

A multi-institutional study of brainstem gliomas in children with neurofibromatosis type 1



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ABSTRACT

Objective: To define the clinical and radiologic features of brainstem gliomas (BSGs) in children with neurofibromatosis type 1 (NF1).

Methods: We performed a retrospective cross-sectional study of 133 children with NF1 and concurrent BSGs cared for at 4 NF1 referral centers. BSG was determined using radiographic criteria. Age at diagnosis, tumor location and appearance, clinical symptoms, treatment, and presence of a concurrent optic pathway glioma were assessed.

Results: The average age at BSG diagnosis was 7.2 years, and tumors occurred most often in the midbrain and medulla (66%). The majority of children with NF1-BSGs were asymptomatic (54%) and were not treated (88%). Only 9 of the 72 asymptomatic children received treatment because of progressive tumor enlargement. In contrast, 61 children presented with clinical signs/symptoms attributable to their BSG; these individuals were older and more often had focal lesions. Thirty-one patients underwent treatment for their tumor, and 14 received CSF diversion only. Progression-free survival was ~3 years shorter for children receiving tumor-directed therapy relative to those who had either no treatment or CSF diversion only. Overall survival was 85% for the tumor-directed therapy group, whereas no deaths were reported in the untreated or CSF diversion groups.

Conclusions: Unlike children with sporadically occurring BSGs, most children with NF1-BSGs were asymptomatic, and few individuals died from complications of their tumor. Those requiring tumor-directed treatment tended to be older children with focal lesions, and had clinically more aggressive disease relative to those who were not treated or underwent CSF diversion only.

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GLOSSARY

BSG = brainstem glioma; **CHOP** = The Children's Hospital of Philadelphia; **CNMC** = Children's National Medical Center; **DIPG** = diffuse intrinsic brainstem glioma; **LCH** = Ann & Robert H. Lurie Children's Hospital of Chicago (Northwestern University); **NF1** = neurofibromatosis type 1; **OPG** = optic pathway glioma; **OS** = overall survival; **PA** = pilocytic astrocytoma; **PFS** = progression-free survival; **WUSM** = Washington University School of Medicine; **WHO** = World Health Organization.

Neurofibromatosis type 1 (NF1) is a common cancer predisposition syndrome in which affected children and adults develop benign and malignant nervous system tumors.¹ WHO grade I gliomas (pilocytic astrocytomas [PAs]), including those involving the optic pathway and brainstem, predominate in children with NF1. Optic pathway gliomas (OPGs), the most frequently encountered of these low-grade gliomas, are seen in 15%–20% of children with NF1. These tumors typically come to medical attention in young preschool children (mean age, 4.5 years) who present with reduced visual acuity or precocious puberty, or who are incidentally discovered on screening neuroimaging.^{2,3}

While OPGs represent 66%–75% of all CNS tumors in children with NF1,⁴ the second most common brain tumor is the brainstem glioma (BSG), representing approximately 18% of NF1-associated brain neoplasms.^{4,5} Unlike NF1-OPG, NF1-BSGs tend to arise at a slightly older age

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(mean age, 7 years).⁵ However, much less is known about their presentation and ensuing clinical course, with only 3 clinical series reported, each with fewer than 30 participants.^{5–7} Our limited understanding of these brain tumors in the context of NF1 is problematic given the dramatic contrast in clinical outcomes when compared to sporadically occurring brainstem gliomas, such as the diffuse intrinsic brainstem glioma (DIPG),^{4,5,8} an aggressive pediatric brain tumor with frequent recurrence and poor overall survival (OS) rates.

To comprehensively characterize the presentation and symptomatology of BSGs arising in the context of NF1, we assembled the largest series of children and young adults with these low-grade brain tumors, representing the collective experience of 4 tertiary care referral centers with longstanding NF clinical programs.

METHODS Study population. A retrospective analysis of the electronic medical records of 133 participants who were followed at 1 of 4 institutions was conducted over a 15-year period (2000–2015). Participating sites included St. Louis Children's Hospital (Washington University School of Medicine [WUSM]), The Children's Hospital of Philadelphia (CHOP), Children's National Medical Center (CNMC), and Ann & Robert H. Lurie Children's Hospital of Chicago (Northwestern University [LCH]).

