



Published in final edited form as:

J Child Neurol. 2009 November ; 24(11): 1397–1408. doi:10.1177/0883073809342005.

Pediatric Low-Grade Gliomas

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Abstract

Pediatric low-grade gliomas encompass a heterogeneous set of tumors of different histologies. Cerebellar pilocytic astrocytomas occur most frequently followed by supratentorial diffuse fibrillary astrocytomas. Recent research has implicated activation of the RAS/RAF/MEK pathway in tumorigenesis of these tumors. Surgery is the mainstay of therapy. Overall survival rates for patients whose tumors are completely resected are 90% or greater, 10 years from diagnosis. Conversely, most optic pathway/hypothalamic, deep midline, and brain stem gliomas have minimal potential for resection; these tumors can be difficult to treat and deserve special attention. Combination chemotherapy is currently recommended as front-line adjuvant treatment for progressive or recurrent tumors. Second-line radiotherapy can also improve overall survival but is associated with more frequent and significant neurocognitive, endocrine, and other long-term toxicities.

Keywords

low-grade; glioma; astrocytoma; pilocytic; fibrillary

Pediatric low-grade gliomas are a heterogeneous set of tumors. They encompass tumors of astrocytic, oligodendroglial, and mixed glial-neuronal histology. Although their clinical behavior can vary, the majority of low-grade gliomas are indolent and do not undergo malignant transformation. Case reports have even described spontaneous regression of some tumors.^{1,2} This is in contrast to adult low-grade gliomas that have a more aggressive phenotype. One reason for the differences between the 2 populations may be the different frequencies of histological subtypes. Pilocytic astrocytomas infrequently occur in adults but are the leading histology in children. Conversely, diffuse gemistocytic astrocytomas, which have been associated with an increased tendency toward malignant progression, are rarely found in children.³ Low-grade gliomas are estimated to account for anywhere from 30% to 50% of central nervous system tumors in children.⁴⁻⁶

Discussion of gliomas can be confusing as it is a descriptive and not a pathological term. Tumors are classified according to the World Health Organization (WHO) criteria, most recently published in 2007, which describes their histological features and also provides a grading or "malignancy scale."³ Low-grade gliomas encompass grade 1 and grade 2 tumors (Table 1).³ Grading is based on a number of factors including presence of necrosis, giant cells, mitosis, endothelial proliferation, hyperchromatic nuclei, and pleomorphic cells. These findings can be subjective, and retrospective studies have documented significant

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The authors have no conflicts of interest to disclose with regard to this article.

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interpathologist disagreement on grading.⁷ Moreover, it can be difficult to distinguish a low-grade from a high-grade glioma.⁸

Pediatric low-grade gliomas can be difficult to categorize as they can occur anywhere in the central nervous system and comprise multiple different tumor histologies. Historically, the cerebellum is the most prevalent location, and cerebellar low-grade gliomas account for 15% to 25% of all pediatric central nervous system tumors. They are followed by hemispheric (cerebral) gliomas (10%-15%), gliomas of the deep midline structures (10%-15%), optic pathway gliomas (5%), and brain stem gliomas (2%-4%; Figure 1).⁴ Children with neurofibromatosis type 1 account for the majority (over 70%) of the optic pathway/hypothalamic gliomas.⁹ In fact, 15% to 20% of children with neurofibromatosis type 1 will develop an optic pathway/hypothalamic glioma. Fortunately, only about half of them will become symptomatic and require treatment, usually before the age of 5.¹⁰⁻¹³ Low-grade brain stem gliomas include the dorsally exophytic, cervicomedullary, and focal brain stem gliomas and are to be distinguished from the more aggressive diffuse intrinsic brain stem gliomas.

The 2 most common low-grade glioma histologies in children are the pilocytic (WHO grade 1) and diffuse fibrillary astrocytoma (WHO grade 2). The former occurs mainly in children aged 5 to 19 years with a peak incidence in the 5- to 9-year-old age range.¹⁴ The age distribution for diffuse fibrillary astrocytomas is older, with only 10% occurring below the age of 20 years.¹⁵ Pilocytic astrocytomas can arise anywhere in the central nervous system; however, they predominate in the cerebellum,¹⁶⁻¹⁸ optic pathway,^{19,20} and dorsally exophytic brain stem.²¹ Conversely, diffuse fibrillary astrocytomas are more frequent in the supratentorial region, deep midline structures, and the cervicomedullary region.^{3,22}

Other, less common, low-grade glioma histologies in children include pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, subependymal giant cell astrocytoma, and oligodendroglioma. The term “pilomyxoid” astrocytoma was first introduced in 1999 to describe a subset of pilocytic tumors with more aggressive clinical behavior and has since been included in the most recent World Health Organization classification of central nervous system tumors.²³ Pilomyxoid astrocytomas (WHO grade 2) tend to occur in very young children (mean age 18 months) and localize in the hypothalamic region.²⁴ Pleomorphic xanthoastrocytomas (WHO grade 2) have a propensity for the supratentorial region, most often the temporal lobe, but their age distribution and clinical phenotype are more similar to pilocytic astrocytoma. Gangliogliomas (WHO grade 2) localize in the temporal lobes and have a mean age at diagnosis of 9.5 years.²⁵ Intraventricular subependymal giant cell astrocytomas (WHO grade 1) occur almost exclusively in children with tuberous sclerosis syndrome. Oligodendrogliomas (WHO grade 2) account for only 2% of brain tumors in children <14 years of age; the most common site of occurrence is the frontal lobe. This review will focus on pilocytic astrocytoma and diffuse fibrillary astrocytoma, as they account for the majority of pediatric low-grade gliomas and approximately one quarter of all primary central nervous system tumors in children.¹⁵

Clinical Presentation

The clinical presentation for children with low-grade gliomas, regardless of histology, can be grouped into generalizing and localizing symptoms. Almost 50% of children will have had 6 months or longer symptom duration prior to the eventual diagnosis.²⁶ Generalizing symptoms are due to increased intracranial pressure from obstruction of the ventricles and include headaches (particularly in the morning), nausea, vomiting, and lethargy. Physical examination findings include decreased upward gaze, sixth cranial nerve palsies, and papilledema. These are most often caused by tumors located in the cerebellum, optic chiasm/

hypothalamus, dorsally exophytic brain stem (which arise from the floor of the fourth ventricle and grow into the ventricle), and tectum (which obstruct the cerebral aqueduct).

Localizing symptoms are dictated by tumor location and include focal neurological findings, seizures and endocrinopathies. In particular, cerebellar tumors are associated with ataxia and dysmetria. The presentation of tumors of the cerebral hemisphere depends upon which lobe is involved and includes seizures, hemiparesis, and behavioral changes. Children with tumors of the hypothalamus and/or pituitary gland can suffer from obesity, failure to thrive, diabetes insipidus, other endocrine dysfunction, and visual field deficits from compression of the optic chiasm. Optic pathway gliomas may arise anywhere along the visual pathway (Figure 2). Children with sporadic optic pathway gliomas are more likely to present with chiasmal and postchiasmal involvement, whereas multifocal and bilateral optic nerve involvement is seen almost exclusively in children with neurofibromatosis type 1.^{10,27} Children can present with decreased visual acuity, optic nerve atrophy, proptosis, or strabismus. Low-grade gliomas of the brain stem are indolent by nature and often have a long clinical course (months to years) before diagnosis. Although they do not significantly infiltrate the brain stem, both the dorsally exophytic and cervicomedullary tumors can cause lower cranial nerve deficits (dysphagia, dysarthria, abnormal breathing) and long tract signs (hemiparesis, spasticity, hyperreflexia, Babinski's sign). The cervicomedullary gliomas also present with torticollis, long tract signs, and sensory loss from involvement of the upper cervical cord. Focal brain stem tumors are predominantly tectal in location and therefore present principally with hydrocephalus, although cranial nerve deficits, hemiparesis, and Parinaud syndrome are rarely seen.

