) is required for DIPG evaluation [7]. On the other side, isolated measurements of solid component and cystic components is necessary to apply the CP response assessment criteria [9]. This approach is justified by the diverse natural history of the different components and/or locations of those tumor subtypes [7, 9].

Should cysts be included in tumoral measurements?

According to the HGG and DIPG RAPNO guidelines, cystic lesions should be included in 2D measurements of target measurable disease only whenever englobed within the solid component or not readily separable from the solid tumor component, but should be excluded otherwise [6, 7].

The LGG RAPNO criteria are more detailed in this topic and mention that clusters of small microcysts within a tumor as well as well as cysts with thick wall enhancement should be included in such measurements [5]. Opposingly, LGG cysts located in the interface between the solid tumor component, intermingled with the surgical cavity or part of a

Fig. 1 Definitions and examples on how to perform 2D measurements and calculate total size of “measurable” disease. Legend: *Maximal number of target lesions depends on the tumor subtype



Total volume of target measurable disease

Single lesion: $a \times b$

Multiple lesions: $(a1 \times b1) + (a2 \times b2) + (a3 \times b3) + \dots + (an \times bn)^*$

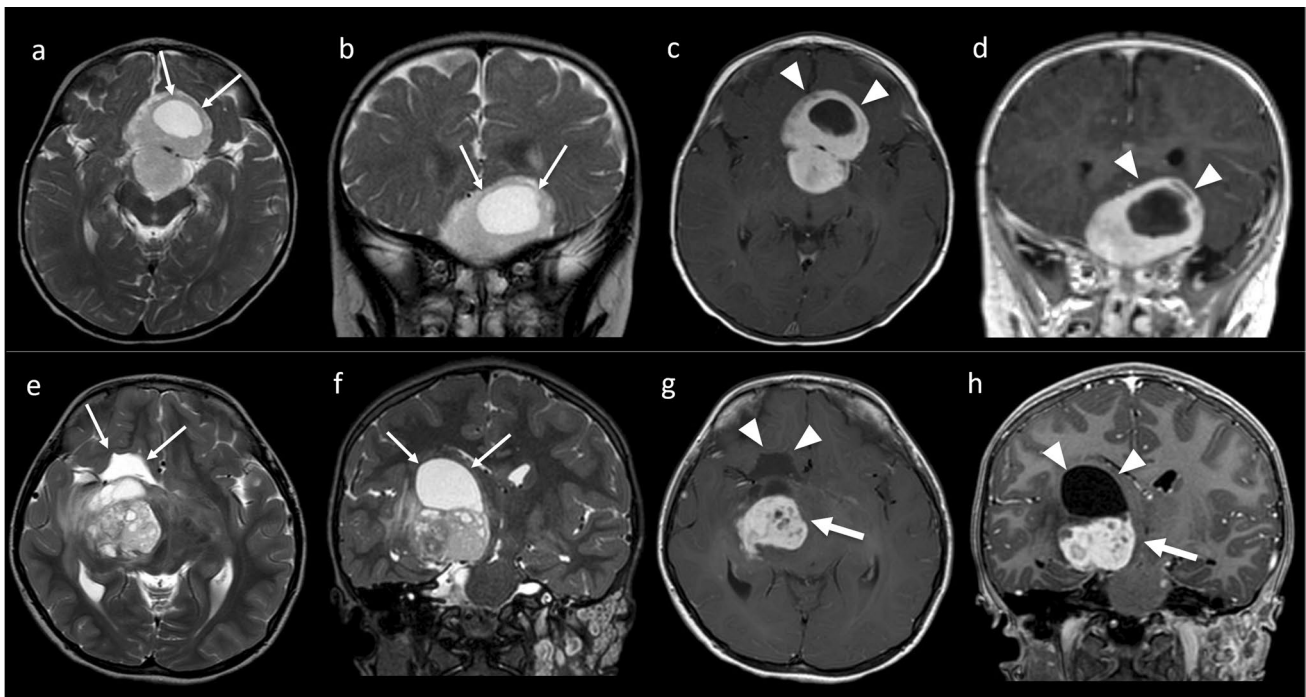


Fig. 2 Example of a tumor cyst in a 19-month-old male with a low-grade glioma (ie. pilocytic astrocytoma) (a-d). Axial (a) and coronal (b) T2WI show a large tumor centered in the hypothalamic-chiasmatic region and extending towards the anterior cranial fossa, with a well-defined cyst completely circumscribed within the most ventral region of the tumor and lateralized to the right (thin arrows). Post-contrast axial (c) and coronal (d) T1WI confirm the integration of the cyst within the solid component with thick circumferential enhancement of the cyst wall (arrowheads). This cyst should be included in 2D tumor measurements according to current low-grade tumor RAPNO criteria. Example of a non-tumor cyst in a 7-year-old female

with NF1 and supratentorial low-grade glioma (pilocytic astrocytoma) (e-h). Axial (e) and coronal (f) T2WI show a large intra-axial tumor in the right diencephalon-mesencephalic region. Note that the largest cyst (thin arrows) is located at the interface between the anterosuperior margin of the solid component of the tumor and the healthy brain and not surrounded by the tumor, and therefore can be readily separated from it. On post-contrast T1WI (g-h), there is heterogeneous enhancement of the solid component of the tumor (thick arrows), while there is no enhancement of the large cyst wall (arrowheads). Accordingly, this cyst should be excluded from 2D tumor measurements according to current low-grade tumor RAPNO criteria

Table 6 Systematization of the non-radiological variables included as independent variables for response assessment by the Response Assessment in Pediatric Neuro-Oncology (RAPNO) subcommittees

	MB	DIPG	HGG	LGG	EP	CP
Neurological examination	X	X	X	X	X	X
Visual assessment	-	-	-	-	-	X
CSF cytology	X	-	-	-	X	-
Serum/CSF AFP and β hCG	X	-	-	-	-	-
Pituitary evaluation	-	-	-	-	-	X ^a
Steroid use	X	X	X	-	X	-
Anti-angiogenic use	-	X	X	-	-	-
Extra-CNS disease	X	-	-	-	-	-

AFP, Alpha fetoprotein; CNS, Central nervous system; CP, Craniopharyngioma; CSF, Cerebrospinal fluid; DIPG, Diffuse intrinsic pontine glioma; EP, Ependymoma; β hCG, β -human chorionic gonadotropin; HGG, High grade glioma; LGG, Low grade glioma; MB, Medulloblastoma and other leptomeningeal seeding tumors

^aExcept if RT is performed

predominantly cystic tumor with a mural nodule and nearly absent wall enhancement should be excluded [5]. Figure 2 depicts examples of both tumoral and non-tumoral cysts.

Different from the aforementioned information, the RAPNO criteria for CP recommend inclusion of the cystic

component in the 2D measurements of the global tumor, regardless of their location and relationship to the solid mass [9]. Importantly, as previously mentioned, besides the joint measurements, separate measurement of solid and cystic components should also be performed as the

Table 7 Review of the imaging recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) subcommittees concerning lumbar puncture/CSF evaluation

	MB	DIPG	HGG	LGG	EP	CP
CSF evaluation of newly dx patients	YES	NO	No formal recommendation made	NO	YES	NO
CSF evaluation at time of recurrence	YES	NO	No formal recommendation made	NO	YES	NO
Collection site	Lumbar sampling, unless contra-indicated ^{a,b,c}	-	-	-	Lumbar sampling, unless contra-indicated ^a	-
Timing of first assessment	< 14D post-cx ^{a,b} If positive: repeat > 15D post-cx and before treatment for confirmation	-	-	-	10-14D post-cx ^c	-
Re-assessment	YES During all clinical trial, concurrently with brain MRI ^d	-	If made and positive at baseline: Only if CR is considered ^e	-	If negative at baseline: NO If positive baseline: Only if CR is considered ^d	-

CP, Craniopharyngioma; CR, Complete response; CSF, Cerebrospinal fluid; Cx, Surgery; D- Days; DIPG- Diffuse intrinsic pontine glioma; Dx, Diagnosed; EP, Ependymoma; HGG, High grade glioma; LGG, Low grade glioma; MB, Medulloblastoma and other leptomeningeal seeding tumors

^aFor patients < 5 years, a minimum of 2.5 ml of cerebrospinal fluid (CSF) should be obtained; for older children and adults, higher sample volumes should be collected as they reduce false negative rates

