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Journal

Pediatric Blood & Cancer, 60(9)

ISSN

1545-5009

Authors

Warren, Katherine E
Poussaint, Tina Y
Vezina, Gilbert
et al.

Publication Date

2013-09-01

DOI

10.1002/pbc.24562

Peer reviewed

Published in final edited form as:

Pediatr Blood Cancer. 2013 September ; 60(9): 1397–1401. doi:10.1002/pbc.24562.

Challenges With Defining Response to Antitumor Agents in Pediatric Neuro-Oncology: A Report From the Response Assessment in Pediatric Neuro-Oncology (RAPNO) Working Group

Katherine E. Warren, MD[1,*], **Tina Y. Poussaint, MD**[2], **Gilbert Vezina, MD**[3], **Darren Hargrave, MD**[4], **Roger J. Packer, MD**[3], **Stewart Goldman, MD**[5], **Patrick Y. Wen, MD**[6], **Ian F. Pollack, MD**[7], **David Zurakowski, PhD**[2], **Larry E. Kun, MD**[8], **Michael D. Prados, MD**[9], **Stefan Rutkowski, MD**[10], and **Mark W. Kieran, MD, PhD**[11]

[1]National Cancer Institute, Bethesda, Maryland [2]Children's Hospital, Boston, Massachusetts [3]Children's National Medical Center, Washington, District of Columbia [4]Great Ormond Street Hospital for Children, London, UK [5]Lurie Children's Hospital of Chicago, Chicago, Illinois [6]Dana-Farber Cancer Institute, Boston, Massachusetts [7]Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania [8]St. Jude Children's Research Hospital, Memphis, Tennessee [9]University of California, San Francisco, California [10]University Medical Center, Hamburg-Eppendorf, Germany [11]Dana-Farber/Children's Hospital Cancer Center, Boston, Massachusetts

Abstract

Criteria for new drug approval include demonstration of efficacy. In neuro-oncology, this is determined radiographically utilizing tumor measurements on MRI scans. Limitations of this method have been identified where drug activity is not reflected in decreased tumor size. The RANO (Response Assessment in Neuro-Oncology) working group was established to address limitations in defining endpoints for clinical trials in adult neuro-oncology and to develop standardized response criteria. RAPNO was subsequently established to address unique issues in pediatric neuro-oncology. The aim of this paper is to delineate response criteria issues in pediatric clinical trials as a basis for subsequent recommendations.

Keywords

brain; imaging; pediatric; RANO; response; tumor

[*]Correspondence to: Katherine E. Warren, Pediatric Oncology Branch, National Cancer Institute, Building 10/Room 1-5750, 9000 Rockville Pike, Bethesda, MD 20892. warrenk@mail.nih.gov.

Author Contributions—Conception and design: All authors. Collection and assembly of data: Katherine E. Warren, Tina Y. Poussaint, Gilbert Vezina, Darren Hargrave, Roger J. Packer, Stewart Goldman. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors.

Presented in part at the International Society of Pediatric Neuro-Oncology (ISPNO) Toronto, June 2012.

INTRODUCTION

Criteria for FDA and EMEA approval of new agents include demonstration of safety and effectiveness. While efficacy determinations for cytotoxic agents include objective tumor shrinkage, the definition of efficacy for cytostatic agents is more challenging because tumor stabilization, rather than regression, may be the appropriate response endpoint. In neuro-oncology, determining effectiveness of an agent is particularly complicated. Patients with brain tumors are followed by MRI to determine treatment response, yet a number of issues unique to this population interfere with interpretation.

The historically used Macdonald criteria take into account clinical status, steroid use, and change in two-dimensional contrast-enhancing tumor measurements on CT or MRI to define objective response or progression in supratentorial high-grade gliomas [1]. In practice, these criteria are frequently applied to non-glioma tumor types and non-enhancing tumors. Because MRI cannot reliably distinguish tumor from treatment effects, interpreting enhancement on MRI scans is difficult, and application of the Macdonald criteria to assess nonenhancing tumors or enhancement after local treatments has not been fully evaluated. Pseudoprog-ression, radiation necrosis, and pseudoresponse hinder response interpretation [2]. Primary endpoints such as progression free survival (PFS) or overall survival (OS) may substitute for decreased tumor size, but the time necessary to determine these and the confounding impact of subsequent therapies preclude use of these endpoints in most clinical trials. Inter-observer variability in tumor measurements is also a well-recognized phenomenon, particularly given the invasive nature and resulting ill-defined borders of high-grade gliomas.