Diagnosis

Pediatric low-grade gliomas share similar characteristics on neuroimaging. On magnetic resonance imaging (MRI), they tend to be hypointense on T1-weighted, hyperintense on T2-weighted, and have varying degrees of enhancement on postgadolinium sequences. Pilocytic astrocytomas usually appear as well-circumscribed tumors, often with a large cystic component and an enhancing mural nodule (Figure 3). Diffuse fibrillary astrocytomas are less circumscribed and typically do not enhance to a large extent (Figure 4).

Surgical biopsy, and total tumor resection when feasible, is recommended to verify tumor histology. To preserve optic nerve function, many children with optic pathway/hypothalamic gliomas do not undergo diagnostic biopsy if the MRI characteristics are consistent with low-grade glioma, especially if there is a prior diagnosis of neurofibromatosis type 1. Biopsies of deep midline and brain stem tumors are also to be pursued cautiously, especially if they are asymptomatic and have not progressed on serial MRI evaluations.

Staging for the majority of tumors includes postoperative MRI of the tumor resection site to determine extent of resection. This should be performed within 24 to 48 hours after surgery to best distinguish residual tumor versus postoperative changes. Dissemination and leptomeningeal involvement are uncommon; however, if suspected, MRI of the entire spine and cerebrospinal fluid sampling for cytology should also be considered.¹⁸

Biology

The tumorigenesis of pediatric low-grade gliomas is not well understood. One of the limiting factors has been failure to identify common molecular abnormalities in tumor specimens. Traditional karyotype analysis has been unrevealing in multiple studies, with chromosome 7 gain the only consistent finding, but present in a minority of tumors.²⁸⁻³² Conventional genomic hybridization and the first generation of single nucleotide polymorphism arrays also failed to identify consistent molecular abnormalities.^{33,34} More

recently, multiple groups have reported a small nonrandom duplication in the 7q34 region in the majority of pilocytic astrocytomas, identified using high-resolution single nucleotide polymorphism arrays.³⁵⁻³⁹ The 7q34 duplication involves a known oncogene, *BRAF*, and appears to result in upregulation of the RAS/RAF/MEK pathway (Figure 5). Studies looking at adult tumors have also shown that the RAS/RAF/MEK pathway is activated in gliomas.⁴⁰ Other biological mechanisms under investigation in low-grade gliomas include angiogenesis and the tumor microenvironment, telomere maintenance, and glioma-associated antigens.
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Pediatric low-grade gliomas do not harbor the same molecular abnormalities as their adult counterparts. For example, adult low-grade gliomas show frequent TP53 mutations, present in up to 88% of gemistocytic and 53% of diffuse fibrillary astrocytomas. TP53 mutations in children appear to be restricted to 5% to 10% of low-grade gliomas that undergo malignant transformation.^{44,45} Loss of heterozygosity of chromosomes 1p36 and 19q13, and in particular codeletion at both loci, is a favorable prognostic factor in adults with oligodendrogliomas (WHO grade 2) but has not been replicated in pediatric tumors.⁴⁶

Tumors in children with genetic susceptibility syndromes such as neurofibromatosis type 1 and tuberous sclerosis syndrome provide some insight into the signal transduction pathways involved in development of low-grade gliomas. The neurofibromatosis type 1 model shows that inactivation of the tumor suppressor neurofibromin results in upregulation of the RAS family of proteins, involved in a number of oncogenic signal transduction pathways in astrocytes.⁴⁷ Attempts to modulate this upregulation by the use of farnesyl transferase inhibitors have been largely unsuccessful. Mutations in 1 of 2 tumor suppressor genes, *TSC1* and *TSC2*, result in tuberous sclerosis syndrome. These 2 genes form an intracellular complex (called the tuberous sclerosis complex) that is also involved in the RAS pathway and contains a guanosine triphosphatase-activating property for a small G protein, Ras homologue enriched in brain. This homologue can directly activate mammalian target of rapamycin.⁴⁸ Interestingly, neurofibromatosis type 1 tumors have also been shown to have increased mammalian target of rapamycin expression, albeit by a different mechanism (Figure 5).⁴⁹ Inhibitors of mammalian target of rapamycin, such as rapamycin, are effective in causing regression of subependymal giant cell astrocytomas in patients with tuberous sclerosis syndrome⁵⁰ and trials are currently being considered for refractory low-grade gliomas in patients with neurofibromatosis type 1.

Treatment and Outcomes

Surgery remains the mainstay of therapy for pediatric low-grade gliomas, and gross total resection is the most consistent prognostic factor for prolonged progression-free and overall survival.^{26,51-55} As such, treatment decisions for children with low-grade gliomas can be stratified into 3 main groups as follows: (1) children with tumors that have been fully resected, (2) children with tumors that have undergone subtotal resection, and (3) children with tumors that have undergone biopsy only or no surgical approach is feasible. The latter group deserves special attention and usually involves tumors in the deep midline supratentorial region, optic pathway/hypothalamus, and brain stem.

Low-grade gliomas in the cerebellum and superficial cerebrum are most amenable to resection. Children in whom a gross total resection has been achieved, confirmed by surgeon's report and/or postoperative brain MRI within 24 to 48 hours of surgery, often do not need any further therapy. In several series, complete resection was associated with 10-year overall survival rates of 90% or greater and rare tumor recurrences.^{18,26,51,53,56,57} Therefore, postoperative management is directed toward close clinical and radiographic follow-up, especially if the tumor histology has concerning features. Reports are conflicting

because of the difficulty distinguishing the prognostic effect of histology from that of extent of resection, but tumor histology does appear to be an independent predictor of progression. Nonpilocytic, and specifically diffuse fibrillary, histology is more highly associated with progression, recurrence, and anaplastic transformation, although the latter is rare in children.^{8,26,51,54,55} Children have better survival than adults,⁵⁸⁻⁶¹ but the role of age as a prognostic factor within children is unclear.^{18,55,62-64}

The treatment decision for children with subtotal resection has been controversial. If the likelihood of functional impairment is minimal and the neurosurgeon thinks it is feasible, a repeat surgery can be attempted to remove the residual tumor.^{65,66} Others advocate a “wait and see approach” with follow-up brain MRI at 3- to 6-month intervals.⁶⁷⁻⁶⁹ Because the tumors tend to be indolent by nature, the decision for a repeat resection or adjuvant treatment can be postponed until there is either measurable progression by neuroimaging or clinical symptoms. This interval may last several years and some tumors may never progress. In 1 series looking at 128 children with subtotal resection of low-grade gliomas, 58% had no evidence of tumor progression 7 years from diagnosis.⁵⁷ A prospective intergroup study between Children's Cancer Group and Pediatric Oncology Group (prior to the creation of the Children's Oncology Group) of 660 children reported a 5-year progression-free survival of 45% to 65% for residual tumor of any size.⁶⁸ In addition, the value of postoperative adjuvant radiotherapy for residual low-grade glioma is unclear. Although it may improve progression-free survival,^{51,52,70} studies suggest this does not necessarily translate into improved overall survival, especially in children.^{51,57,58} Other studies show no advantage in progression-free survival with immediate irradiation.^{26,57} Thus, adjuvant therapy should be reserved for when tumors progress and re-resection is not feasible. The role of radiotherapy and chemotherapy in this setting will be discussed below.