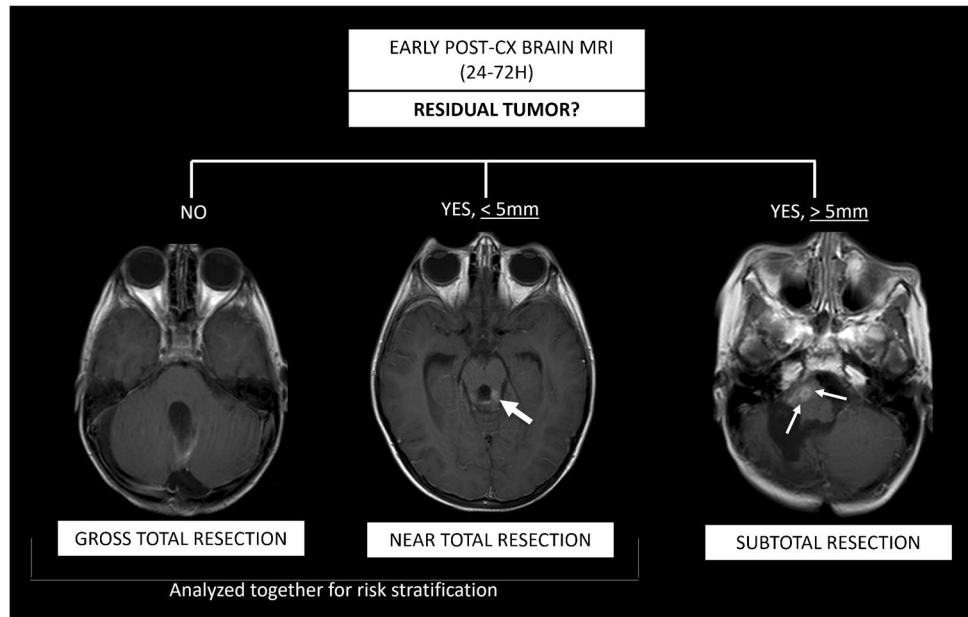
^bSamples should be cytospun immediately or alternatively refrigerated without alcohol and processed as soon as possible and no longer than 24 h to minimize false negatives

^cThe CSF should be obtained immediately after the post-surgical spine MRI while the child is sedated in case a presurgical spine baseline study has not been obtained

^dFor complete response, CSF cytology must become negative in ≥ 2 samples collected ≥ 2 weeks apart

^eFor complete response, CSF cytology must become negative but no further details provided

Fig. 3 Appropriate classification of postsurgical residual tumor according to the ependymoma RAPNO response assessment criteria, including gross total resection, near total resection (thick arrow) and subtotal resection (thin arrows)



response assessment criteria of CP vary according to the nature of these individual components [9]. Moreover, interpretation of size changes of CP cysts varies depending on previous treatment with radiotherapy and its time of completion [9].

How to evaluate non-target disease (including non-measurable disease/leptomeningeal metastasis and non-target measurable disease) and new lesions in the brain and/or spine?

Besides evaluating any possible longitudinal size changes within target measurable disease according to the above-mentioned methodology, radiologists should also scrutinize presence of any new intracranial/spinal tumoral lesions and/or signs of clear progression of previously identified non-measurable disease (including leptomeningeal metastasis) and/or non-target measurable disease in the setting of a multifocal/disseminated tumor. In any case, evaluation should be performed according to a binary classification (*present* versus *absent*) [4–9].

What is the role of DWI according to the RAPNO criteria?

All RAPNO subcommittees except the DIPG one incorporate DWI images as part of their recommended brain MRI protocol, but only the HGG guidelines have included this sequence as an independent, qualitative measure for tumor response assessment [4–9]. More specifically, in the setting

of pediatric HGG neuroradiologists should verify if there is any size change (reduction, increase or disappearance) of the areas of restricted diffusion previously seen (if present) as well as appearance of new focus of restricted diffusion, not attributable to therapy or therapy-related complications [6]. However, for assumption of disease progression, DWI evaluation needs to be jointly made with contrast-enhanced T1WI and T2/FLAIR changes [6]. Moreover, in case DWI images are not acquired at baseline in HGG, tumor response assessment (including response and progression) can still be performed after exclusion of this criterion in subsequent evaluations [6].

Whilst DWI is not incorporated in the formal RAPNO response assessment criteria of MB and other leptomeningeal seeding tumors, the corresponding subcommittee acknowledges that this sequence is particularly useful for imaging evaluation of these tumors (including primary lesions and leptomeningeal deposits as well as recurrent disease) due to their typical hypercellularity [4].

Additional clinical, laboratory and therapeutic variables

In addition to neuroimaging data, all RAPNO committees require the use of clinical/neurological evaluation and in some instances also treatment-related, functional and/or laboratorial information for response assessment classification [4–9], as systematized in Table 6 and explained below in more detail.

Table 8 Categorization of the Response Assessment in Pediatric Neuro-Oncology (RAPNO) Response Criteria for Assessment of Pediatric tumors according to target measurable disease

Target measurable disease	COMPLETE RESPONSE	MAJOR RESPONSE	PARTIAL RESPONSE	MINOR RESPONSE	STABLE DISEASE	PROGRESSIVE DISEASE
MB ^a DIPG ^b	NO EVIDENCE/ COMPLETE RESOLUTION (enhancing and non-enhancing)	-	≥ 50% decrease* Pons: ≥ 25% decrease Extrapontine: ≥ 50% decrease	-	NO OTHER CRITERIA ARE MET	≥ 25% increase Pons: ≥ 25% increase Extrapontine: ≥ 25% increase
HGG ^c LGG ^d	-	≥ 75% decrease	≥ 50% decrease	25–49% decrease		≥ 25% increase**
EP ^e CP ^f	-	-	≥ 50% decrease* (solid and cystic components con- sidered jointly)	-		≥ 25% increase Solid component: ≥ 25% increase OR lesser change caus- ing new functional impairment Cystic component: Any change requir- ing surgical inter- vention or causing new functional impairment ^g

CP, Craniopharyngioma; DIPG, Diffuse intrinsic pontine glioma; EP, Ependymoma; HGG, High grade glioma; LGG, Low grade glioma; MB, Medulloblastoma and other leptomeningeal seeding tumors

^aUp to 4 target lesions; any form of response must be sustained ≥ 4 weeks

^bUp to 3 target lesions; any form of response must be sustained at least for ≥ 8 weeks

^cUp to 3 target lesions; any form of response must be sustained at least for ≥ 8 weeks

^dUp to 5 target lesions; any form of response must be sustained at least for ≥ 12 weeks

^eUp to 3 target lesions; any form of response must be sustained at least for ≥ 8 weeks

^fUp to 4 cysts; any form of response must be sustained ≥ 12 weeks

^gExcept < 12 months of radiotherapy completion

* If spine MRI negative at baseline, it must remain negative

** ≥ 25% increase in the size of restricted diffusion does not account for progressive disease on its own but has to be accompanied by other criteria, including: > 25% size increase in the area of the lesion on T1 postcontrast/T2 FLAIR, presence of a new lesion, or clinical deterioration

Clinical and neurological examination

Physical and neurological evaluation should be made by the referring physician at baseline and every time point of follow-up, using standardized methods and performance scores whenever available and ideally concurrently with the neuroimaging assessment [4–9]. In particular, the HGG RAPNO guidelines suggest the application of the Karnofsky performance score for patients ≥ 16 years and the Lansky performance score for patients < 16 years and/or the Eastern Cooperative Oncology group performance status and provide specific cut-offs for classification of clinical deterioration [6].

Importantly, for all tumor subtypes, whenever clinical worsening is detected, contribution of other non-tumoral causes must be first ruled out, namely any intercurrent diseases or therapy-related changes [4–9].

Concomitant treatments

The MB [4] and EP [8] RAPNO criteria consider *steroid use* and the HGG [6] and DIPG [7] RAPNO criteria recognize both *steroid use and angiogenic inhibitor (eg. bevacizumab) use* as independent variable(s) of tumor response assessment, as these medications can influence tumor volume and/or edema changes. If *immunotherapy* is used to treat patients

Table 9 Categorization of the Response Assessment in Pediatric Neuro-Oncology (RAPNO) Response criteria for Assessment of Pediatric tumors according to non-measurable disease/non-target measurable disease changes

Non-measurable disease/ non-target measurable disease	COMPLETE RESPONSE	MAJOR RESPONSE	PARTIAL RESPONSE	MINOR RESPONSE	STABLE DISEASE	PRO- GRES- SIVE DIS- EASE
MB	NO EVI- DENCE/	-	NO PROGRESSION	-	OTHER	CLEAR
DIPG	COMPLETE	-		-	CRITE- RIA NOT	PRO- GRES- SION
HGG	RESOLU- TION	-	NO PROGRESSION	NO PROGRESSION	MET	
LGG	(enhancing and non- enhancing)	-		-		
EP	NA	NA	NA	NA	NA	NA
CP	NA	NA	NA	NA	NA	NA

CP, Craniopharyngioma; DIPG, Diffuse intrinsic pontine glioma; EP, Ependymoma; HGG, High grade glioma; LGG, Low grade glioma; MB, Medulloblastoma and other leptomeningeal seeding tumors; NA, Non applicable

Table 10 Systematization of the Response Assessment in Pediatric Neuro-Oncology (RAPNO) Response criteria for Assessment of Pediatric tumors concerning categorization according to new lesions

New lesions	COMPLETE RESPONSE	MAJOR RESPONSE	PARTIAL RESPONSE	MINOR RESPONSE	STABLE DISEASE	PROGRES- SIVE DIS- EASE
MB	NO	-	NO	-	OTHER CRITERIA NOT MET	YES
DIPG		-		-		
HGG		-		NO		
LGG		NO		NO		
EP		-		-		
CP	NA	NA	NA	NA		NA

CP, Craniopharyngioma; DIPG, Diffuse intrinsic pontine glioma; EP, Ependymoma; HGG, High grade glioma; LGG, Low grade glioma; MB, Medulloblastoma and other leptomeningeal seeding tumors; NA, Non applicable

with pediatric HGG, they should be assessed instead according to the iRANO criteria already published for adults [6, 13].