Standard protocol approvals, registrations, and patient consents. This study was approved by the institutional review boards at WUSM, CHOP, CNMC, and LCH. All participants included in the study had a diagnosis of NF1 based on NIH Consensus Development criteria⁹ and were identified as having a brainstem glioma based on the following radiographic criteria: (1) a T2-hyperintense lesion with an associated T1 hypointensity relative to gray matter, (2) a T2-hyperintense lesion with mass effect with or without an associated T1 hypointensity relative to gray matter, or (3) an enhancing lesion with or without mass effect on MRI. Participants were excluded from the study when (1) a diagnosis of NF1 could not be established, (2) there was an ill-defined T2 hyperintensity lacking either T1 hypointensity or gadolinium enhancement and not exhibiting mass effect or architectural distortion, likely representing a non-neoplastic T2 hyperintensity (unidentified bright object) commonly observed in children with NF1,^{10,11} or (3) there was incomplete clinical information available in the electronic medical record. The average length of follow-up was 7.5 years.

Record review and data collection. Data analyzed included age at diagnosis, patient sex (male/female), location of tumor (midbrain, pons, medulla, midbrain and pons, midbrain and medulla, pons and medulla, or entire brainstem), focal or diffuse mass on MRI (defined as discrete mass vs an infiltrative mass without a defined border; figure e-1 at [Neurology.org](#)), clinical symptoms, treatment (chemotherapy, radiation, or surgery), the presence of a concurrent optic glioma (on MRI), family history of

Table 1 Patient demographics

Characteristics	Values
Age, y, mean ± SD	7.18 ± 4.38
Female, n (%)	59 (44.4)
Symptomatic at diagnosis, n (%)	61 (45.9)
Presence of concurrent OPG, n (%)	70 (52.6)
Positive family history, n (%)	45 (33.8) ^a
Length of follow-up, y, average ± SD	7.5 ± 4.50
Alive at last follow-up, n (%)	123 (92.5)

Abbreviation: OPG = optic pathway glioma.

^aFour participants did not have a documented family history.

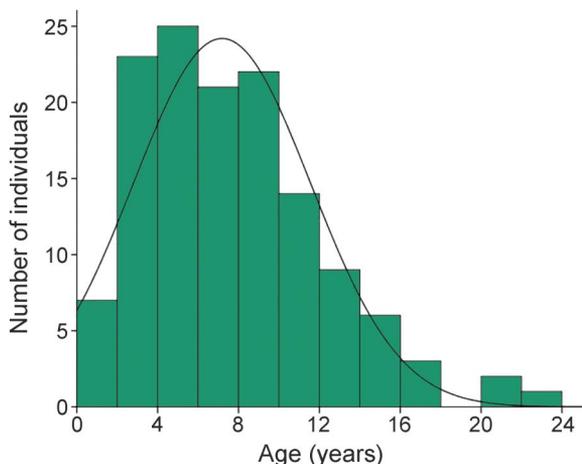
NF1 (yes/no), and progression-free survival (PFS). The collected data were de-identified and stored within a password-protected spreadsheet on a secure laptop and were only accessed by study team members at WUSM.

Statistical analysis. Data were analyzed using IBM (Armonk, NY) SPSS, version 23. Categorical variables were reported as frequencies and proportions, and compared using logistic regression methods. Continuously distributed traits adhering to conventional normality assumptions were reported as mean and SD, and compared using analysis of variance methods. PFS was estimated using the Kaplan-Meier method and a log-rank test was used to compare survival curves. Statistical significance was defined as a *p* value of <0.05.

RESULTS A total of 133 individuals were included in the study (59 from CHOP, 35 from WUSM, 22 from LCH, and 17 from CNMC), with a total of 59 female and 74 male participants. The mean age at diagnosis of a BSG was 7.18 ± 4.38 years (age range 0.6–23 years; table 1). There was a normal and continuous distribution for the age at initial diagnosis (figure 1). No statistically significant differences in mean age at diagnosis based on the region of brainstem involvement were observed, and the location of BSG did not appear to differ by sex (*p* = 0.58). While some BSGs crossed anatomic boundaries and occurred in the midbrain and pons (n = 5; 3.8%), midbrain and medulla (n = 3; 2.2%), pons and medulla (n = 14; 10.5%), and entire brainstem (n = 4; 3.0%), the majority of tumors were localized to only one anatomical segment (n = 107; 80.5%). When confined to a single segment, tumors were statistically less likely to occur in the pons (n = 19; 14.2%) compared to the midbrain (n = 48; 36.1%) or medulla (n = 40; 30.1%, *p* = 0.002) (figure 2).