Low-grade gliomas in the supratentorial midline areas are often not amenable to initial resection (Figure 4). For this cohort of children, observation until radiographic progression has been an accepted approach if there are minimal clinical symptoms. When progression occurs, adjuvant therapy should be considered. Historically, focal radiotherapy was used in this setting with standard doses of 45 to 54 Gy.⁷¹⁻⁷⁵ Although the data looking at the impact of radiotherapy on overall survival are conflicting, retrospective studies combining adults and children reveal improved survival associated with administration of conventional radiotherapy.^{59,76,77} Other studies focused on children reveal the value of radiotherapy, particularly for optic pathway/hypothalamic gliomas (10-year progression-free survival of 65%-90%).^{73,74,78,79} In addition, it appears that almost half of irradiated low-grade gliomas in children have at least a 25% reduction in tumor size.^{79,80} Despite these potential benefits, the risks of radiotherapy to the developing nervous system have been well documented.⁸¹⁻⁸⁶ Radiotherapy of low-grade gliomas of the cerebral hemisphere is associated with both hormone deficits and cognitive impairment.^{51,87,88} Treatment of optic pathway/hypothalamic gliomas can result in endocrine dysfunction,^{73,74,89} cerebrovascular disease,^{90,91} secondary malignant neoplasms,⁹² and neurocognitive deficits,^{20,79,93} particularly in young children.

To defer radiotherapy and its adverse effects, especially in infants and young children, chemotherapy is now the front-line adjuvant therapy for children with progressive low-grade gliomas. The combination of carboplatin and vincristine has been shown to result in tumor reduction or stable disease and a 3-year PFS of 68%.⁹⁴ Unfortunately, up to 40% of children experience hypersensitivity reactions with carboplatin, more common with increased number and frequency of doses.^{95,96} An alternative regimen of 6-thioguanine, procarbazine, lomustine (CCNU), dibromodulcitol, and vincristine has also been shown to be effective, with a 3-year PFS of 45%.⁹⁷ Because of side effects and drug availability, dibromodulcitol was not included in a randomized Children's Oncology Group protocol comparing

thioguanine/procarbazine/CCNU/vincristine (TPCV), with the combination of carboplatin and vincristine. Preliminary results of this study show a trend for improved event-free survival for the TPCV regimen, but this is not significant.⁹⁸

Initial management of optic pathway/hypothalamic gliomas is usually observation with serial MRI scans and ophthalmologic examinations.^{27,99} Most tumors remain indolent, and when they progress, it is often slow in pace.^{100,101} A concurrent diagnosis of neurofibromatosis type 1 appears to be associated with a favorable progression-free survival and lower likelihood of visual morbidity.^{10,63,102-104} Location is also important; tumors in the anterior visual pathway (optic nerves and chiasm) have a better visual outcome than tumors involving the hypothalamus and optic tracts/radiations.^{105,106} Treatment is reserved for patients with a documented decline in visual acuity or significant tumor progression on MRI scan with associated symptoms and signs. Rarely, treatment is advocated at diagnosis for patients with severe visual impairment, extensive tumor, and/or involvement of the posterior visual pathway. Surgical resection is rarely pursued because of the risk of further visual decline as well as the endocrinologic and cerebrovascular risks. Exceptions include unilateral optic nerve tumors with absent or severe impairment of vision and painful or disfiguring proptosis. Tumor debulking is sometimes undertaken for large chiasmal/hypothalamic tumors that cause hydrocephalus via obstruction of the third ventricle or exert mass effect on surrounding structures. Although radiotherapy for optic pathway/hypothalamic glioma is associated with excellent, long-term, progression-free survival, its use is rarely advocated because of the profound risk of unacceptable morbidity (as described above), particularly in patients with neurofibromatosis type 1. Therefore, chemotherapy, specifically carboplatin with vincristine, has become the mainstay of initial therapy for optic pathway/hypothalamic gliomas.²⁷ To date, this regimen is associated with the best progression-free survival, especially in patients with neurofibromatosis type 1, and allows radiotherapy to be deferred until patients are older.^{94,107} Other regimens, such as TPCV, are avoided in patients with neurofibromatosis type 1 because of their underlying leukemia predisposition¹⁰⁸⁻¹¹¹ and the risk of secondary leukemia associated with lomustine and procarbazine.¹¹²⁻¹¹⁴

Brain stem gliomas also constitute a unique category of low-grade gliomas, and specific location provides guidance for treatment. The primary treatment for dorsally exophytic brain stem gliomas is surgical (Figure 6A). However, aggressive surgery to achieve a gross total resection is not advocated, due to the risks associated with this approach and because the majority of patients remain progression free after near total resection.^{21,115} Tumors that recur can be controlled with repeat resection and/or radiotherapy. Chemotherapy is primarily used to delay radiotherapy in young patients. Cervicomedullary gliomas tend to grow slowly and are often managed conservatively with close observation for an extended period of time (Figure 6B). Evidence of radiographic or clinical progression should prompt referral to neurosurgery. Gross total resections are possible, but more often the tumor cannot be removed completely without unacceptable risk. For tumors that progress following surgery, adjuvant therapy is recommended. Five-year progression-free survival after initial surgical management exceeds 60%.^{22,116} Tectal gliomas also tend to be indolent and rarely cause functional impairment (Figure 6C). Progression occurs in 15% to 25% of tumors.¹¹⁷ Therefore, management is directed toward resolution of the hydrocephalus via shunting or endoscopic third ventriculostomy. Patients are then observed and biopsy and adjuvant therapy reserved for patients with radiographic and clinical progression.¹¹⁷⁻¹²⁰

Future Directions

Despite the excellent overall survival for these patients, the management of pediatric low-grade gliomas remains a challenge. Because a number of these tumors will be indolent, the

treatment must not be worse than the disease. The focus of therapy is to provide long-term survival with as few potential long-term sequelae as possible. Fortunately, complete resection is able to provide cure for many children. When this is not possible, front-line chemotherapy regimens, such as the combinations of carboplatin and vincristine, or TPCV can result in stable disease or even tumor regression for an extended period of time. Unfortunately, there are few, proven, effective, second-line chemotherapy regimens for refractory or recurrent low-grade gliomas. Cisplatin plus etoposide has been evaluated in a small group of children with unresectable low-grade gliomas with a reported 3-year progression-free survival of 78%;¹²¹ however, this approach should be taken cautiously given the risk of moderate-to-severe hearing loss and secondary leukemia with these agents.¹²²⁻¹²⁴ Weekly vinblastine is promising with initial studies indicating stable disease in the majority of children who were switched to it because of carboplatin sensitivity¹²⁵ or recurrent/refractory disease.¹²⁶ Temozolomide as a single agent has shown to be active in pediatric low-grade gliomas¹²⁷⁻¹²⁹ and is currently being explored in combination with other agents. More recently, the combination of bevacuzimab and irinotecan, a regimen used to treat high-grade gliomas, has been shown to result in objective durable responses.¹³⁰ Additionally, as we learn more about the signal transduction pathways that lead to pediatric low-grade glioma tumorigenesis, molecularly targeted drugs may also be developed as therapeutic options.

Radiotherapy should also be considered for refractory or recurrent tumors, especially in older children. In considering the use of this modality, careful consideration of the long-term morbidity of radiotherapy, particularly the potential neurocognitive effects, must be weighed. Multiple studies confirm the adverse impact of whole brain irradiation on intelligence quotient (IQ) in survivors of pediatric brain tumors.^{86,131,132} Focal radiotherapy to tumors of the cerebral hemispheres and optic pathway can also affect IQ^{79,85,93} and is associated with the child's need for special education.^{20,51} Other neurocognitive effects of radiotherapy to the brain include memory impairment and attention problems, and these effects are not limited to young children.¹³³⁻¹³⁵

Newer approaches to minimize the long-term morbidity of radiotherapy are being evaluated. Conformal radiotherapy with a tighter margin around the tumor achieved a 2-year actuarial event-free survival of 88% in 38 children with low-grade astrocytoma.¹³⁶ More sophisticated techniques, such as intensity-modulated, proton and stereotactic radiotherapy, have been developed that enable delivery of targeted therapy to the tumor while limiting exposure to surrounding normal brain tissue.¹³⁷⁻¹⁴⁰ One large study of 50 children with low-grade gliomas treated with stereotactic radiotherapy reported a 5-year progression-free survival of 82.5%.¹⁴⁰ Although the short-term progression-free survival for this and other studies appear equivalent to conventional radiotherapy,¹³⁷⁻¹⁴⁰ the long-term toxicity, particularly neurocognitive, has yet to be carefully evaluated.