Although radiotherapy has not been directly incorporated in any of the RAPNO criteria, information regarding any previous radiotherapy regimen and its time of completion is required for the application of such criteria according to CP guidelines, as it will be explained below in more detail [9]. Furthermore, pituitary dysfunction is considered as an independent variable in response assessment of CP if patients have not been previously submitted to radiotherapy (see section below) [9].

Finally, in the setting of CP *cyst-directed therapies*, the corresponding RAPNO subcommittee suggests that except for progressive disease, specific response criteria should be defined in individual clinical trials by the treating physician or the principal investigator [9].

Hypothalamic function

In patients with CP, RAPNO guidelines recommend that the hypothalamic function (including height, growth velocity) is

assessed at baseline and every 3 months for the first 2 years, although this information has not yet been included in the formal response assessment criteria of this tumor subtype [9].

Visual assessment

According to the RAPNO guidelines published so far, visual assessment should be systematically performed in children with either optic pathway and hypothalamic LGG (NF1-related or not) [5] or adamantinomatous CP [9], in both cases following the REiNS International Collaboration guidelines [14]. However, visual assessment has been formally integrated into the RAPNO response assessment of CP [9], but not LGG [5]. Indeed, in children with CP detection of visual acuity decrease of ≥ 0.2 log MAR from baseline (new or worsening) sustained for 4 weeks if not attributable to another cause should be considered as a sign of progressive disease [9].

Ideally, visual assessment should be performed at the same time points as the neuroimaging acquisition, ie, every

Table 11 Categorization of the Response Assessment in Pediatric Neuro-Oncology (RAPNO) Response criteria for Assessment of Pediatric tumors according to qualitative evaluation of DWI sequences

Qualitative DWI evaluation	COMPLETE RESPONSE	MAJOR RESPONSE	PARTIAL RESPONSE	MINOR RESPONSE	STABLE DISEASE	PROGRESSIVE DISEASE
HGG	Complete resolution of previously seen area(s) of restricted diffusion	–	Decrease size of previously seen area(s) of restricted diffusion	Increase size of restricted area(s) of restricted diffusion ^{a,b}	OTHER CRITERIA NOT MET	Increase size of area of restricted diffusion ^{a,b} OR New focus of restricted diffusion ^a

HGG, High grade glioma

^aNot attributable to therapy or therapy-related complications

^bHas to be accompanied by other criteria, including: > 25% size increase in the area of the lesion on T1 postcontrast/T2 FLAIR, presence of a new lesion, or clinical deterioration

12 weeks [4–9]. Additional details concerning the frequency, appropriate tools, and exact definitions of visual decline in both tumor subtypes at baseline and follow-up have been provided in the corresponding RAPNO papers [5, 9], but fall beyond the scope of this review.

Assessment of extra-CNS metastasis

Although some of the RAPNO tumor subtypes can rarely metastasize to extra-CNS locations, so far none of the subcommittees has given specific recommendations for their routine assessment. Nevertheless, in case of a MB or other leptomeningeal seeding tumor with a known/suspected extra-CNS tumor deposit at trial entrance, imaging reassessment and total disappearance of that lesion is required after therapy for complete response and this variable has been included in the corresponding assessment, as this has been included as an independent variable in the corresponding guidelines [4].

Patient-reported outcomes, quality of life outcomes and neurocognitive neuropsychological assessment

So far, none of the RAPNO guidelines incorporates any of these measures in the formal guidelines for response tumor assessment as no consensus has been achieved regarding the readiness for their routine application within individual clinical trials, with the need of further research on the topic and prospective validation addressed by most subcommittees [4–9].

Cerebrospinal fluid testing

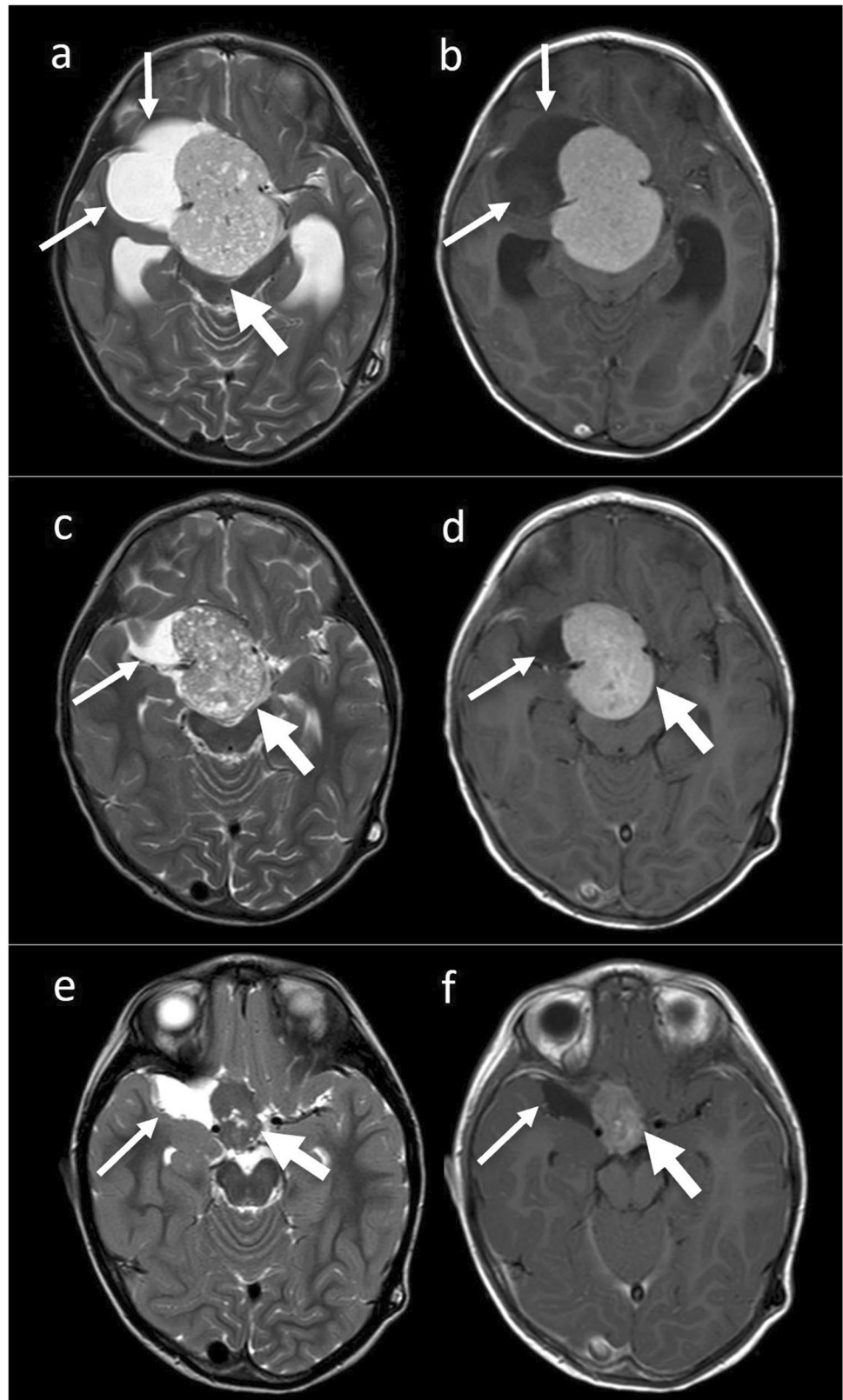
Current RAPNO guidelines concerning CSF cytology/flow cytometry are provided in Table 7. When this laboratorial testing is indicated (as it is the case of MB and other leptomeningeal seeding tumors and ependymomas), results should be analyzed qualitatively and in a binary fashion, that is, tumor cells present vs absent [6, 8]. Importantly, samples should not be collected intraoperatively but instead through lumbar puncture unless clinically indicated, as the former increases the risk of false positives [4–9].