The RANO (Response Assessment in Neuro-Oncology) working group was established to address the limitations in defining endpoints for clinical trials in adult neuro-oncology and to develop standardized response criteria for clinical trials. Since its establishment in 2008, a number of manuscripts redefining response assessment in adults with gliomas have been published [3–6]. For example, RANO has proposed that response assessment criteria in adults with high-grade glioma include two-dimensional measurements of the enhancing lesion as well as evaluation of tumor size based on T2 or FLAIR sequences [3]. RANO response criteria for low-grade glioma assess two-dimensional measurements on T2 or FLAIR sequences and include a Minor Response (MR) category in which there is a 25–50% decrease in T2 or FLAIR signal abnormality compared with baseline [5]. Response criteria for brain metastases, meningiomas, and schwannomas are being developed and validated [4].

A number of issues identified by RANO are applicable to the pediatric neuro-oncology population. However, while RANO guidelines may prove valuable for assessing response and progression in adult patients, the pediatric neuro-oncology population poses unique challenges, prompting the institution of the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. This is an international group of cooperative group leaders and senior, experienced individuals from several disciplines including radiology, neurosurgery, radiation oncology, neuro-oncology, neurology and statistics, involved in development and oversight of pediatric CNS clinical trials. In addition to response

assessment issues identified in the neuro-oncology population as a whole, RAPNO has identified additional issues specific to pediatric neuro-oncology.

Pediatric CNS Tumors Are a Heterogeneous Group of Diseases

Gliomas account for 80% of malignant tumors in adults and the majority are high-grade, enhancing, supratentorial lesions [7–8]. In contrast, pediatric brain tumors represent a much more heterogeneous group of diseases. According to the Central Brain Tumor Registry of the United States (CBTRUS), pilocytic astrocytomas represent 17.7% of CNS tumors in children ages 0–14 years, while embryonal tumors including medulloblastomas represent 15.1%, ependymomas 5.7%, neuronal-glial tumors 7.8%, glioblastomas 2.6%, and the remainder continuing to represent small subgroups (Fig. 1) [7]. Overall, the largest proportion of pediatric brain tumors are low-grade gliomas and many do not enhance radiographically. Nearly half of all pediatric brain tumors are located infratentorially, and a higher percentage of tumors are located in the brainstem with 10.4% of childhood brain tumors located in the brainstem compared to 1.6% of all age-groups [9].

Some pediatric tumor types, such as diffuse intrinsic pontine gliomas (DIPG) and optic pathway gliomas, are infrequently biopsied and management relies heavily on imaging characteristics. Because of these differences in histology, location, and imaging characteristics, it is unlikely that a single standard set of response criteria will be applicable to the many different types of tumors.

There Are Relatively Small Numbers of Patients Available for Clinical Trials

An estimated 4,030 new cases of primary malignant and nonmalignant CNS tumors were diagnosed in children in the United States in 2010, compared to over 60,000 cases in adults [7]. Clinical trial designs must take into consideration tumor heterogeneity and the relatively small numbers of patients, which limit the number of available study participants. One approach for Phase II study design is a randomized trial comparing objective outcome between the cohort receiving study agent with that receiving placebo. In practice, this is difficult to carry out given the limited number of patients and therefore low statistical power, and hesitancy to enroll on a trial in which patients may be assigned to the placebo arm, and, so presumably, have no potential clinical benefit. An alternative design involves comparison of the treatment arm to a historical cohort. Defining appropriate historical cohorts is complicated by different study eligibility criteria, disease definition, lack of consensus on histological diagnosis [10,11], response definition and assessment, and, in some cases, an absence of a proven standard of care treatment.

There Are No Standard Definitions of Response or Progression

There is currently no agreed upon standard to define response or progression in clinical trials for pediatric brain tumors. We reviewed the response definitions employed in recent and current clinical trials (Phase I and II) for children with brain tumors within the Children’s Oncology Group (COG), the Pediatric Brain Tumor Consortium (PBTC), the European Society for Pediatric Oncology (SIOPE), and the Innovative Therapies for Children with Cancer Consortium (ITCC) as shown in Table I. Definitions differ according to study group, within study groups, and by tumor type. While some consider only radiologic definitions of

response, others incorporate criteria similar to that of Macdonald [1], that is, steroid use and clinical status. In the majority of its recent studies, the PBTC defines complete response by all of the following: the disappearance of all enhancing tumor and mass effect on MRI, a stable or decreasing dose of corticosteroids, a stable or improving neurologic examination, and sustained for a variable time frame. In comparison, the COG and the European groups frequently define CR as complete disappearance of all tumor based upon MR imaging. Quality of life was not included in the definition of response for any study.