Despite these advances in therapy, it is becoming increasingly recognized that a number of pediatric long-term survivors have significant adverse outcomes that are not always associated with radiotherapy. Cerebral hemisphere location, younger age at diagnosis, and hydrocephalus requiring a shunt have all been found to be significant predictors of lower cognitive performance on IQ scales.¹³⁵ Children with infratentorial tumors can have significant language, cognitive, behavioral, and social dysfunctions.¹⁴¹⁻¹⁴⁴ A combined analysis of Children's Cancer Group (CCG-9891) and Pediatric Oncology Group (POG-9130) data of 103 children with low-grade cerebellar astrocytomas treated with surgery alone revealed an elevated risk of cognitive and adaptive-behavioral impairment that was not associated with complications of the tumor or surgery.¹⁴⁵ Similar deficits were found in 93 children with extracerebellar tumors treated with surgery alone.¹⁴⁶

Therefore, even in the absence of radiotherapy, parents of children with low-grade gliomas must be properly counseled not only on the risk of tumor progression or recurrence but also the risk of neurocognitive and behavioral impairments. Physicians caring for children with low-grade glioma should consider early referral to neuropsychologists for baseline evaluations that may identify potential deficits in learning and processing, so that appropriate interventions can be put in place. Outcomes research needs to focus not just on the effects of radiotherapy and IQ but more on specific cognitive domains associated with the regions of brain affected by the tumor and treatments. In addition, a better understanding of the adaptive, social, and behavioral outcomes of survivors of pediatric low-grade glioma is essential.

Acknowledgments

The authors would like to thank Jane E. Minturn, MD, PhD, for her help with figure design.

References

1. Rozen WM, Joseph S, Lo PA. Spontaneous regression of low-grade gliomas in pediatric patients without neurofibromatosis. *Pediatr Neurosurg* 2008;44(4):324–328. [PubMed: 18504420]
2. Parsa CF, Hoyt CS, Lesser RL, et al. Spontaneous regression of optic gliomas: thirteen cases documented by serial neuroimaging. *Arch Ophthalmol* 2001;119(4):516–529. [PubMed: 11296017]
3. Louis, D. WHO Classification of Tumors of the CNS. 4th. World Health Organization; 2007.
4. Freeman CR, Farmer JP, Montes J. Low-grade astrocytomas in children: evolving management strategies. *Int J Radiat Oncol Biol Phys* 1998;41(5):979–987. [PubMed: 9719106]
5. Blaney, SM.; Kun, LE.; Hunter, J., et al. Tumors of the Central Nervous System. In: Pizzo, PA.; Poplack, DG., editors. *Principles and Practice of Pediatric Oncology*. 5th. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 786-864.
6. Pollack IF. The role of surgery in pediatric gliomas. *J Neurooncol* 1999;42(3):271–288. [PubMed: 10433110]
7. Gilles FH, Tavare CJ, Becker LE, et al. Pathologist interobserver variability of histologic features in childhood brain tumors: results from the CCG-945 study. *Pediatr Dev Pathol* 2008;11(2):108–117. [PubMed: 17990938]
8. Fouladi M, Hunt DL, Pollack IF, et al. Outcome of children with centrally reviewed low-grade gliomas treated with chemotherapy with or without radiotherapy on Children's Cancer Group high-grade glioma study CCG-945. *Cancer* 2003;98(6):1243–1252. [PubMed: 12973849]
9. Listernick R, Charrow J, Tomita T, Goldman S. Carboplatin therapy for optic pathway tumors in children with neurofibromatosis type-1. *J Neurooncol* 1999;45(2):185–190. [PubMed: 10778734]
10. Czyzyk E, Jozwiak S, Roszkowski M, Schwartz RA. Optic pathway gliomas in children with and without neurofibromatosis 1. *J Child Neurol* 2003;18(7):471–478. [PubMed: 12940652]
11. Listernick R, Charrow J, Greenwald M, Mets M. Natural history of optic pathway tumors in children with neurofibromatosis type 1: a longitudinal study. *J Pediatr* 1994;125(1):63–66. [PubMed: 8021787]
12. Listernick R, Charrow J, Greenwald MJ, Esterly NB. Optic gliomas in children with neurofibromatosis type 1. *J Pediatr* 1989;114(5):788–792. [PubMed: 2497236]
13. Blazo MA, Lewis RA, Chintagumpala MM, Frazier M, McCluggage C, Plon SE. Outcomes of systematic screening for optic pathway tumors in children with neurofibromatosis type 1. *Am J Med Genet A* 2004;127A(3):224–229. [PubMed: 15150770]
14. Central Brain Tumor Registry of the United States. Table 8: Number of childhood cases by major histology groupings, histology and age at diagnosis, CBTRUS, 2000-2004, 16 states combined. CBTRUS 2005-2006 Statistical Report Tables. 2000-2004 (Years of Data Collected). [October 2008]. from <http://www.cbtrus.org>
15. Central Brain Tumor Registry of the United States. CBTRUS 2007-2008 Primary brain tumors in the United States statistical report, 2000-2004 (years of data collected). [November 2008]. from <http://www.cbtrus.org>

16. Hayostek CJ, Shaw EG, Scheithauer B, et al. Astrocytomas of the cerebellum. A comparative clinicopathologic study of pilocytic and diffuse astrocytomas. *Cancer* 1993;72(3):856–869. [PubMed: 8334640]
17. Fernandez C, Figarella-Branger D, Girard N, et al. Pilocytic astrocytomas in children: prognostic factors—a retrospective study of 80 cases. *Neurosurgery* 2003;53(3):544–553. discussion 554–545. [PubMed: 12943571]
18. Gajjar A, Sanford RA, Heideman R, et al. Low-grade astrocytoma: a decade of experience at St. Jude Children's Research Hospital. *J Clin Oncol* 1997;15(8):2792–2799. [PubMed: 9256121]
19. Hoffman HJ, Humphreys RP, Drake JM, et al. Optic pathway/hypothalamic gliomas: a dilemma in management. *Pediatr Neurosurg* 1993;19(4):186–195. [PubMed: 8329303]
20. Sutton LN, Molloy PT, Sernyak H, et al. Long-term outcome of hypothalamic/chiasmatic astrocytomas in children treated with conservative surgery. *J Neurosurg* 1995;83(4):583–589. [PubMed: 7674005]
21. Khatib ZA, Heideman RL, Kovnar EH, et al. Predominance of pilocytic histology in dorsally exophytic brain stem tumors. *Pediatr Neurosurg* 1994;20(1):2–10. [PubMed: 8142279]
22. Weiner HL, Freed D, Woo HH, Rezai AR, Kim R, Epstein FJ. Intra-axial tumors of the cervicomedullary junction: surgical results and long-term outcome. *Pediatr Neurosurg* 1997;27(1):12–18. [PubMed: 9486831]
23. Tihan T, Fisher PG, Kepner JL, et al. Pediatric astrocytomas with monomorphous pilomyxoid features and a less favorable outcome. *J Neuropathol Exp Neurol* 1999;58(10):1061–1068. [PubMed: 10515229]
24. Komotar RJ, Burger PC, Carson BS, et al. Pilocytic and pilomyxoid hypothalamic/chiasmatic astrocytomas. *Neurosurgery* 2004;54(1):72–79. discussion 79–80. [PubMed: 14683543]
25. Johnson JHJ, Hariharan S, Berman J, et al. Clinical outcome of pediatric gangliomas: ninety-nine cases over 20 years. *Pediatr Neurosurg* 1997;27(4):203–207. [PubMed: 9577974]
26. Fisher PG, Tihan T, Goldthwaite PT, et al. Outcome analysis of childhood low-grade astrocytomas. *Pediatr Blood Cancer* 2008;51(2):245–250. [PubMed: 18386785]
27. Listernick R, Ferner RE, Liu GT, Gutmann DH. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. *Ann Neurol* 2007;61(3):189–198. [PubMed: 17387725]
28. White FV, Anthony DC, Yunis EJ, Tarbell NJ, Scott RM, Schofield DE. Nonrandom chromosomal gains in pilocytic astrocytomas of childhood. *Hum Pathol* 1995;26(9):979–986. [PubMed: 7672798]
29. Bhattacharjee MB, Armstrong DD, Vogel H, Cooley LD. Cytogenetic analysis of 120 primary pediatric brain tumors and literature review. *Cancer Genet Cytogenet* 1997;97(1):39–53. [PubMed: 9242217]
30. Bigner SH, McLendon RE, Fuchs H, McKeever PE, Friedman HS. Chromosomal characteristics of childhood brain tumors. *Cancer Genet Cytogenet* 1997;97(2):125–134. [PubMed: 9283596]
31. Roberts P, Chumas PD, Picton S, Bridges L, Livingstone JH, Sheridan E. A review of the cytogenetics of 58 pediatric brain tumors. *Cancer Genet Cytogenet* 2001;131(1):1–12. [PubMed: 11734311]
32. Orr LC, Fleitz J, McGavran L, Wyatt-Ashmead J, Handler M, Foreman NK. Cytogenetics in pediatric low-grade astrocytomas. *Med Pediatr Oncol* 2002;38(3):173–177. [PubMed: 11836716]
33. Jones DT, Ichimura K, Liu L, Pearson DM, Plant K, Collins VP. Genomic analysis of pilocytic astrocytomas at 0.97 Mb resolution shows an increasing tendency toward chromosomal copy number change with age. *J Neuropathol Exp Neurol* 2006;65(11):1049–1058. [PubMed: 17086101]
34. Wong KK, Tsang YT, Chang YM, et al. Genome-wide allelic imbalance analysis of pediatric gliomas by single nucleotide polymorphic allele array. *Cancer Res* 2006;66(23):11172–11178. [PubMed: 17145861]
35. Sievert A, Jackson E, Gai X, et al. Duplication of 7q34 in pediatric low-grade astrocytomas detected by high-density single nucleotide polymorphism-based genotype arrays results in a novel BRAF fusion gene. *Brain Pathol* 2009;19(3):449–458. [PubMed: 19016743]