Other laboratory variables

Serum and/or CSF alpha fetoprotein (AFP) and β–human chorionic gonadotropin (βhCG)

In the specific setting of germ cell tumors (a subtype of tumor to which the MB and other CSF seeding tumor RAPNO guidelines apply), serum and/or CSF AFP and βhCG are considered independent response assessment criteria when obtained. In such cases, analysis of results of these biomarkers should be made qualitatively (negative, ie within

Fig. 4 Major response after chemotherapy according to the corresponding RAPNO criteria in a 3-year-old girl with a hypothalamic-chiasmatic pilocytic astrocytoma. Baseline brain MRI including axial T2WI (a) and axial post-contrast T1WI (e) shows a large hypothalamic lesion (thick arrows) causing obstructive hydrocephalus. There is a non-tumor cystic component adjacent to the right anterolateral margin of the lesion that is not integrated into the solid component nor shows peripheral enhancement (thin arrows) and therefore should not be included in 2D tumor measurements. Follow-up brain MRI studies including axial T2WI (c,e) and axial post-contrast T1WI (d, f) performed at 6 (c, d) and 18 months (e, f) after treatment, demonstrate progressive size reduction of the target measurable component of this tumor (represented only by the solid component of the tumor, as explained above) (thick arrows), that reached approximately an 80% decrease compared to baseline, in keeping with radiological major response. Note that the non-tumor cystic component also decreased in size over time (thin arrows), with overall marked reduction in mass effect. The patient has also shown progressive improvement in functional and neurological assessments over time



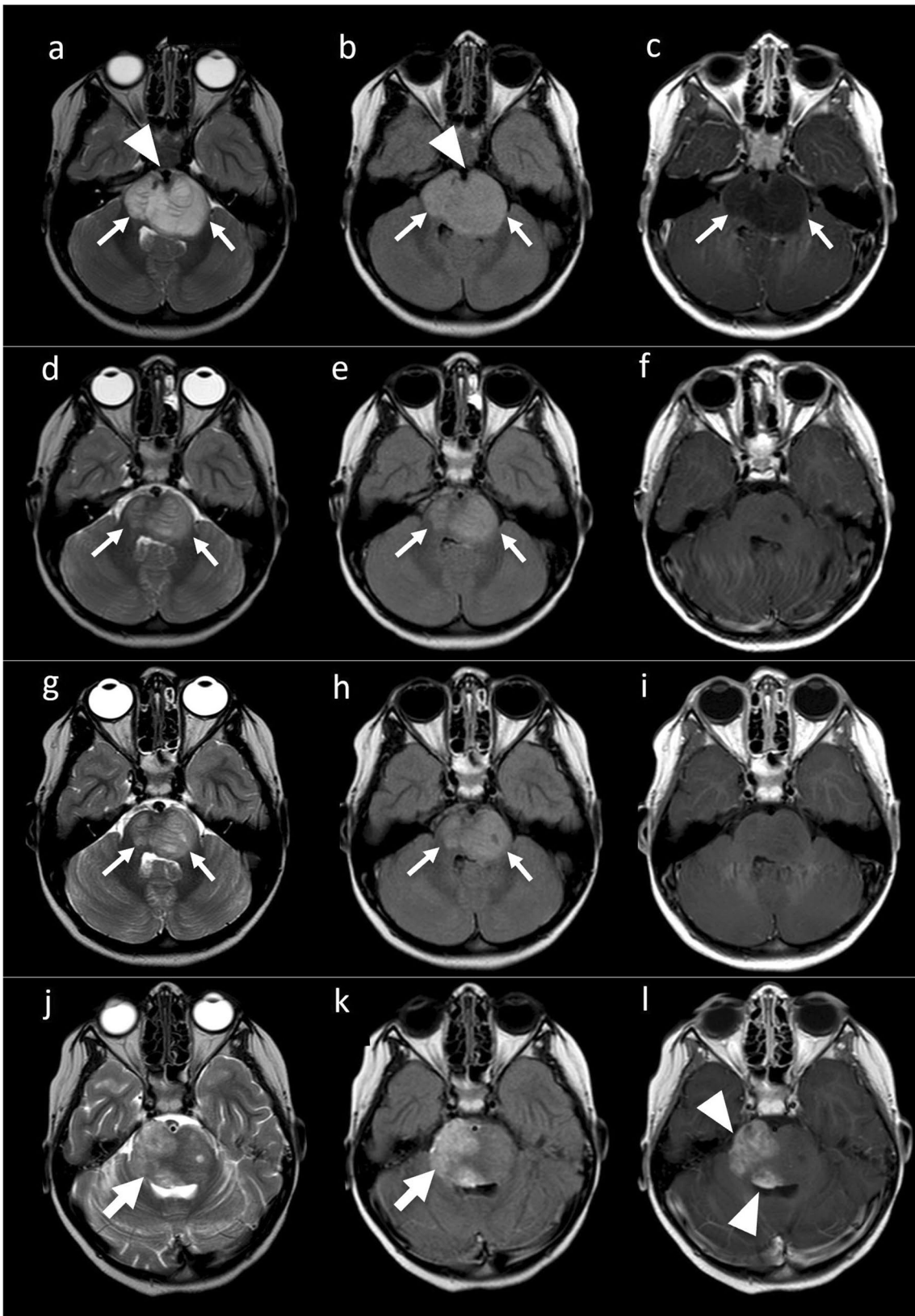


Fig. 5 Partial response followed by disease progression after chemotherapy according to the corresponding RAPNO criteria in a 7-year-old girl with a diffuse midline pontine glioma (DIPG). Baseline brain MRI (a-c) including axial T2WI (a), FLAIR (b) and contrast-enhanced T1WI images (c) shows a relatively homogeneous hyperintense infiltrative mass centered in the pons and expanding this structure (thin arrows), occupying > 80% of its transverse area, without associated contrast enhancement but encasing the basilar artery (arrowheads), compatible with a DIPG. There was no extra-pontine extension of the lesion. At 2 months post-radiotherapy (d-f), approximately 32% of tumoral size reduction was noticed, which persisted until the next follow-up brain MRI obtained 8 weeks after (g-i), in keeping with radiological partial response (thick arrows). Follow-up brain MRI performed at 15 months (j-l) depicts progressive growth of the pontine lesion (larger than 25% compared to the best response) as well as presence of new foci of nodular enhancement (arrowheads). The patient also clinically deteriorated, and these aspects are in keeping with disease progression

normal range for age versus positive) [4]. Of note, whenever a previously normal AFP/βhCG assessment becomes positive during longitudinal assessment of germ cell tumors, the RAPNO criteria consider that progressive disease can be assumed independently of all the other clinical, therapeutic and imaging variables [4].

Pituitary hormone testing

Pituitary hormonal evaluation is part of the CP RAPNO response assessment criteria of all enrolled patients except in those who have undergone radiotherapy as part of their treatment regimen in clinical trials not evaluating very long outcomes [9]. Indeed, radiotherapy frequently causes endocrinopathies as a side-effect, with most being diagnosed up to 6 years after treatment (more commonly

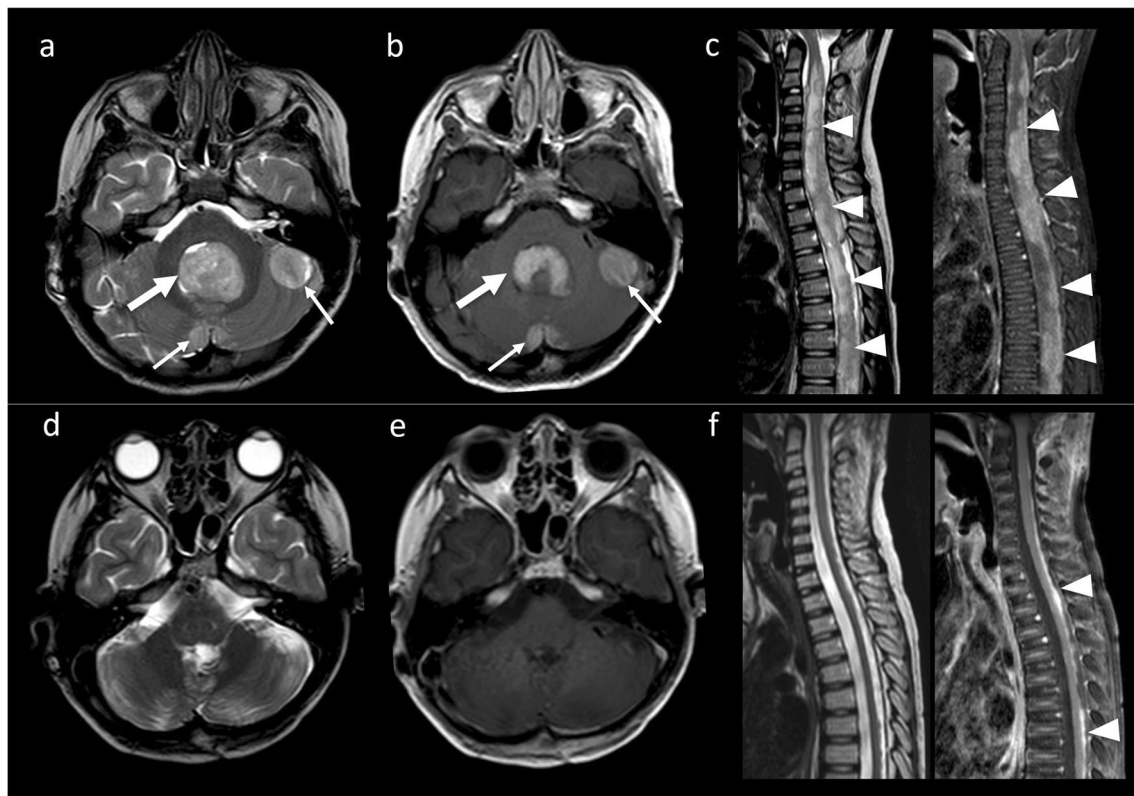


Fig. 6 Partial response after surgery and urgent chemoradiotherapy according to the corresponding RAPNO criteria in a 6-year-old male with a metastatic medulloblastoma. Presurgical brain MRI including axial T2WI (a) and post-contrast T1WI (b) shows an expansile lesion centered in the fourth ventricle compatible with a medulloblastoma (thick arrows) as well as signs of disseminated intracranial disease (thin arrows). Baseline sagittal T2WI (d) and post-contrast T1WI (e) of the cervicodorsal spine reveal extensive nodular leptomeningeal lesions with spinal cord invasion and compression (arrowheads). The patient underwent urgent chemoradiotherapy and posterior fossa