Most studies use two-dimensional tumor measurements in their criteria for response, while some utilize three-dimensional tumor measurements; the majority do not specify measurement of the enhancing lesion, nor instruct on which MR sequences to use, although the COG has incorporated general measurement instructions in the past decade. Many studies require a sustained response, and the length of time necessary to meet this definition varies from 21 days to 8 weeks. To be classified as stable disease, several studies allow an increase in tumor size beyond the 25% definition of progression providing the patient is clinically stable, citing the possibility of delayed response with anti-angiogenic agents.

Enhancement Is Variable, Nonspecific, and Not Representative of Tumor Burden

Response assessment based on extent of tumor enhancement is problematic. Many pediatric CNS tumors do not enhance or enhance inhomogeneously (Fig. 2). Typical radiographic findings in pilocytic astrocytoma include an enhancing cyst wall and a solid enhancing mural nodule. Some readers include cysts in tumor measurements, while others do not, yet it is unclear whether changes in cyst size indicate treatment activity.

As in the adult neuro-oncology population, pseudoprogression and pseudoresponse can complicate interpretation of MRI scans, making it difficult to distinguish treatment effect from tumor progression. These phenomena, which are due to an increase or decrease in enhancement, respectively, from nontumoral processes, illustrate that enhancement primarily reflects a disrupted blood: brain barrier and is not specific for tumor (Fig. 3). Enhancement can vary for the same tumor, even without intervening treatment. Gaudino et al. [12] evaluated thirty-nine non-neurofibromatosis type 1 children with histologically confirmed pilocytic astrocytoma. Patients were followed an average of 4.5 years, during which time they did not receive any tumor-directed therapy. Twelve (31%) patients had a change in contrast enhancement (either increase or decrease) without a change in overall tumor size. The authors concluded that FLAIR or T2-weighted images were more reliable than T1-weighted post-contrast sequences in assessing tumor size in this population.

Decreased Tumor Size Does Not Always Correlate With Improved Survival

Defining activity of an agent by decreases in tumor size does not take into account long-term stable disease as a measure of response. Several pediatric studies have documented no correlation between objective response and PFS [13–15]. In a study using vincristine and carboplatin in children with newly diagnosed, progressive low-grade gliomas, 44 of 78 patients (56%) showed an objective response, and 3-year PFS was 68 7% [14]. There was no relationship to PFS between those patients with an objective response versus those with stable disease (71±10% vs. 78 ± 16%, P=0.8). Similarly, in a study of 34 children with low-

grade gliomas who received cisplatin and etoposide, 3-year PFS was 78% in the 24 patients experiencing an objective response and 83% in those with stable disease [15]. In contrast, a study of 85 children with progressive optic pathway tumors treated with chemotherapy alternating procarbazine plus carboplatin, etoposide plus cisplatin, and vincristine plus cyclophosphamide, demonstrated a significant relationship between 3-year PFS in those with an objective response confirmed by central review versus those with stable disease (68% vs. 53%, $P = 0.0029$) [16].

Correlation of decreased tumor size and outcome is also unclear for DIPG. In one study, no standard MRI parameter in either the baseline or post-treatment scans was associated with prognosis [17], yet, in a report from the PBTC, the cohort of children with DIPG who had a 25% decrease in tumor volume (as measured by FLAIR sequences on MRI) and diffusion had a higher 6-month survival rate compared to those who did not (70% vs. 20%) [18]. Although Macdonald criteria are based upon measurement of enhancing lesions, enhancement is not specific for tumor burden, which is readily apparent in DIPG (Fig. 4). In the PBTC study above [18] and others [19], any increase in enhancement was associated with poor outcome.

Inter-Observer Variability

Variability in tumor measurements and discrepancies in response categorizations amongst readers have been demonstrated in several studies, particularly for invasive high-grade gliomas [20–23]. As in adults, inter-observer variability is noted in measurement of pediatric brain tumors, including DIPG [24]. Measurement of these tumors is difficult given their invasive nature, ill-defined borders, and sometimes-hazy patterns of enhancement.