36. Jones DT, Kocialkowski S, Liu L, et al. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. *Cancer Res* 2008;68(21):8673–8677. [PubMed: 18974108]
37. Pfister S, Janzarik WG, Remke M, et al. BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. *J Clin Invest* 2008;118(5):1739–1749. [PubMed: 18398503]
38. Deshmukh H, Yeh TH, Yu J, et al. High-resolution, dual-platform aCGH analysis reveals frequent HIPK2 amplification and increased expression in pilocytic astrocytomas. *Oncogene* 2008;27(34):4745–4751. [PubMed: 18408760]
39. Bar EE, Lin A, Tihan T, Burger PC, Eberhart CG. Frequent gains at chromosome 7q34 involving BRAF in pilocytic astrocytoma. *J Neuropathol Exp Neurol* 2008;67(9):878–887. [PubMed: 18716556]
40. Jeuken J, van den Broecke C, Gijzen S, Boots-Sprenger S, Wesseling P. RAS/RAF pathway activation in gliomas: the result of copy number gains rather than activating mutations. *Acta Neuropathol* 2007;114(2):121–133. [PubMed: 17588166]
41. Bartels U, Hawkins C, Jing M, et al. Vascularity and angiogenesis as predictors of growth in optic pathway/hypothalamic gliomas. *J Neurosurg* 2006;104(5 suppl):314–320. [PubMed: 16848088]
42. Tabori U, Vukovic B, Zielenska M, et al. The role of telomere maintenance in the spontaneous growth arrest of pediatric low-grade gliomas. *Neoplasia* 2006;8(2):136–142. [PubMed: 16611406]
43. Okada H, Low KL, Kohanbash G, McDonald HA, Hamilton RL, Pollack IF. Expression of glioma-associated antigens in pediatric brain stem and non-brain stem gliomas. *J Neurooncol* 2008;88(3):245–250. [PubMed: 18324354]
44. Felix C, Slavic I, Dunn M, et al. p53 gene mutations in pediatric brain tumors. *Med Pediatr Oncol* 1995;25(6):431–436. [PubMed: 7565304]
45. Broniscer A, Baker SJ, West AN, et al. Clinical and molecular characteristics of malignant transformation of low-grade glioma in children. *J Clin Oncol* 2007;25(6):682–689. [PubMed: 17308273]
46. Mariani L, Deiana G, Vassella E, et al. Loss of heterozygosity 1p36 and 19q13 is a prognostic factor for overall survival in patients with diffuse WHO grade 2 gliomas treated without chemotherapy. *J Clin Oncol* 2006;24(29):4758–4763. [PubMed: 16966689]
47. Gutmann DH. Using neurofibromatosis-1 to better understand and treat pediatric low-grade glioma. *J Child Neurol* 2008;23(10):1186–1194. [PubMed: 18952585]
48. Jozwiak J, Jozwiak S, Wlodarski P. Possible mechanisms of disease development in tuberous sclerosis. *Lancet Oncol* 2008;9(1):73–79. [PubMed: 18177819]
49. Dasgupta B, Yi Y, Chen DY, Weber JD, Gutmann DH. Proteomic analysis reveals hyperactivation of the mammalian target of rapamycin pathway in neurofibromatosis 1-associated human and mouse brain tumors. *Cancer Res* 2005;65(7):2755–2760. [PubMed: 15805275]
50. Franz DN, Leonard J, Tudor C, et al. Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. *Ann Neurol* 2006;59(3):490–498. [PubMed: 16453317]
51. Pollack IF, Claassen D, al-Shboul Q, Janosky JE, Deutsch M. Low-grade gliomas of the cerebral hemispheres in children: an analysis of 71 cases. *J Neurosurg* 1995;82(4):536–547. [PubMed: 7897512]
52. Griffin TW, Beaufait D, Blasko JC. Cystic cerebellar astrocytomas in childhood. *Cancer* 1979;44(1):276–280. [PubMed: 455252]
53. Pencolet P, Maixner W, Sainte-Rose C, et al. Benign cerebellar astrocytomas in children. *J Neurosurg* 1999;90(2):265–273. [PubMed: 9950497]
54. Smoots DW, Geyer JR, Lieberman DM, Berger MS. Predicting disease progression in childhood cerebellar astrocytoma. *Childs Nerv Syst* 1998;14(11):636–648. [PubMed: 9840364]
55. Desai KI, Nadkarni TD, Muzumdar DP, Goel A. Prognostic factors for cerebellar astrocytomas in children: a study of 102 cases. *Pediatr Neurosurg* 2001;35(6):311–317. [PubMed: 11786699]
56. Sutton LN, Cnaan A, Klatt L, et al. Postoperative surveillance imaging in children with cerebellar astrocytomas. *J Neurosurg* 1996;84(5):721–725. [PubMed: 8622142]