surgery for resection of the primary tumoral lesion. Immediate post-surgical imaging was not obtained due to the patient's hemodynamic instability and extensive craniospinal leptomeningeal dissemination. Follow-up brain and spine MRI performed 2 months after treatment (not shown) demonstrated disappearance of all the posterior fossa lesions, with marked reduction in size of the spinal leptomeningeal lesions, and minimal posterior peri-medullary enhancement and this favorable evolution persisted at follow-up brain (e,f) and spine MRI (g,h) performed at 5 months post treatment (arrowheads), in keeping with partial response

within the first 2 years), therefore being a confounding bias in patients treated regimens including this modality [9]. When pituitary function testing is indicated in the setting of a CP trial, it should include TSH, T4, ACTH, 8am cortisol, IGF1, IGFBP3 and sodium level and be complemented by DHEAS, LH, FSH, estrogen or testosterone in pubertal patients [9]. In addition, testing should be performed before and after surgery and every 3–6 months thereafter [9]. Due to some variability in normal range values according to different laboratories, a binary classification should be used, and the results considered either normal or abnormal when compared to the institutional reference parameters or specific clinical trials values. In case of development of diabetes insipidus in the peri-operative period, confirmation at 4–6 weeks after surgery is required using either laboratory testing and/or sustained requirement of desmopressin treatment, as most cases are transitory and surgery-related [9].

It is also important to note that, according to CP RAPNO criteria, whenever a new neuroendocrine deficit requiring medical treatment is detected (including diabetes insipidus, thyroid, growth or adrenal insufficiency as well as hypogonadism), progressive disease should be assumed regardless of other considered variables.

How to classify post-surgical residual disease

So far only the EP RAPNO guidelines provide specific definitions for post-surgical evaluation of residual intracranial disease [8]. Indeed, such guidelines consider three different categories: *gross total resection* (no radiological evidence of disease), *near total resection* (residual tumor with a maximal diameter in any plane ≤ 5 mm) and *subtotal resection* (residual tumor with a maximal diameter in any plane > 5 mm or biopsy-only submitted cases) (Fig. 3)[8].

How to define radiological tumor response according to the available criteria

Which MRI time point should be used for comparison when applying the RAPNO criteria?

As a general rule, comparisons should be made during longitudinal assessment with either the corresponding baseline MRI (see Table 5) or the best recorded response, whichever applies [4–9].

How many response assessment categories do exist?

All RAPNO guidelines published so far include at least the following 4 categories: complete response, partial response, stable disease, and progressive disease [4–9]. Moreover, the HGG RAPNO criteria includes minor response [6] and the LGG RAPNO includes both minor and major responses as additional categories [5].

Regardless of the tumor subtype, all of the imaging and non-imaging criteria must be met to determine stable disease, partial response and/or complete response (as well as minor response and major response when applicable). Oppositely, progressive disease can be assumed even when only one criteria for this category is met [4–9].

A systematization of the categorization of each of the imaging variables considered in the Response Assessment Criteria published so far (that is, measurable target disease, non-measurable/non-target measurable disease, presence of new lesion(s) and qualitative DWI changes) is presented in Tables 8, 9, 10 and 11 [4–9]. Importantly, this neuroimaging categorization should always be always correlated with the remainder non-radiological variables, that in turn vary according to the tumor subtype (reviewed in Table 5) to reach the final classification [4–9]. A few examples of partial response/major response, stable disease and disease progression according to RAPNO criteria for different tumor subtypes are presented for illustration on Figs. 4, 5, 6, 7, 8, 9 and 10.

How to categorize tumoral cyst changes over time in LGG and CP?

The LGG and CP RAPNO criteria for tumor assessment include specific instructions on how to approach and categorize size changes in cysts during longitudinal follow-up [5, 9]. Organigrams summarizing those instructions are provided in Figs. 10 and 11, respectively, and practical examples presented in Figs. 12 and 13.

How long must tumor response assessment be observed?

All RAPNO guidelines require that, for classification as any form of response (but not as stable disease or disease progression), changes must be sustained for at least two pre-defined study time-points, that vary according to the tumor subtype, namely a minimum of 4 weeks for MB [4], a minimum of 8 weeks for HGG, DIPG and EP [6–9] and a minimum of 12 weeks for LGG and CP [5, 9].

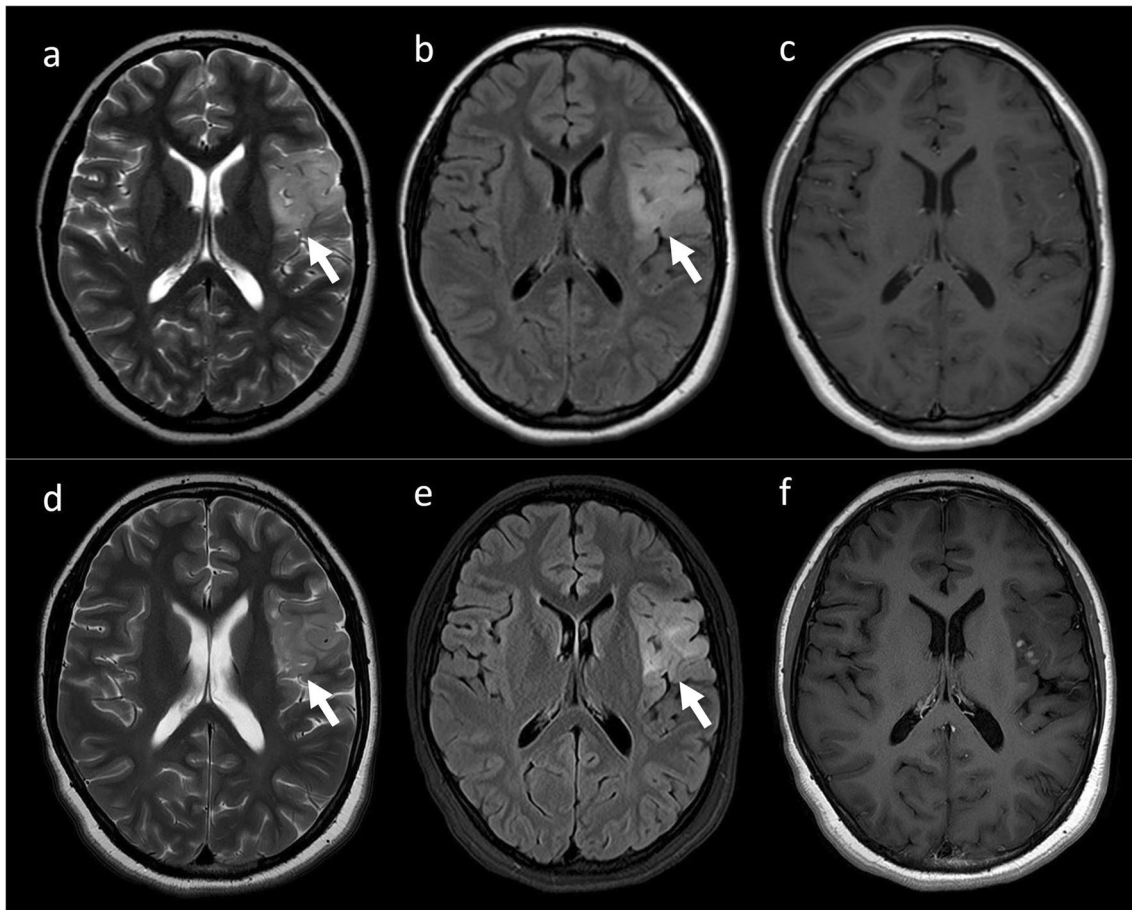


Fig. 7 Stable disease after chemoradiation according to the corresponding RAPNO criteria in a 7-year-old girl with a supratentorial H3 and IDH wild-type high-grade glioma criteria. Baseline brain MRI including axial T2WI (a), FLAIR (b), and post-contrast T1-WI (c) depict a cortical-subcortical T2/FLAIR hyperintensity in the left inferior frontal and insular lobule, with loss of gray-white matter differentiation, minimal mass effect, and absence of contrast

enhancement (thick arrows). Follow-up brain MRI studies were performed every 3 months, without significant changes (not shown). The latest brain MRI performed at 9 months reveals a small reduction in the dimensions of the measurable target lesion (but inferior to 25% decrease compared to the initial baseline study), in keeping with stable disease

How to proceed in case of unclear classification?