Because of known variability in tumor measurements, central review is frequently undertaken, particularly for consortia trials. Disagreements between site radiologists and central reviewers in defining a patient's disease burden are common. For example, the eligibility criteria for COG A9961, a study for children newly diagnosed with localized medulloblastoma, required ≤ 1.5 cm^2 of residual tumor postoperatively and no evidence of metastatic disease on **MRI** of the brain and spine. Two neuroradiologists centrally reviewed the pre-operative, post-operative, and relapse **MRI** scans of 421 enrolled patients. They found that 28 patients (7%) were ineligible by imaging criteria, with either >1.5 cm^2 of residual tumor or presence of metastatic disease, and 62 patients (15%) were not evaluable because metastatic disease could not be confidently excluded [25]. The most common cause of discrepancies included dissemination to the 3rd ventricle, non-enhancing dissemination, unrecognized residual non-enhancing tumor or the presence of small enhancing nodules in the posterior fossa. Proper imaging assessment was crucial in this study because of a significant difference in outcome in the ineligible patients [25]. Similarly, disagreement in response assessment between site radiologists and central review was common in COG A9952, a study comparing two chemotherapy regimens in children with low-grade gliomas. The reasons for these discrepancies included extensive, infiltrative tumors, mixed responses within the same tumor, change in cyst size without changes in solid tumor volume, and response assessments based on extent of tumor enhancement.

CONCLUSION

Although the RANO working group has developed criteria to assess response to therapy in adults with brain tumors, unique issues in pediatric brain tumors require adjustments for use in assessing children. The goal of RAPNO is to propose optimal endpoints and study designs, develop a consensus on the radiological assessment for clinical trials involving children with brain tumors, and better define response so that it reflects drug activity. RAPNO has initially targeted development of response criteria for three tumor subtypes, namely high-grade glioma, low-grade glioma, and diffuse intrinsic pontine glioma, due to the inherent radiographic features of each. Radiographic response criteria will be proposed by each committee and included in subsequent clinical trials for validation. Whether to include newer MR sequences such as perfusion imaging, spectroscopy, and diffusion will be determined for each tumor type. Ultimately, a more personalized imaging approach based on tumor characteristics, treatment modality and clinical factors may be necessary to adequately define radiographic response. With the abundance of genomic and pharmacodynamic data being studied at present, it is not clear if separate radiographic and biologic response criteria will be necessary for response definition. New trial designs may require inclusion of objectives evaluating drug activity by tumor size, biologic response, and clinical benefit.

ACKNOWLEDGMENTS

Research was supported in part by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Center for Cancer Research. The views expressed do not necessarily represent the views of the National Institutes of Health or the United States Government.

REFERENCES

1. Macdonald D, Cascino T, Schold SJ, et al. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 1990;8:1277–1280. [PubMed: 2358840]
2. van den Bent M, Vogelbaum M, Wen P, et al. End point assessment in gliomas: Novel treatments limit usefulness of classical Macdonald's criteria. J Clin Oncol 2009;27:2905–2908. [PubMed: 19451418]
3. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. J Clin Oncol 2010;28:1963–1972. [PubMed: 20231676]
4. Quant E, Wen P. Response assessment in neuro-oncology. Curr Oncol Rep 2011;13:50–56. [PubMed: 21086192]
5. van den Bent M, Wefel J, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): Assessment of outcome in trials of diffuse low-grade gliomas. Lancet Oncol 2011;12:583–593. [PubMed: 21474379]
6. Vogelbaum M, Jost S, Aghi M, et al. Application of novel response/progression measures for surgically delivered therapies for gliomas: Response assessment in neuro-oncology working group. Neurosurgery 2012;70:234–244. [PubMed: 21593697]
7. CBTRUS. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2004–2006 Hinsdale, IL; 2010.
8. Norden A, Wen P. Glioma therapy in adults. Neurologist 2006;12:279–292. [PubMed: 17122724]
9. CBTRUS. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2004–2008 Hinsdale, IL; 2012.