Asymptomatic children with NF1-BSG. Seventy-two of the 133 children (54%) with NF1-BSGs were asymptomatic at the time of BSG diagnosis. The majority of asymptomatic individuals (n = 63; 88%) did not receive tumor-directed therapy; however, 9 children (12.5%) without clinical symptoms

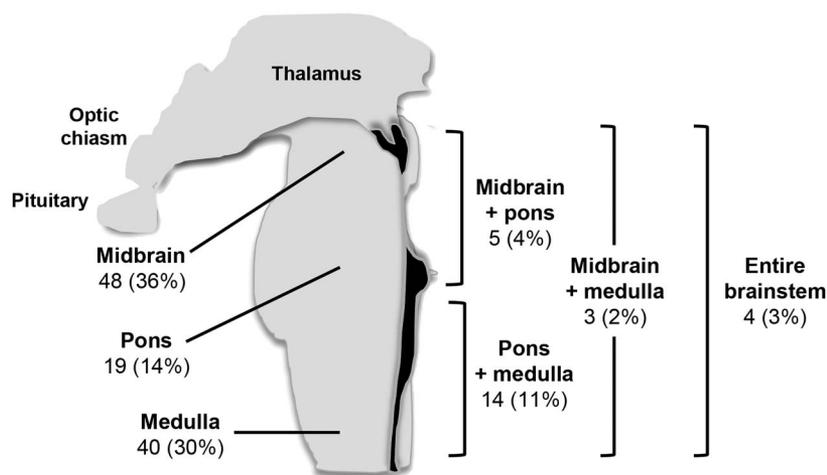
Figure 1 Age distribution of individuals with neurofibromatosis type 1 (NF1) presenting with brainstem glioma (BSG)



The number of individuals with NF1-BSG is represented as a function of age (years).

underwent treatment due to progressive tumor enlargement. There were no other distinguishing features (tumor anatomic location, age, sex, tumor appearance, family history, or presence of concurrent OPG) between the asymptomatic children who received treatment and those who did not. All 9 of the children who were treated received tumor-directed therapy with 4 receiving chemotherapy and surgery, 4 receiving chemotherapy only, and 1 undergoing tumor debulking. Five of these individuals had biopsies performed, with 4 of 5 biopsies revealing WHO grade I tumors (PAs), with MIB-1/Ki67 indices ranging from <1 to 3% (pathology from 1 tumor was not available). One of these individuals had an exophytic tumor that recurred twice with a MIB-1/Ki67 index of 8%. He is still alive.

Figure 2 Location of brainstem gliomas in individuals with neurofibromatosis type 1



The number and percentage of tumors arising in specific locations within the brainstem.

Symptomatic children with NF1-BSG. Sixty-one (45.9%) participants had clinical symptoms at the time of BSG diagnosis, which included, but were not limited to, headaches, nausea/vomiting, cranial neuropathies (e.g., dysarthria), and ataxia/gait instability. Of these 61 participants, 45 individuals (74%) received either tumor-directed therapy (chemotherapy, radiation, or surgical debulking) or CSF diversion to correct BSG-associated obstructive hydrocephalus. A total of 14 participants, whose tumors were predominantly located in the midbrain, underwent a CSF diversion procedure only (ventriculo-peritoneal shunt or endoscopic third ventriculostomy). Thirty-one participants received tumor-directed therapy, which included chemotherapy alone (n = 15), chemotherapy and surgical debulking (n = 5), chemotherapy and CSF diversion (n = 6), chemotherapy and radiation (n = 3), tumor debulking only (n = 1), and radiation alone (n = 1).

Symptomatic children with NF1-BSG who received tumor-directed therapy tended to be older (9.27 ± 5.09 years; $p = 0.092$) and harbored focal tumors (74%; $p = 0.007$) relative to those who had no treatment or underwent CSF diversion only (6.06 ± 4.7 years, 40% focal tumors) (table 2). There were no other features that distinguished symptomatic children who received tumor-directed treatment relative to those who did not (sex, tumor location, concurrent OPG, or positive family history).

Of those who were symptomatic and treated, 12 individuals had biopsies performed. In stark contrast to individuals who were asymptomatic and treated, only 3 tumors in the symptomatic and treated group were WHO grade I gliomas (25%). Rather, the majority of the gliomas were classified as WHO grade II neoplasms (n = 8; 75%), with 1 individual harboring a malignant grade III glioma.