57. Fisher BJ, Leighton CC, Vujovic O, Macdonald DR, Stitt L. Results of a policy of surveillance alone after surgical management of pediatric low grade gliomas. *Int J Radiat Oncol Biol Phys* 2001;51(3):704–710. [PubMed: 11597812]
58. Kandil A, Khafaga Y, ElHusseiny G, Allam A, Jamshed A, Schultz H. Low-grade astrocytoma—a retrospective analysis of 102 patients. *Acta Oncol* 1999;38(8):1051–1056. [PubMed: 10665762]
59. Laws ER Jr, Taylor WF, Clifton MB, Okazaki H. Neurosurgical management of low-grade astrocytoma of the cerebral hemispheres. *J Neurosurg* 1984;61(4):665–673. [PubMed: 6470776]
60. North CA, North RB, Epstein JA, Piantadosi S, Wharam MD. Low-grade cerebral astrocytomas. Survival and quality of life after radiation therapy. *Cancer* 1990;66(1):6–14. [PubMed: 2354409]
61. Lote K, Egeland T, Hager B, et al. Survival, prognostic factors, and therapeutic efficacy in low-grade glioma: a retrospective study in 379 patients. *J Clin Oncol* 1997;15(9):3129–3140. [PubMed: 9294476]
62. Ahn Y, Cho BK, Kim SK, et al. Optic pathway glioma: outcome and prognostic factors in a surgical series. *Childs Nerv Syst* 2006;22(9):1136–1142. [PubMed: 16628460]
63. Opocher E, Kremer LC, Da Dalt L, et al. Prognostic factors for progression of childhood optic pathway glioma: a systematic review. *Eur J Cancer* 2006;42(12):1807–1816. [PubMed: 16809032]
64. Palma L, Guidetti B. Cystic pilocytic astrocytomas of the cerebral hemispheres. Surgical experience with 51 cases and long-term results. *J Neurosurg* 1985;62(6):811–815. [PubMed: 3998829]
65. Khan RB, Sanford RA, Kun LE, Thompson SJ. Morbidity of second-look surgery in pediatric central nervous system tumors. *Pediatr Neurosurg* 2001;35(5):225–229. [PubMed: 11741114]
66. Palma L, Celli P, Mariottini A. Long-term follow-up of childhood cerebellar astrocytomas after incomplete resection with particular reference to arrested growth or spontaneous tumour regression. *Acta Neurochir (Wien)* 2004;146(6):581–588. discussion 588. [PubMed: 15168226]
67. Benesch M, Eder HG, Sovinz P, et al. Residual or recurrent cerebellar low-grade glioma in children after tumor resection: is retreatment needed? A single center experience from 1983 to 2003. *Pediatr Neurosurg* 2006;42(3):159–164. [PubMed: 16636617]
68. Shaw EG, Wisoff JH. Prospective clinical trials of intracranial low-grade glioma in adults and children. *Neuro Oncol* 2003;5(3):153–160. [PubMed: 12816721]
69. Saunders DE, Phipps KP, Wade AM, Hayward RD. Surveillance imaging strategies following surgery and/or radiotherapy for childhood cerebellar low-grade astrocytoma. *J Neurosurg* 2005;102(2 suppl):172–178. [PubMed: 16156227]
70. Garcia DM, Marks JE, Latifi HR, Kliefoth AB. Childhood cerebellar astrocytomas: is there a role for postoperative irradiation? *Int J Radiat Oncol Biol Phys* 1990;18(4):815–818. [PubMed: 2323970]
71. Kortmann RD, Timmermann B, Taylor RE, et al. Current and future strategies in radiotherapy of childhood low-grade glioma of the brain. Part I: treatment modalities of radiation therapy. *Strahlenther Onkol* 2003;179(8):509–520. [PubMed: 14509949]
72. Flickinger JC, Torres C, Deutsch M. Management of low-grade gliomas of the optic nerve and chiasm. *Cancer* 1988;61(4):635–642. [PubMed: 3338030]
73. Grabenbauer GG, Schuchardt U, Buchfelder M, et al. Radiation therapy of optico-hypothalamic gliomas (OHG)—radiographic response, vision and late toxicity. *Radiother Oncol* 2000;54(3):239–245. [PubMed: 10738082]
74. Horwich A, Bloom HJ. Optic gliomas: radiation therapy and prognosis. *Int J Radiat Oncol Biol Phys* 1985;11(6):1067–1079. [PubMed: 3997589]
75. Karim AB, Maat B, Hatlevoll R, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. *Int J Radiat Oncol Biol Phys* 1996;36(3):549–556. [PubMed: 8948338]
76. Shibamoto Y, Kitakabu Y, Takahashi M, et al. Supratentorial low-grade astrocytoma. Correlation of computed tomography findings with effect of radiation therapy and prognostic variables. *Cancer* 1993;72(1):190–195. [PubMed: 8508405]
77. Leibel SA, Sheline GE, Wara WM, Boldrey EB, Nielsen SL. The role of radiation therapy in the treatment of astrocytomas. *Cancer* 1975;35(6):1551–1557. [PubMed: 1148989]

78. Jenkin D, Angyalfi S, Becker L, et al. Optic glioma in children: surveillance, resection, or irradiation? *Int J Radiat Oncol Biol Phys* 1993;25(2):215–225. [PubMed: 8420869]
79. Cappelli C, Grill J, Raquin M, et al. Long-term follow up of 69 patients treated for optic pathway tumours before the chemotherapy era. *Arch Dis Child* 1998;79(4):334–338. [PubMed: 9875044]
80. Fisher BJ, Bauman GS, Leighton CE, Stitt L, Cairncross JG, Macdonald DR. Low-grade gliomas in children: tumor volume response to radiation. *Neurosurg Focus* 1998;4(4):e5. [PubMed: 17168505]
81. Meadows AT, Gordon J, Massari DJ, Littman P, Fergusson J, Moss K. Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukaemia treated with cranial irradiation. *Lancet* 1981;2(8254):1015–1018. [PubMed: 6118478]
82. Muirhead SE, Hsu E, Grimard L, Keene D. Endocrine complications of pediatric brain tumors: case series and literature review. *Pediatr Neurol* 2002;27(3):165–170. [PubMed: 12393125]
83. Silber JH, Radcliffe J, Peckham V, et al. Whole-brain irradiation and decline in intelligence: the influence of dose and age on IQ score. *J Clin Oncol* 1992;10(9):1390–1396. [PubMed: 1517781]
84. Halberg FE, Kramer JH, Moore IM, Wara WM, Matthay KK, Ablin AR. Prophylactic cranial irradiation dose effects on late cognitive function in children treated for acute lymphoblastic leukemia. *Int J Radiat Oncol Biol Phys* 1992;22(1):13–16. [PubMed: 1727109]
85. Reimers TS, Ehrenfels S, Mortensen EL, et al. Cognitive deficits in long-term survivors of childhood brain tumors: identification of predictive factors. *Med Pediatr Oncol* 2003;40(1):26–34. [PubMed: 12426683]
86. Packer RJ, Sutton LN, Atkins TE, et al. A prospective study of cognitive function in children receiving whole-brain radiotherapy and chemotherapy: 2-year results. *J Neurosurg* 1989;70(5):707–713. [PubMed: 2709111]
87. West CG, Gattamaneni R, Blair V. Radiotherapy in the treatment of low-grade astrocytomas. I. A survival analysis. *Childs Nerv Syst* 1995;11(8):438–442. [PubMed: 7585678]
88. Chadderton RD, West CG, Schuller S, Quirke DC, Gattamaneni R, Taylor R. Radiotherapy in the treatment of low-grade astrocytomas. II. The physical and cognitive sequelae. *Childs Nerv Syst* 1995;11(8):443–448. [PubMed: 7585679]
89. Pierce SM, Barnes PD, Loeffler JS, McGinn C, Tarbell NJ. Definitive radiation therapy in the management of symptomatic patients with optic glioma. Survival and long-term effects. *Cancer* 1990;65(1):45–52. [PubMed: 2104571]
90. Grill J, Couanet D, Cappelli C, et al. Radiation-induced cerebral vasculopathy in children with neurofibromatosis and optic pathway glioma. *Ann Neurol* 1999;45(3):393–396. [PubMed: 10072056]
91. Kestle JR, Hoffman HJ, Mock AR. Moyamoya phenomenon after radiation for optic glioma. *J Neurosurg* 1993;79(1):32–35. [PubMed: 8315466]
92. Sharif S, Ferner R, Birch JM, et al. Second primary tumors in neurofibromatosis 1 patients treated for optic glioma: substantial risks after radiotherapy. *J Clin Oncol* 2006;24(16):2570–2575. [PubMed: 16735710]
93. Lacaze E, Kieffer V, Streri A, et al. Neuropsychological outcome in children with optic pathway tumours when first-line treatment is chemotherapy. *Br J Cancer* 2003;89(11):2038–2044. [PubMed: 14647135]
94. Packer RJ, Ater J, Allen J, et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. *J Neurosurg* 1997;86(5):747–754. [PubMed: 9126887]
95. Yu DY, Dahl GV, Shames RS, Fisher PG. Weekly dosing of carboplatin increases risk of allergy in children. *J Pediatr Hematol Oncol* 2001;23(6):349–352. [PubMed: 11563768]
96. Lafay-Cousin L, Sung L, Carret AS, et al. Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma: a Canadian Pediatric Brain Tumor Consortium experience. *Cancer* 2008;112(4):892–899. [PubMed: 18098210]
97. Prados MD, Edwards MS, Rabbitt J, Lamborn K, Davis RL, Levin VA. Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen. *J Neurooncol* 1997;32(3):235–241. [PubMed: 9049885]
98. Ater J, Holmes E, Zhou T, et al. Abstracts from the thirteenth international symposium on pediatric neuro-oncology: results of COG protocol A9952—a randomized phase 3 study of two