10. Warren K, Gururangan S, Geyer J, et al. A phase II study of O6-benzylguanine and temozolomide in pediatric patients with recurrent or progressive high-grade gliomas and brainstem gliomas: A Pediatric Brain Tumor Consortium study. J Neurooncol 2011;106:643–649. [PubMed: 21968943]
11. Hales R, Shokek O, Burger P, et al. prognostic factors in pediatric high-grade astrocytoma: The importance of accurate pathologic diagnosis. J Neurooncol 2010;99:65–71. [PubMed: 20043190]
12. Gaudino S, Quaglio F, Schiarelli C, et al. Spontaneous modifications of contrast enhancement in childhood non-cerebellar pilocytic astrocytomas. Neuroradiology 2012;54:989–995. [PubMed: 22286205]
13. Gnekow A, Kortmann R, Pietsch T, et al. Low grade chiasmatic-hypothalamic glioma-carboplatin and vincristin chemotherapy effectively defers radiotherapy within a comprehensive treatment strategy–report from the multicenter treatment study for children and adolescents with a low grade glioma–HIT-LGG 1996–of the Society of Pediatric Oncology and Hematology (GPOH). Klin Padiatr 2004;16:331–342.
14. Packer R, Ater J, Allen J, et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. J Neurosurg 1997;86:747–754. [PubMed: 9126887]
15. Massimino M, Spreafico F, Cefalo G, et al. High response rate to cisplatin/etoposide regimen in childhood low-grade glioma. J Clin Oncol 2002;20:4209–4216. [PubMed: 12377964]
16. Laithier V, Grill J, Le Deley M-C, et al. Progression-free survival in children with optic pathway tumors: Dependence on age and the quality of response to chemotherapy—Results of the first French prospective study for the French Society of Pediatric Oncology. J Clin Oncol 2003;21:4572–4578. [PubMed: 14673044]
17. Hargrave D, Chuang N, Bouffet E. Conventional MRI cannot predict survival in childhood diffuse intrinsic pontine glioma. J Neurooncol 2008;86:313–319. [PubMed: 17909941]
18. Poussaint T, Kocak M, Vajapeyam S, et al. MRI as a central component of clinical trials in brainstem glioma: A report from the Pediatric Brain Tumor Consortium (PBTC). Neuro-Oncol 2011;13:417–427. [PubMed: 21297126]
19. Hipp S, Steffen-Smith E, Hammoud D, et al. Predicting outcome of children with diffuse intrinsic pontine gliomas using multiparametric imaging. Neuro Oncol 2011;13:904–909. [PubMed: 21757444]
20. Henson J, Ulmer S, Harris G. Brain tumor imaging in clinical trials. Am J Neuroradiol 2008;29:419–424. [PubMed: 18272557]
21. Shah G, Kesari S, Xu R, et al. Comparison of linear and volumetric criteria in assessing tumor response in adult high-grade gliomas. Neuro Oncol 2006;8:38–46. [PubMed: 16443946]
22. Sorensen A, Patel S, Harmath C, et al. Comparison of diameter and perimeter methods for tumor volume calculation. J Clin Oncol 2001;19:551–557. [PubMed: 11208850]
23. Vos M, Uitdehaag B, Barkhof F, et al. Interobserver variability in the radiological assessment of response to chemotherapy in glioma. Neurology 2003;60:826–830. [PubMed: 12629241]
24. Hayward R, Patronas N, Baker E, et al. Inter-observer variability in the measurement of diffuse intrinsic pontine gliomas. J Neurooncol 2008;90:57–61. [PubMed: 18587536]
25. Packer R, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 2006;24:4202–4208. [PubMed: 16943538]