The 16 individuals who were symptomatic, but did not receive tumor-directed treatment or undergo CSF diversion, presented with poorly localizing clinical signs and symptoms, such as hypotonia, head tilt, and seizures, which the responsible clinicians believed were insufficient to warrant intervention. The majority of these patients (11 of 16; 69%) had medullary involvement.

Treatment course. The majority of individuals who underwent tumor-directed treatment received only 1 course of therapy regardless of the presence or absence of symptoms (62.5%). Of the 31 children who were symptomatic and treated, 12 individuals (38.7%) required additional tumor-directed therapy: 9 received multiple successive courses of chemotherapy with different agents, 1 required multiple courses of chemotherapy with surgical debulking, and 2 required multiple courses of chemotherapy with

Table 2 Symptomatic children with neurofibromatosis type 1–brainstem glioma

	Tumor-directed therapy (n = 31)	CSF diversion or untreated (n = 30)	p Value
Age, mean (SD)	9.27 (5.09)	6.06 (4.70)	0.09
Female, n (%)	12 (39)	14 (47)	0.53
Location, n (%)			
Midbrain	13 (42)	15 (50)	0.53
Medulla	15 (48)	13 (43)	0.69
Focal	23 (74)	12 (40)	0.007
Hydrocephalus	11 (35)	14 (47)	0.37
Concurrent OPG	19 (61)	12 (40)	0.10

Abbreviation: OPG = optic pathway glioma.

radiation. A similar proportion of individuals who were asymptomatic and underwent tumor-directed treatment required multiple courses of chemotherapy (3 of 9 individuals; 33%). There were no differences in the location of tumor or radiographic appearance among the individuals in the symptomatic and asymptomatic cohorts who required multiple courses of treatment.

PFS and OS. Participants who were symptomatic were followed for an average of 8.05 ± 5.0 years from the time of initial BSG diagnosis, whereas participants who were asymptomatic were followed for an average of 7.07 ± 4.0 years (table 1). As a group, OS was 92.5% (123/131 subjects), with a documented PFS of 66.90 ± 5.11 months.

In the entire cohort (133 individuals), children who received tumor-directed therapy (n = 40) had shorter PFS (41.33 ± 7.51 months; $p = 0.01$) relative to those who received either CSF diversion or no treatment (n = 93; 76.69 ± 6.07 months) (figure 3A). Interestingly, there was no difference in PFS ($p = 0.13$) between those who received CSF diversion only (n = 14; 105.57 ± 19.4 months) vs those who received no intervention at all (n = 79; 71.09 ± 6.05 months). In the subset of children who were symptomatic from their BSG, those who underwent tumor-directed therapy also exhibited reduced PFS (n = 31; 45.68 ± 8.76 months; $p = 0.001$) relative to children who received no treatment or CSF diversion only (n = 30; 78.29 ± 12.84 months) (figure 3B).

With respect to tumor location, children with BSGs located in the midbrain had increased PFS (83.05 ± 9.40 months; $p = 0.008$) relative to those located in the pons (48.79 ± 8.87 months) or medulla (60.41 ± 9.50 months) (figure e-2).

Of the 133 participants in the study, 123 (92.5%) are currently alive, 6 (4.5%) are dead, and 4 (3.0%) subjects were lost to follow-up. All 6 deaths occurred in children who were symptomatic and received tumor-directed therapy. Among the 6 participants