- chemotherapy regimens for incompletely resected low-grade glioma in young children. *Neuro Oncol* 2008;10(3):451.
99. Astrup J. Natural history and clinical management of optic pathway glioma. *Br J Neurosurg* 2003;17(4):327–335. [PubMed: 14579898]
 100. King A, Listernick R, Charrow J, Piersall L, Gutmann DH. Optic pathway gliomas in neurofibromatosis type 1: the effect of presenting symptoms on outcome. *Am J Med Genet A* 2003;122A(2):95–99. [PubMed: 12955759]
 101. Thiagalingam S, Flaherty M, Billson F, North K. Neurofibromatosis type 1 and optic pathway gliomas: follow-up of 54 patients. *Ophthalmology* 2004;111(3):568–577. [PubMed: 15019338]
 102. Deliganis AV, Geyer JR, Berger MS. Prognostic significance of type 1 neurofibromatosis (von Recklinghausen Disease) in childhood optic glioma. *Neurosurgery* 1996;38(6):1114–1118. discussion 1118–1119. [PubMed: 8727140]
 103. Chateil JF, Soussotte C, Pedespan JM, Brun M, Le Manh C, Diard F. MRI and clinical differences between optic pathway tumours in children with and without neurofibromatosis. *Br J Radiol* 2001;74(877):24–31. [PubMed: 11227773]
 104. Kornreich L, Blaser S, Schwarz M, et al. Optic pathway glioma: correlation of imaging findings with the presence of neurofibromatosis. *AJNR Am J Neuroradiol* 2001;22(10):1963–1969. [PubMed: 11733333]
 105. Tow SL, Chandela S, Miller NR, Avellino AM. Long-term outcome in children with gliomas of the anterior visual pathway. *Pediatr Neurol* 2003;28(4):262–270. [PubMed: 12849878]
 106. Balcer LJ, Liu GT, Heller G, et al. Visual loss in children with neurofibromatosis type 1 and optic pathway gliomas: relation to tumor location by magnetic resonance imaging. *Am J Ophthalmol* 2001;131(4):442–445. [PubMed: 11292406]
 107. Ater J, Mazewski C, Roberts W, et al. ISPNO 2006 abstract—Phase 3 randomized study of two chemotherapy regimens for treatment of progressive low-grade glioma in young children: preliminary report from the children's oncology group protocol A9952. *Neuro Oncol* 2006;9(2):169–221.
 108. Maris JM, Wiersma SR, Mahgoub N, et al. Monosomy 7 myelodysplastic syndrome and other second malignant neoplasms in children with neurofibromatosis type 1. *Cancer* 1997;79(7):1438–1446. [PubMed: 9083167]
 109. Stiller CA, Chessells JM, Fitchett M. Neurofibromatosis and childhood leukaemia/lymphoma: a population-based UKCCSG study. *Br J Cancer* 1994;70(5):969–972. [PubMed: 7947106]
 110. Matsui I, Tanimura M, Kobayashi N, Sawada T, Nagahara N, Akatsuka J. Neurofibromatosis type 1 and childhood cancer. *Cancer* 1993;72(9):2746–2754. [PubMed: 8402499]
 111. Shannon KM, O'Connell P, Martin GA, et al. Loss of the normal NF1 allele from the bone marrow of children with type 1 neurofibromatosis and malignant myeloid disorders. *N Engl J Med* 1994;330(9):597–601. [PubMed: 8302341]
 112. Leone G, Mele L, Pulsoni A, Equitani F, Pagano L. The incidence of secondary leukemias. *Haematologica* 1999;84(10):937–945. [PubMed: 10509043]
 113. Devereux S, Selassie TG, Vaughan Hudson G, Vaughan Hudson B, Linch DC. Leukaemia complicating treatment for Hodgkin's disease: the experience of the British National Lymphoma Investigation. *BMJ* 1990;301(6760):1077–1080. [PubMed: 2249071]
 114. Perry JR, Brown MT, Gockerman JP. Acute leukemia following treatment of malignant glioma. *J Neurooncol* 1998;40(1):39–46. [PubMed: 9874184]
 115. Pollack IF, Hoffman HJ, Humphreys RP, Becker L. The long-term outcome after surgical treatment of dorsally exophytic brain-stem gliomas. *J Neurosurg* 1993;78(6):859–863. [PubMed: 8487066]
 116. Robertson PL, Allen JC, Abbott IR, Miller DC, Fidel J, Epstein FJ. Cervicomedullary tumors in children: a distinct subset of brainstem gliomas. *Neurology* 1994;44(10):1798–1803. [PubMed: 7936224]
 117. Stark AM, Fritsch MJ, Claviez A, Dorner L, Mehdorn HM. Management of tectal glioma in childhood. *Pediatr Neurol* 2005;33(1):33–38. [PubMed: 15876519]