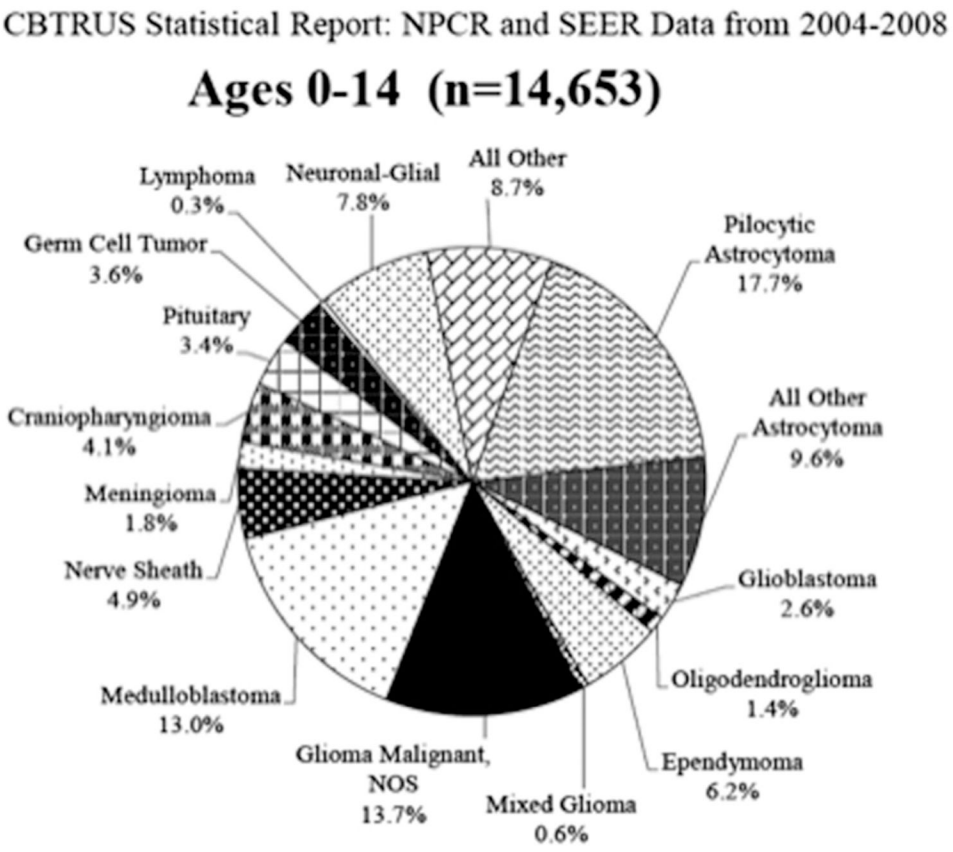

Fig. 1.

CNS tumor distribution by diagnosis in children ages 0–14 years as reported by the Central Brain Tumor Registry of the United States (with permission) [9].