In some rare instances, the response may be temporarily considered indeterminate, namely if a relevant variable has not been properly evaluated and no criteria for disease progression have been fulfilled [4] or in the setting of measurements meeting criteria for progressive disease but believed to reflect instead treatment effects [6, 7]. In this context, it is recommended to keep the patient in the study until progression is eventually considered definitive in longitudinal assessment (with a follow-up MRI scheduled earlier than usual, namely within 4–8 weeks), and in such cases backdate the date of progression to the onset of clinical/radiological deterioration [4, 6, 7].

Advantages of RAPNO criteria

The RAPNO criteria represent an objective, consistent and standardized tool for assessment of treatment response in children with brain tumors that can be applied internationally and prospectively. Therefore, they aim to increase uniformity, establish minimal imaging quality and achieve a more reliable risk stratification across clinical trials and a more accurate evaluation of imaging endpoints, thereby facilitating comparison of results across different studies, minimizing confounding factors and allowing more valid evaluation of therapeutic efficacy and safety [4–9].

Importantly, they recommend imaging evaluation of primary study endpoints with routine MRI sequences that

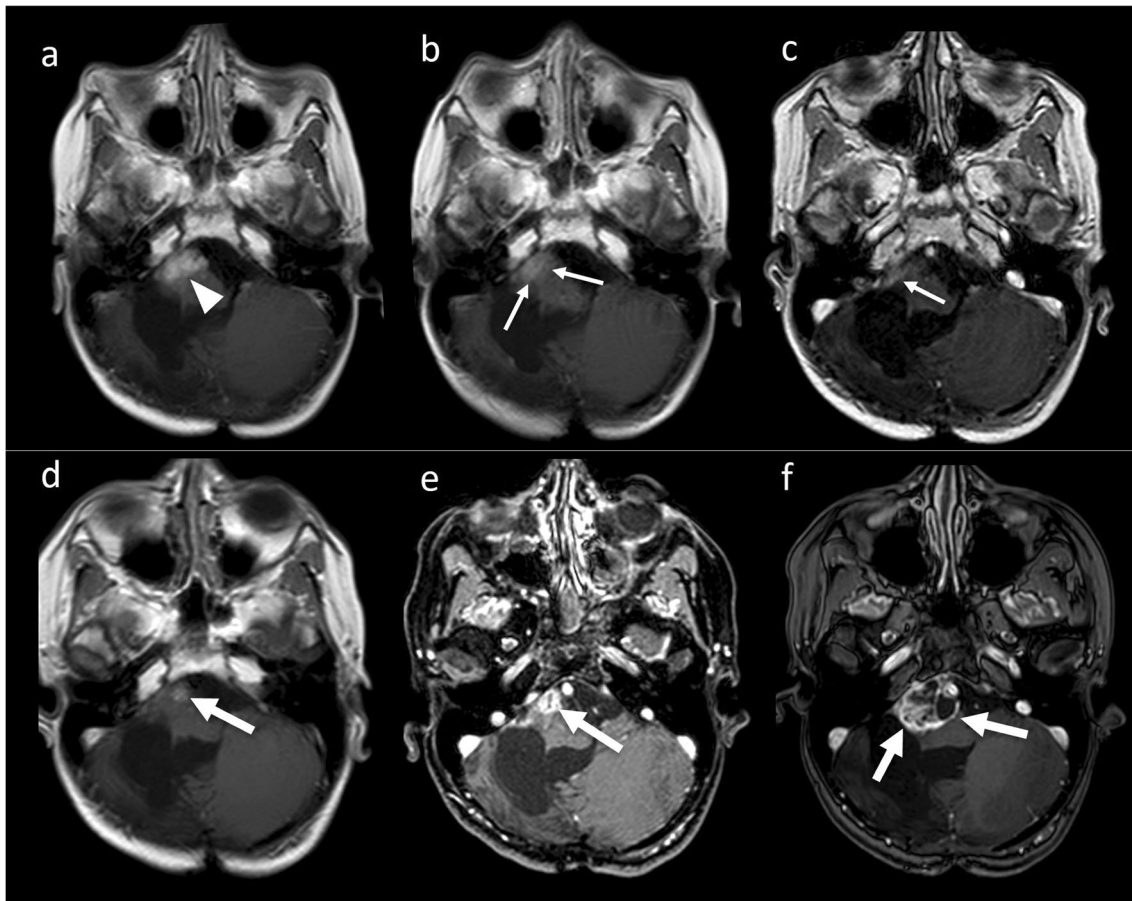


Fig. 8 Partial response followed by late disease progression after surgery, local radiotherapy and chemotherapy according to the corresponding RAPNO criteria in a 4-year-old girl a posterior fossa ependymoma, non-metastatic at diagnosis. Early post-surgical brain MRI including axial contrast-enhanced T1WI (a) demonstrates signs of subtotal resection (arrowhead). Follow-up brain MRI studies including axial contrast-enhanced T1WI performed at 12 months (b) and 24 months (c) shows progressive reduction of the measurable target

disease larger than 25% compared to baseline, in keeping with partial response (thin arrows). Subsequent longitudinal neuroimaging assessment including axial contrast-enhanced T1WI performed 6 years (d), 7 years (e) and 8 years (f) after treatment reveal progressive growth of the measurable target disease in the margins of the surgical loca (thick arrows), reaching more than 25% increase when compared with the best response and accompanied by clinical deterioration, in keeping with late radiological disease progression

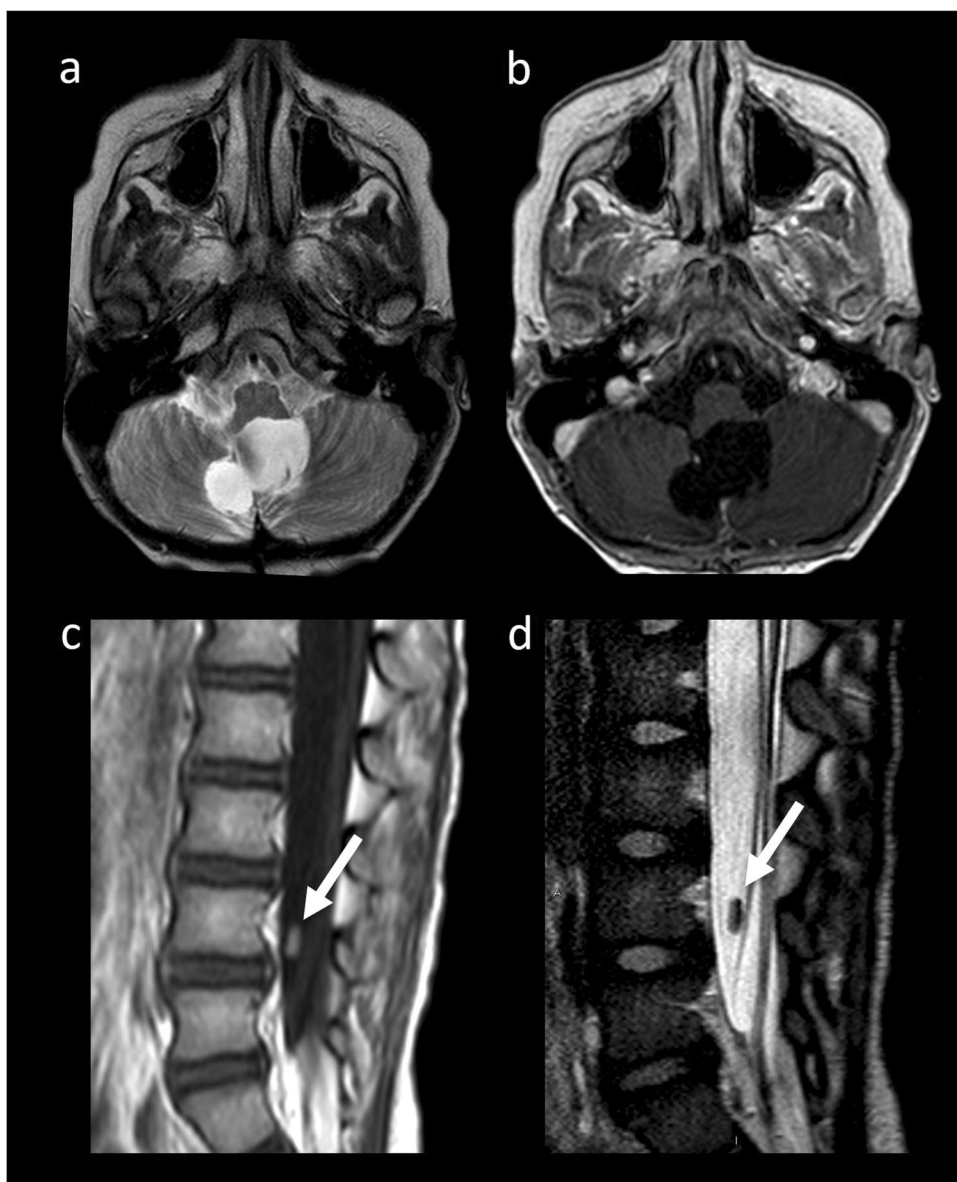
are widely available at most institutions (ranging from small community units to large university tertiary hospitals), thereby facilitating inclusion of as many centers as possible in pediatric oncology clinical trials (including those with less capacity) and maximizing compliance with RAPNO guideline standards [4–9].