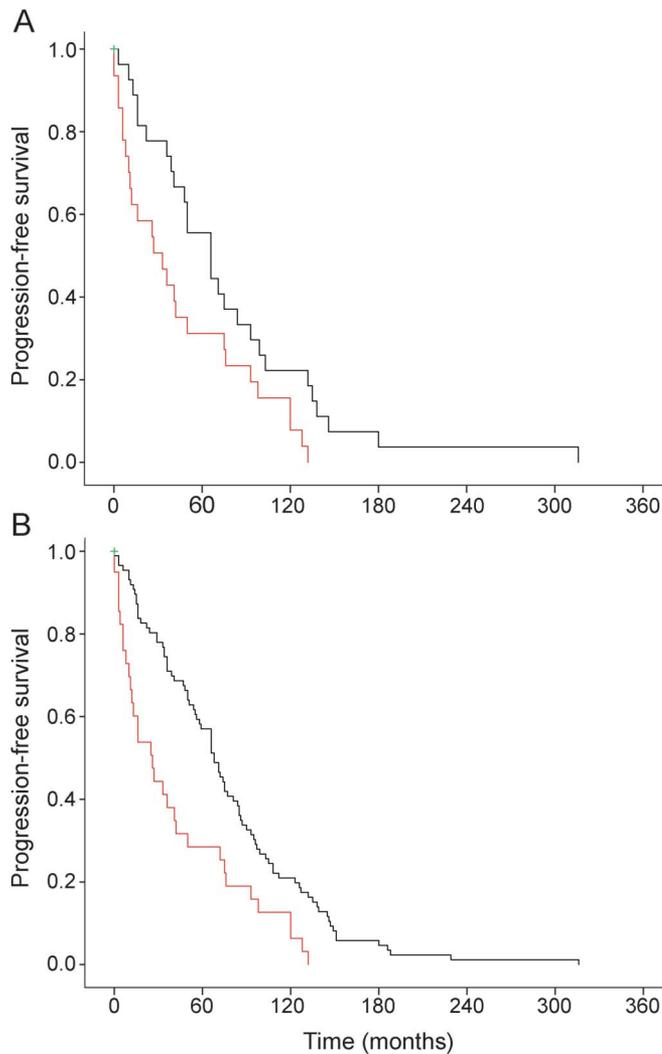
who died, 3 died of a malignant peripheral nerve sheath tumor (age at death, 6–25 years) unrelated to prior radiation, and 3 died as a result of their BSG an average of 9 years after diagnosis (age at death, 11–28 years). The 3 children who died from their BSG were boys who initially presented with hydrocephalus, none of which involved the midbrain (medulla, n = 2; pons and medulla, n = 1). These 3 tumors were not biopsied, and no pathologic information is available. Two of these individuals had continued radiographic progression of their brainstem gliomas. All 3 participants who had malignant peripheral nerve sheath tumors received alkylator chemotherapy, but only 1 out of 3 received radiation therapy. Correspondingly, 2 of the 3 participants who died from complications of their BSG received both radiation therapy and alkylator chemotherapy. The one patient who did not receive either radiation therapy or alkylator chemotherapy died prior to receiving treatment.

DISCUSSION BSGs represent the second most common brain tumor occurring in children with NF1; however, their comparative infrequency (~18% of all NF1 brain tumors) has resulted in fewer studies aimed at characterizing these gliomas. Moreover, the previous 3 reports on NF1-BSGs each contained fewer than 30 participants,^{5–7} leaving significant information gaps relevant to counseling families when children present with BSGs. In this report, we leveraged the experience of 4 major NF1 tertiary referral centers, and present an analysis of 133 children with NF1-BSGs. This study makes several important points relevant to the management of these brain tumors arising in the context of NF1.

First, BSGs tend to present in a slightly older pediatric population (mean age, 7 years) relative to NF1-OPG (mean age, 4.2 years).^{2,3} The majority of these tumors are localized to one anatomic segment, with the majority involving the midbrain or the medulla, rather than the pons. This is in contrast to sporadic BSGs, where pontine involvement is most common.^{12–14}

Second, half of the NF1-BSG cases in our series were identified as incidental findings on MRI, which is a similar proportion to that reported in previous studies.⁵ The incidental identification of these tumors in the setting of NF1 is important, as MRI scans in children with NF1 frequently reveal nonenhancing T2 hyperintense lesions within the brainstem, which historically have been difficult to distinguish from gliomas.¹⁵ Herein, we employed more uniform criteria for NF1-BSG classification, and suggest that these standards be employed in future studies to avoid misclassifying clinically insignificant T2 hyperintensities as brain tumors. The implementation of consistent

Figure 3 Progression-free survival (PFS)



(A) All participants ($n = 133$): PFS was reduced for children with neurofibromatosis type 1 (NF1)-brainstem glioma (BSG) who received tumor-directed therapy (red line; $n = 40$; 41.33 ± 7.51 months) relative to those who received no treatment or underwent CSF diversion only (black line; $n = 93$; 76.69 ± 6.07 months); $p = 0.01$. (B) Symptomatic participants ($n = 31$): PFS was reduced for symptomatic children with NF1-BSG who received tumor-directed therapy (red line; $n = 31$; 45.68 ± 8.76 months) relative to those who received no treatment or underwent CSF diversion (black line; $n = 30$; 78.29 ± 12.84 months); $p = 0.02$.

radiographic criteria will also be of importance for future studies examining gliomas occurring in other regions of the CNS in children with NF1.