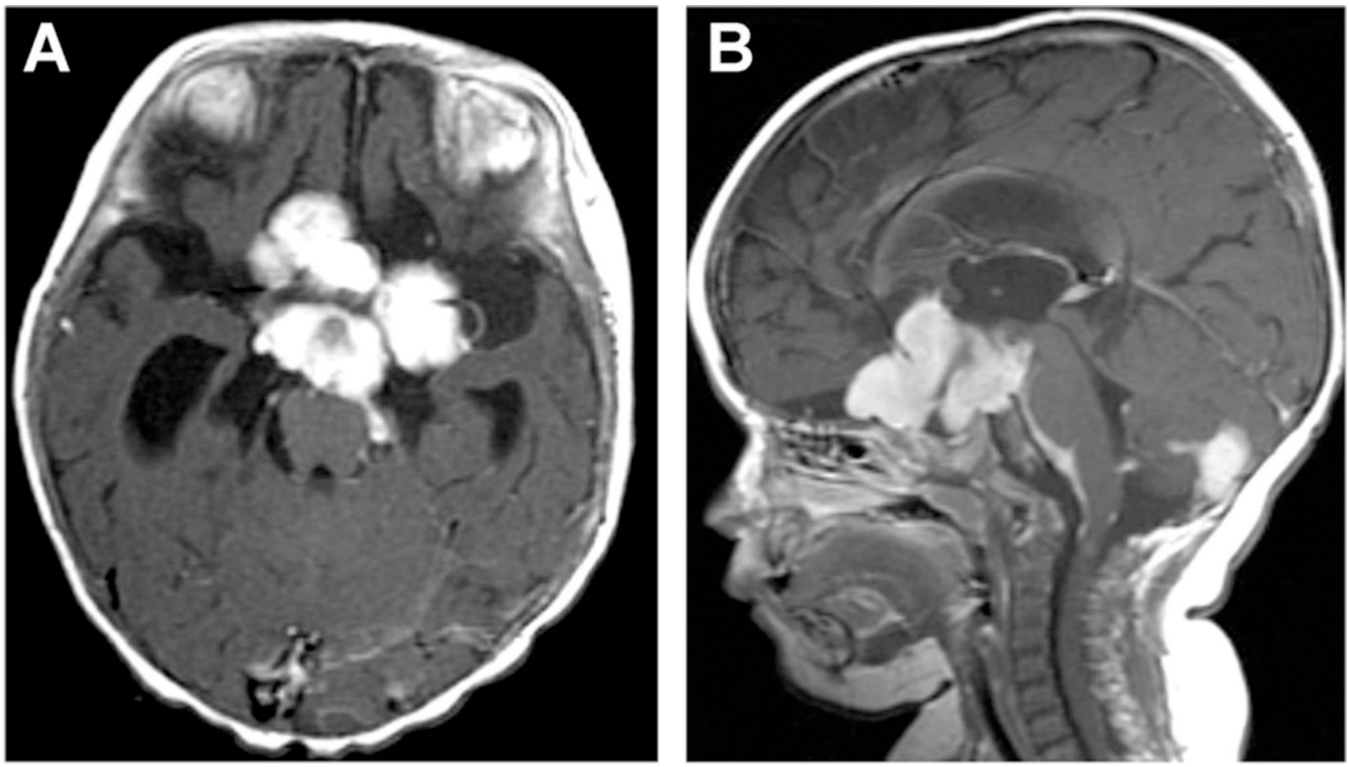

Fig. 2.

T1-weighted, post-contrast axial (**A**) and sagittal (**B**) images from a 7-month-old infant with pilocytic astrocytoma (WHO I) demonstrating irregular, lobulated shape, and metastatic spread.

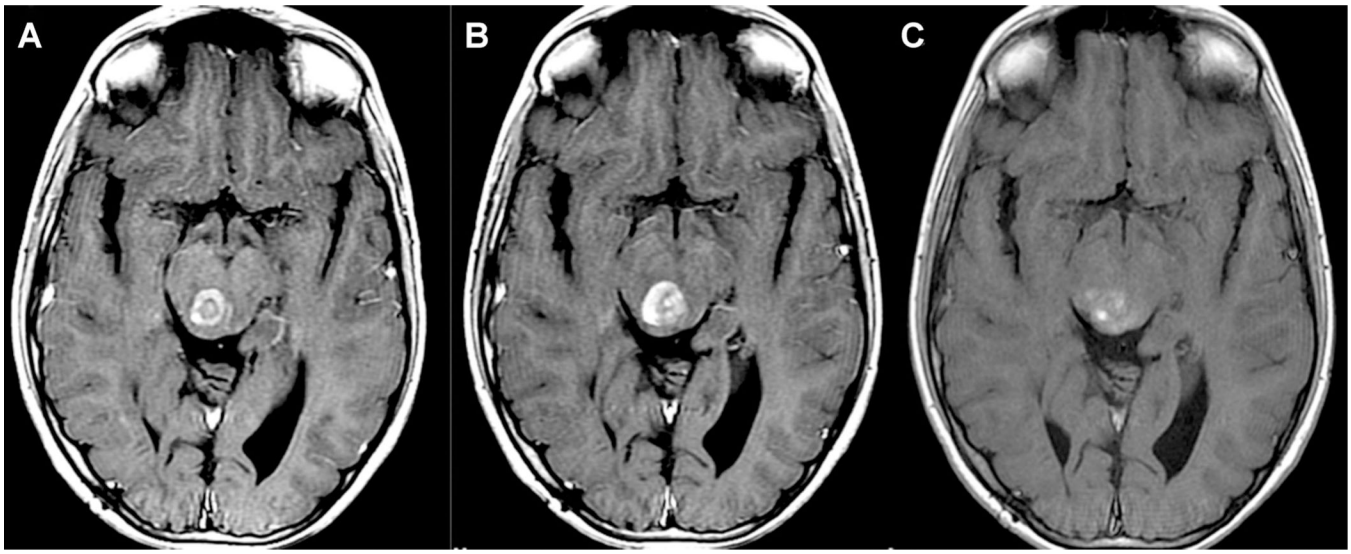

Fig. 3.

Low-grade dorsal midbrain glioma in a 15-year-old patient treated with proton beam radiotherapy after prior progression on vincristine/carboplatin. **A**: Pre-radiation. **B**: Three months post-radiation therapy showing increase in enhancement. **C**: Twelve months post-radiation therapy showing subsequent regression in the area of enhancement.