In addition, they embody not only neuroimaging aspects but also other relevant brain tumor-related features in children, including clinical evaluation and in some instances also biological tumoral characteristics, therapeutic approaches, laboratory parameters and functional outcomes [4–9].

Limitations of RAPNO criteria and future directions

Although RAPNO criteria were based whenever possible in available literature, many areas lacked scientific support and in the latter case recommendations were based on expert experience of committee members, after discussion and consensus [4–9]. Therefore, efforts need to be made to foment pediatric neuro-oncology research, especially the number and quality of randomized clinical trials, aiming to reduce those knowledge gaps and increase the level of evidence of future RAPNO criteria.

Fig. 9 Disease progression after surgery and local radiotherapy according to the corresponding RAPNO criteria in a 4-year-old girl with a non-metastatic posterior fossa ependymoma at diagnosis. Brain MRI (a) performed at 6 months after surgical resection including axial T2WI (a) and T1WI post-GAD (b) shows no evidence of disease at the primary tumor site. However, spine MRI performed at the same imaging session including a sagittal T1WI post-GAD (c) and a sagittal 3D CISS (d) reveals presence of new small leptomeningeal tumoral deposit with contrast enhancement adjacent to the cauda equina roots (arrowheads), corresponding to radiological disease progression



It is also important to note that none of the RAPNO criteria have been prospectively validated in international clinical trials. However, this task is of paramount importance, as it will allow evaluation of their performance and rational for future applicability or the need for modifications if appropriate, as already seen with the 2.0 RANO criteria [15]. Despite the absence of prospective validations of the RAPNO guidelines, a multicenter study published in 2020 has retrospectively evaluated the RAPNO criteria in medulloblastoma and other seeding tumors with encouraging results [16]. According to this study (including $n = 266$ children), overall interobserver agreement of RAPNO criteria application was 83.8% and both radiological response and progression free survival as determined by them were significant predictors of overall survival [16]. However, this work was developed before

specific RAPNO guidelines for high-grade gliomas were published and included 29% of such tumors, potentially biasing results [16].

Currently, most RAPNO guidelines do not systematically require acquisition of pre and post contrast 3D isotropic T1WI images, and consider them instead “alternative” or “optional” sequences [4–9]. The advantages of two-dimensional (2D) images over 3D images include more robust data, less sensitivity to artifacts, less variation in the quality (especially at 1.5 T scanners), overall higher clinical experience and frequently lower acquisition time. However, isotropic 3D sequences allow improved resolution (leading to detection of smaller lesions and better differentiation between vessels and tumoral enhancement), multiplanar reconstruction and better alignment with the planes of measurement, as well as volumetric analysis,

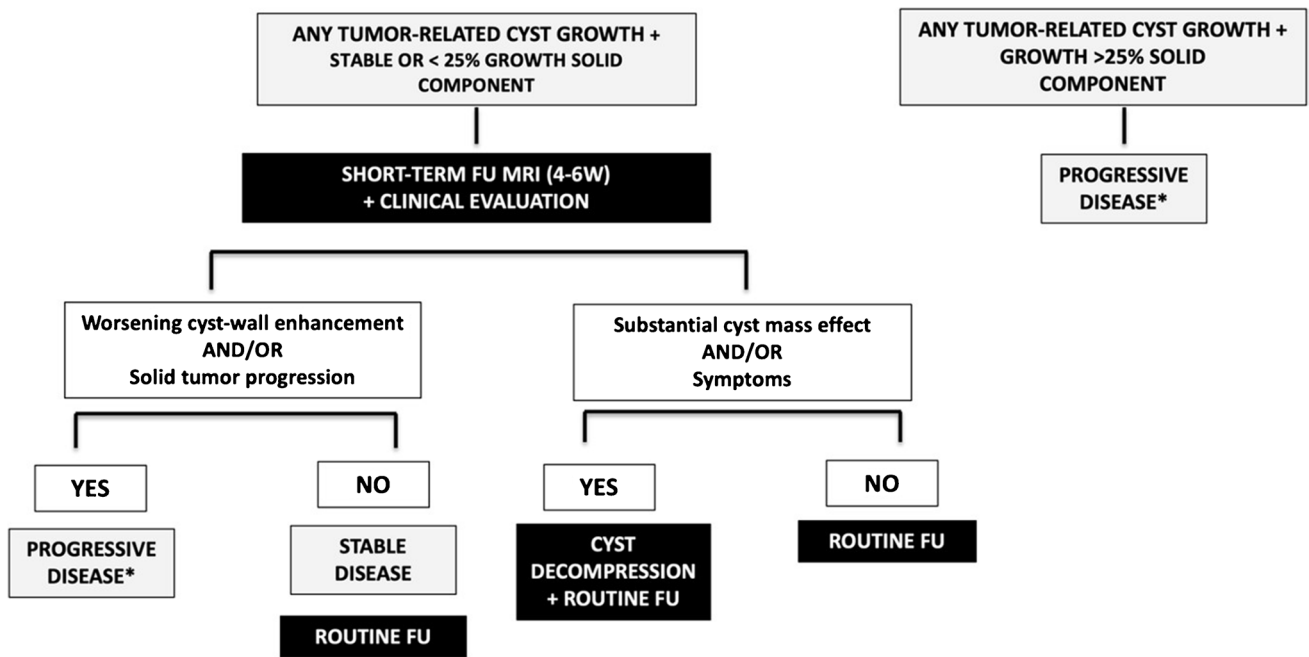


Fig. 10 Flow-chart of evaluation and management of cyst growth in low-grade gliomas according to the corresponding RAPNO guidelines. Legend: FU- Follow-up; w- Weeks

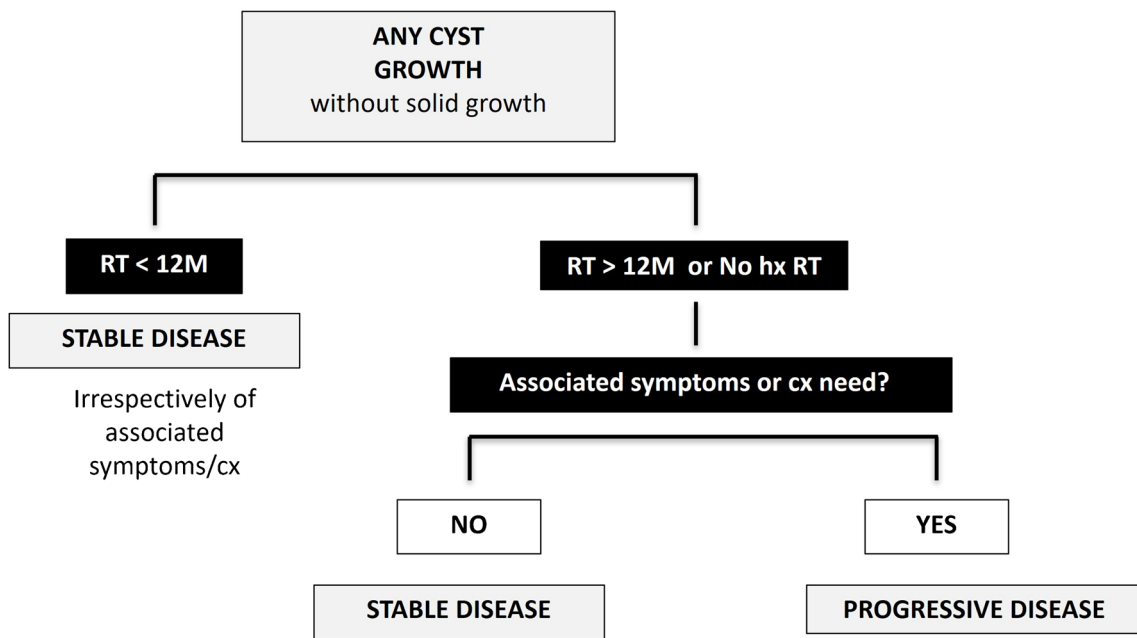


Fig. 11 Flow-chart of evaluation and management of cyst growth in craniopharyngiomas according to the corresponding RAPNO guidelines. Legend: Cx- Surgery; hx- history; RT- Radiotherapy

co-registration and surgical navigation. Therefore, evolution towards incorporation of 3D T1WI acquisition in pediatric neuro-oncology imaging in standard imaging protocols of future RAPNO guidelines (as already suggested in a recent white paper from the Children’s Oncology

Group, the American Society of Pediatric Radiology and the American Society of Pediatric Neuroradiology)[17] and progression from 2 to 3D tumor measurements or more likely automated quantitative tumor size calculation using validated software, as these approaches are likely more