Third, and most importantly, the majority of children with NF1-BSGs (54%) were asymptomatic, and the vast majority of individuals did not require any intervention. In the small number of asymptomatic children with NF1-BSG who received treatment for their BSG, the majority were treated because of progressive increase in tumor size and were most likely to have WHO grade I tumors on pathology. All of the asymptomatic individuals who underwent treatment for NF1-BSG responded well to therapy and are currently alive. Overall, only 30% of NF1-BSGs required tumor-directed treatment. This is similar

to the percentage of children with NF1-OPG who require treatment, which ranges between 30% and 50%.¹⁶ As above, this is in striking contrast to children without NF1 who harbor a brainstem glioma (DIPG). Children with these sporadically occurring BSGs most often present with cerebellar signs, long tract signs, and cranial nerve palsies, and die of their tumor within 12 months.^{17–19} Since the presence of localizing signs/symptoms was the most frequent reason for treatment, the incidental identification of these tumors infrequently changed clinical management, similar to that reported for NF1-OPG.²⁰

Fourth, and not surprisingly, children with NF1-BSG who received tumor-directed therapy had shorter PFS than those who did not require treatment for their tumor (whether they received CSF diversion or not), likely reflecting a different biology that drove tumor progression in the first place. However, those who received CSF diversion only had a PFS similar to those who received no intervention (CSF diversion or tumor-directed therapy). This finding is likely accounted for by tumor location, as most children who required CSF diversion had midbrain tumors, and children with BSGs located in the midbrain had longer PFS than those with pontine or medullary tumors. Given this finding, similar to tectal tumors arising in the general pediatric population,^{21,22} the need for CSF diversion should not be an indication for initiating tumor-directed treatment for NF1-BSG.

Fifth, most children with NF1-BSG who presented with clinical symptoms required intervention, with the majority of these individuals receiving tumor-directed therapy. As a group, the latter tended to be older (~ 9.3 years of age) with focal lesions, and exhibited reduced PFS relative to those who did not require treatment for their tumor. While only 3 children died from complications of their BSG, all of these individuals (3/31; 9.7%) were symptomatic and treated with tumor-directed therapy. Interestingly, the tumors in this symptomatic and treated group, when biopsied, were most often WHO grade II gliomas, rather than the more typical pilocytic astrocytoma. However, it is important to note that it can be difficult to distinguish a grade I glioma from a grade II glioma on biopsy, as the classic histopathologic features of a pilocytic astrocytoma (Rosenthal fibers, eosinophilic granular bodies) may not be seen if the biopsy sample is small. In contrast, 16 symptomatic children with NF1-BSG did not require CSF diversion or tumor-directed therapy, and the majority of these patients (69%) had a tumor involving the medulla and presented with poorly localizing symptoms (ataxia, reduced vision, seizure, dysphagia, uvula deviation). Most of these patients (81%) did not demonstrate radiographic progression of their tumors despite not receiving treatment, and all are currently alive.

We describe the largest series of NF1-BSGs reported to date. Relative to their sporadic counterparts, these NF1-associated brainstem tumors are less clinically progressive and rarely result in early death. However, while the mortality rate from BSGs is low, the prompt recognition of these tumors is critical for optimal surgical and chemotherapeutic management of this population of at-risk individuals. As such, these data support monitoring NF1-BSGs with serial neuroimaging and only initiating treatment for tumor progression or development of clear neurologic signs or symptoms. However, those children who receive tumor-directed therapy need to be closely monitored, as one third of these individuals will require another treatment.

AUTHOR CONTRIBUTIONS

J.M. collated the data, performed the analyses, and wrote the manuscript. A.C.S. collated the data from Children's Hospital of Philadelphia and participated in the generation of the final manuscript. A.S. collated the data from Children's National Medical Center and participated in the generation of the final manuscript. S.M.M. performed the statistical analyses and participated in the generation of the final manuscript. R.L. collated the data from Lurie Children's Hospital and participated in the generation of the final manuscript. R.J.P. participated in the generation of the final manuscript. M.J.F. participated in the collection of data from Children's Hospital of Philadelphia and participated in the generation of the final manuscript. R.C.M. established the radiographic criteria used in this report. D.H.G. collated the data from Washington University, provided the funding, and was responsible for generation of the final manuscript.

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DISCLOSURE

J. Mahdi, A. Shah, A. Sato, and S. Morris report no disclosures relevant to the manuscript. R. McKinstry received honoraria for attending the Guerbet, LLC Advisory Board meeting and delivering a keynote lecture for Siemens Healthcare. R. Listernick, R. Packer, M. Fisher, and D. Gutmann report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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