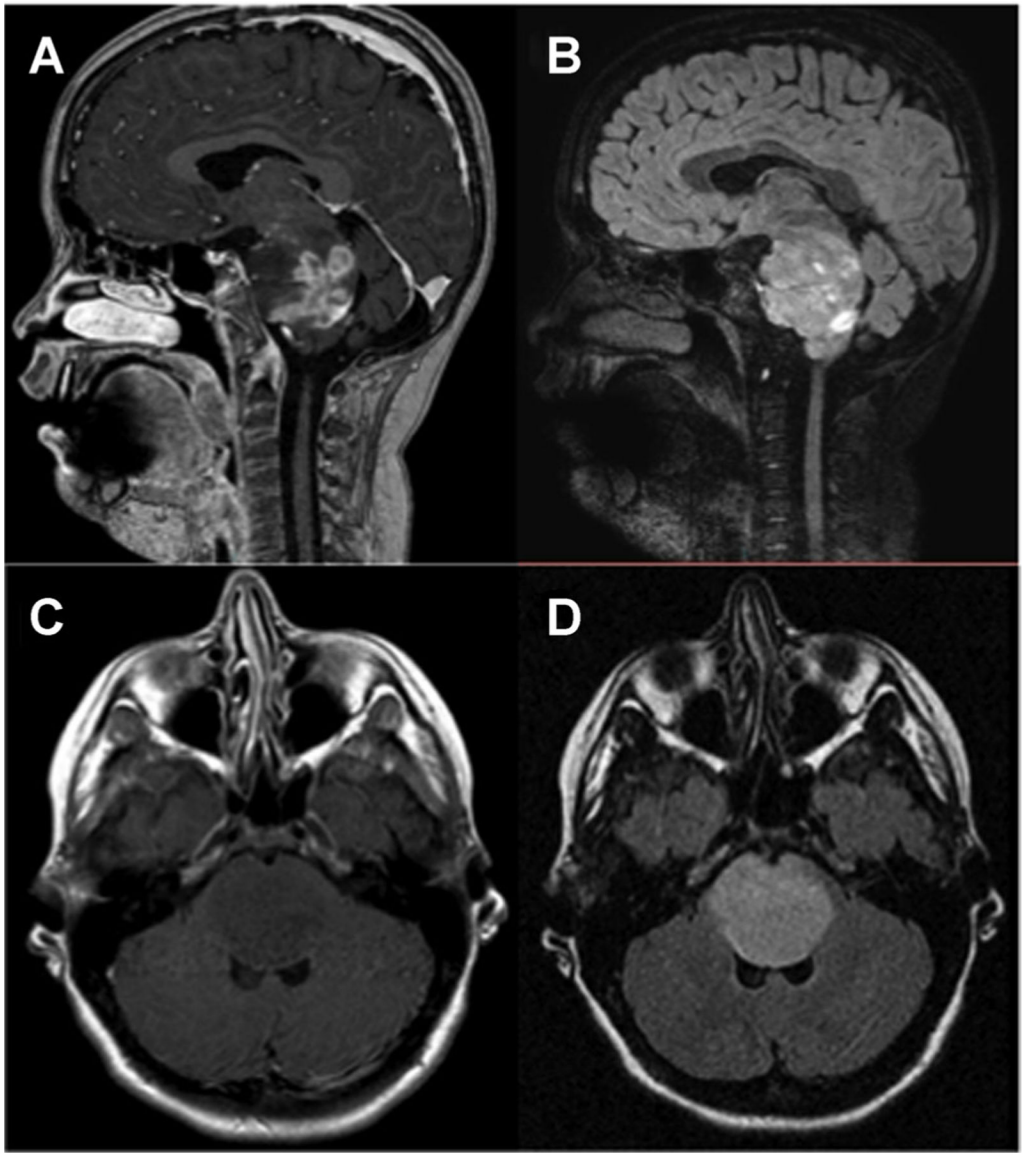

Fig. 4.

Tumor burden assessed by post-contrast and FLAIR imaging in two patients with DIPG. **A**: Sagittal T1-weighted post-contrast and (**B**) FLAIR sequences for Patient 1 demonstrating heterogeneous enhancement, and (**C**) axial T1-weighted and (**D**) FLAIR sequences for Patient 2 demonstrating tumor burden on FLAIR in a non-enhancing lesion.

TABLE I.

Criteria Used in Response Definitions for Consortia Trials (n=# of Trials)

Criteria	n=56
1D (RECIST)	4
2D	39
3D	20
Included caveat allowing increased tumor size up to 50% (cytostatic, antiangiogenic agents)	15
Specific instructions on what to measure	2
Central review	19
Sustained response	29 (21 days to 8 weeks)
Clinical exam	30
Steroids	28
Cytology	22
Tumor markers	2
QOL	0

Note Some trials incorporated more than one method of tumor measurement.