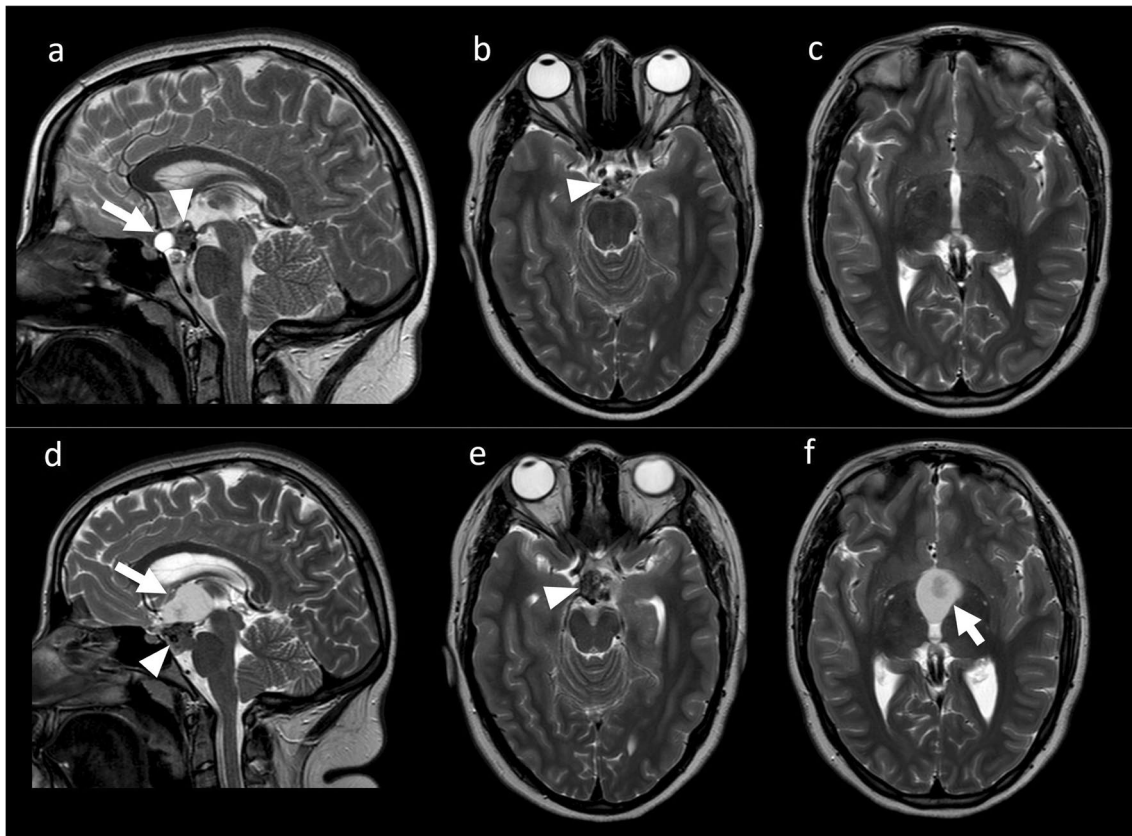


Fig. 12 Disease progression after radiotherapy according to the corresponding RAPNO criteria in a 14-year-old girl with an adamantinomatous craniopharyngioma. Baseline brain MRI obtained 12 months after radiotherapy including sagittal (**a**) and axial (**b**, **c**) T2WI shows a partially solid (arrowheads) and cystic (thick arrow) suprasellar mass corresponding to a craniopharyngioma. Follow-up brain MRI performed 2 years after radiotherapy including a sagittal (**d**) and axial

(**e**, **f**) T2WI reveals marked growth of the cystic component (thick arrows), with increased mass effect over the third ventricle, the optic tract and the hypothalamus and corresponding deterioration of visual assessment. Note that the solid component also has also increased in size in more than 25% when compared with the baseline post-radiotherapy MRI (arrowheads). These findings are in keeping with progressive disease

accurate in assessing overall tumor dimensions. Indeed, with infiltrative, extensive and diffuse disease, accurate manual measurement of lesions becomes a more complicated task.

On the other hand, although the minimum mandatory MRI sequence acquisition recommended by all RAPNO criteria requires relatively simple imaging techniques that are available in most settings, the potential of these techniques in neuro-oncology is recognized by most subcommittees, in some cases with suggestion of their inclusion in the protocols as secondary endpoints of clinical trials or in separate clinical trials [4–9]. Within this line, and due to the increased research and accumulated knowledge in the topic as well as the expected improvement of technical capability at most centers over time [18], it is probable that in a near future, all RAPNO subcommittees will develop an alternative or complementary response assessment criteria that formally include advanced

imaging techniques, which should be applied whenever these sequences are available.

It is also likely that intraoperative MRI will become accepted as the baseline study of most tumor subtypes in future RAPNO guidelines and recommended protocols for such studies developed [19] and that novel targeted therapies are integrated in the response assessment criteria.

Moreover, although a few biologic/molecular features have already been included in the EP RAPNO criteria (namely the chromosome 1q gain status) [8], it is anticipated that separate response criteria that apply to different tumor histological and molecular subgroups will soon be developed, as they are characterized by distinct epidemiological features and biological behavior as well as variable prognosis [20]. This is particularly expected for RAPNO guidelines that were published before the new 2021 World Health Organization classification of CNS tumors was released [20].

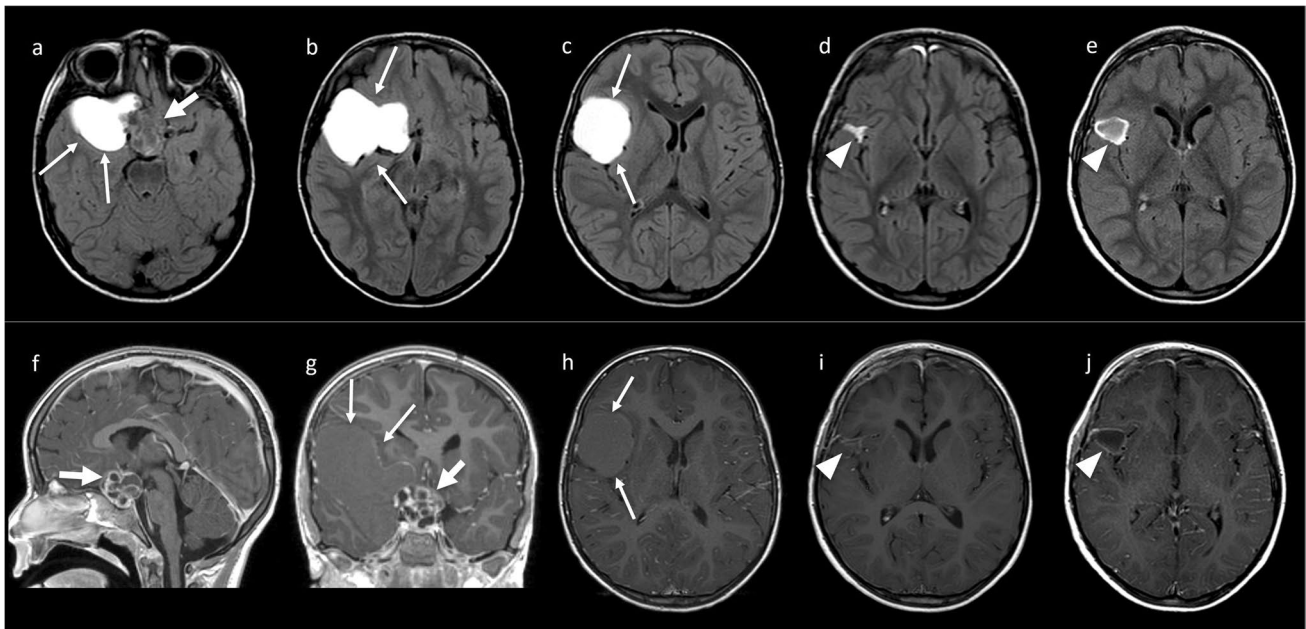


Fig. 13 Stable disease after surgery according to the corresponding RAPNO criteria in a 4-year-old girl with an adamantinomatous craniopharyngioma. Presurgical brain MRI including axial FLAIR (a–c) and sagittal (f), coronal (g) and axial (h) contrast-enhanced T1WI shows a partially solid (arrowheads) and cystic (arrows) sellar and suprasellar mass corresponding to a craniopharyngioma, with a large cystic component extending along the right sylvian fissure (thick arrows). Early post-surgical baseline brain MRI including axial FLAIR (d) and contrast-enhanced T1WI (i) shows a small residual

cystic component in the right sylvian fissure (arrows). Adjuvant radiotherapy was not performed. Follow-up brain MRI performed 12 months after including axial FLAIR (e) and contrast-enhanced T1WI (j) depicts small growth of the residual cystic component (arrows), without the need of surgical decompression nor associated clinical signs or symptoms. There was no growth of the solid component in the sellar/suprasellar region. These findings are in keeping with radiological stable disease

Finally, it is expected that new RAPNO criteria for specific pediatric CNS tumors that currently lack such criteria (including the different subtypes of tumors currently included in the category of MB and other leptomeningeal seeding tumors) will be published over time, incorporating a more modern approach of neuro-oncology as well as and lessons learned so far with application other RAPNO subtypes guidelines.

Authors' contributions AF Geraldo: study concept and design; AF Geraldo: drafting the manuscript; AF Geraldo, F Maldonado, M Severino, C Rugilo, A Rossi: analysis and interpretation of imaging data; AF Geraldo, F Maldonado, M Severino, Dahmouh H, K Mankad, B Soares, C Rugilo, A Rossi: revising the manuscript.

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Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

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