118. Pollack IF, Pang D, Albright AL. The long-term outcome in children with late-onset aqueductal stenosis resulting from benign intrinsic tectal tumors. *J Neurosurg* 1994;80(4):681–688. [PubMed: 8151347]
119. Freeman CR, Farmer JP. Pediatric brain stem gliomas: a review. *Int J Radiat Oncol Biol Phys* 1998;40(2):265–271. [PubMed: 9457808]
120. Bowers DC, Georgiades C, Aronson LJ, et al. Tectal gliomas: natural history of an indolent lesion in pediatric patients. *Pediatr Neurosurg* 2000;32(1):24–29. [PubMed: 10765135]
121. 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(20):4209–4216. [PubMed: 12377964]
122. Bertolini P, Lassalle M, Mercier G, et al. Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. *J Pediatr Hematol Oncol* 2004;26(10):649–655. [PubMed: 15454836]
123. Lewis MJ, Dubois SG, Fligor B, Li X, Goorin A, Grier HE. Ototoxicity in children treated for osteosarcoma. *Pediatr Blood Cancer* 2009;52(3):387–391. [PubMed: 19061216]
124. Le Deley MC, Vassal G, Taibi A, Shamsaldin A, Leblanc T, Hartmann O. High cumulative rate of secondary leukemia after continuous etoposide treatment for solid tumors in children and young adults. *Pediatr Blood Cancer* 2005;45(1):25–31. [PubMed: 15795880]
125. Lafay-Cousin L, Holm S, Qaddoumi I, et al. Weekly vinblastine in pediatric low-grade glioma patients with carboplatin allergic reaction. *Cancer* 2005;103(12):2636–2642. [PubMed: 15861409]
126. Bouffet E, Jakacki R, Goldman S, et al. Abstracts from the thirteenth international symposium on pediatric neuro-oncology: phase II study of weekly vinblastine in recurrent/refractory pediatric low-grade gliomas. *Neuro Oncol* 2008;10(3):450.
127. Kuo DJ, Weiner HL, Wisoff J, Miller DC, Knopp EA, Finlay JL. Temozolomide is active in childhood, progressive, unresectable, low-grade gliomas. *J Pediatr Hematol Oncol* 2003;25(5):372–378. [PubMed: 12759623]
128. Khaw SL, Coleman LT, Downie PA, Heath JA, Ashley DM. Temozolomide in pediatric low-grade glioma. *Pediatr Blood Cancer* 2007;49(6):808–811. [PubMed: 17588234]
129. Gururangan S, Fisher MJ, Allen JC, et al. Temozolomide in children with progressive low-grade glioma. *Neuro Oncol* 2007;9(2):161–168. [PubMed: 17347491]
130. Packer RJ, Jakacki R, Horn M, et al. Objective response of multiply recurrent pediatric low-grade gliomas to bevacizumab and irinotecan. *Pediatr Blood Cancer* 2009;52(7):791–795. [PubMed: 19165892]
131. Mulhern RK, Kepner JL, Thomas PR, Armstrong FD, Friedman HS, Kun LE. Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. *J Clin Oncol* 1998;16(5):1723–1728. [PubMed: 9586884]
132. Spiegler BJ, Bouffet E, Greenberg ML, Rutka JT, Mabbott DJ. Change in neurocognitive functioning after treatment with cranial radiation in childhood. *J Clin Oncol* 2004;22(4):706–713. [PubMed: 14966095]
133. Roman DD, Sperduto PW. Neuropsychological effects of cranial radiation: current knowledge and future directions. *Int J Radiat Oncol Biol Phys* 1995;31(4):983–998. [PubMed: 7860415]
134. Armstrong CL, Hunter JV, Ledakis GE, et al. Late cognitive and radiographic changes related to radiotherapy: initial prospective findings. *Neurology* 2002;59(1):40–48. [PubMed: 12105305]
135. Reimers TS, Mortensen EL, Schmiegelow K. Memory deficits in long-term survivors of childhood brain tumors may primarily reflect general cognitive dysfunctions. *Pediatr Blood Cancer* 2007;48(2):205–212. [PubMed: 16526054]
136. Merchant TE, Zhu Y, Thompson SJ, Sontag MR, Heideman RL, Kun LE. Preliminary results from a Phase II trial of conformal radiation therapy for pediatric patients with localized low-grade astrocytoma and ependymoma. *Int J Radiat Oncol Biol Phys* 2002;52(2):325–332. [PubMed: 11872277]
137. Hug EB, Muentner MW, Archambeau JO, et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. *Strahlenther Onkol* 2002;178(1):10–17. [PubMed: 11977386]

138. Landy HJ, Schwade JG, Houdek PV, Markoe AM, Feun L. Long-term follow-up of gliomas treated with fractionated stereotactic irradiation. *Acta Neurochir Suppl* 1994;62:67–71. [PubMed: 7717140]
139. Combs SE, Schulz-Ertner D, Moschos D, Thilmann C, Huber PE, Debus J. Fractionated stereotactic radiotherapy of optic pathway gliomas: tolerance and long-term outcome. *Int J Radiat Oncol Biol Phys* 2005;62(3):814–819. [PubMed: 15936565]
140. Marcus KJ, Goumnerova L, Billett AL, et al. Stereotactic radiotherapy for localized low-grade gliomas in children: final results of a prospective trial. *Int J Radiat Oncol Biol Phys* 2005;61(2):374–379. [PubMed: 15667955]
141. Aarsen FK, Paquier PF, Reddingius RE, et al. Functional outcome after low-grade astrocytoma treatment in childhood. *Cancer* 2006;106(2):396–402. [PubMed: 16353203]
142. Turkel SB, Shu Chen L, Nelson MD, et al. Case series: acute mood symptoms associated with posterior fossa lesions in children. *J Neuropsychiatry Clin Neurosci* 2004;16(4):443–445. [PubMed: 15616170]
143. Pollack IF. Posterior fossa syndrome. *Int Rev Neurobiol* 1997;41:411–432. [PubMed: 9378600]
144. Levisohn L, Cronin-Golomb A, Schmahmann JD. Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. *Brain* 2000;123(pt 5):1041–1050. [PubMed: 10775548]
145. Beebe DW, Ris MD, Armstrong FD, et al. Cognitive and adaptive outcome in low-grade pediatric cerebellar astrocytomas: evidence of diminished cognitive and adaptive functioning in National Collaborative Research Studies (CCG 9891/POG 9130). *J Clin Oncol* 2005;23(22):5198–5204. [PubMed: 16051961]
146. Ris MD, Beebe DW, Armstrong FD, et al. Cognitive and adaptive outcome in extracerebellar low-grade brain tumors in children: a report from the Children's Oncology Group. *J Clin Oncol* 2008;26(29):4765–4770. [PubMed: 18779602]

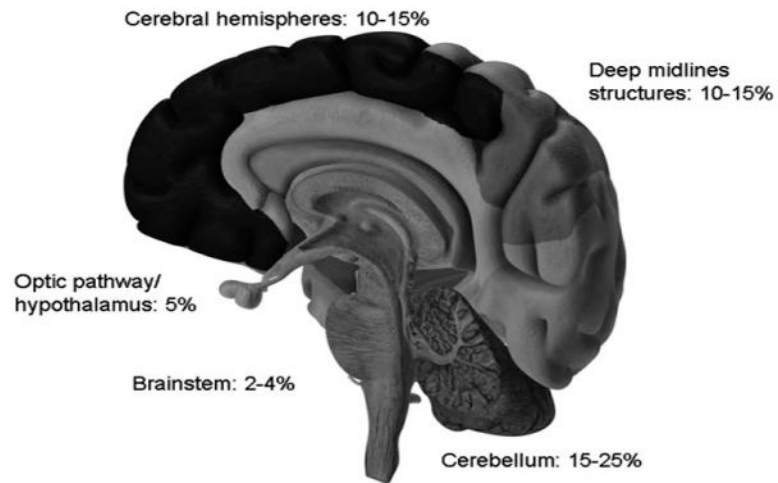


Figure 1. Distribution by location of pediatric low-grade gliomas. Shown are the approximate frequencies of low-grade gliomas compared with all pediatric central nervous system tumors.

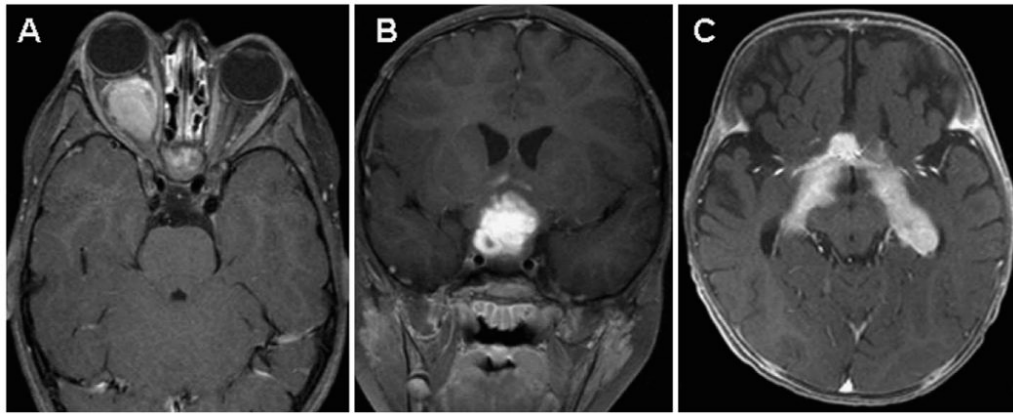


Figure 2. Postgadolinium magnetic resonance (MR) images of (A) optic nerve glioma (axial), (B) optic chiasm/hypothalamic glioma (coronal), and (C) optic tract/radiation tumor (axial).

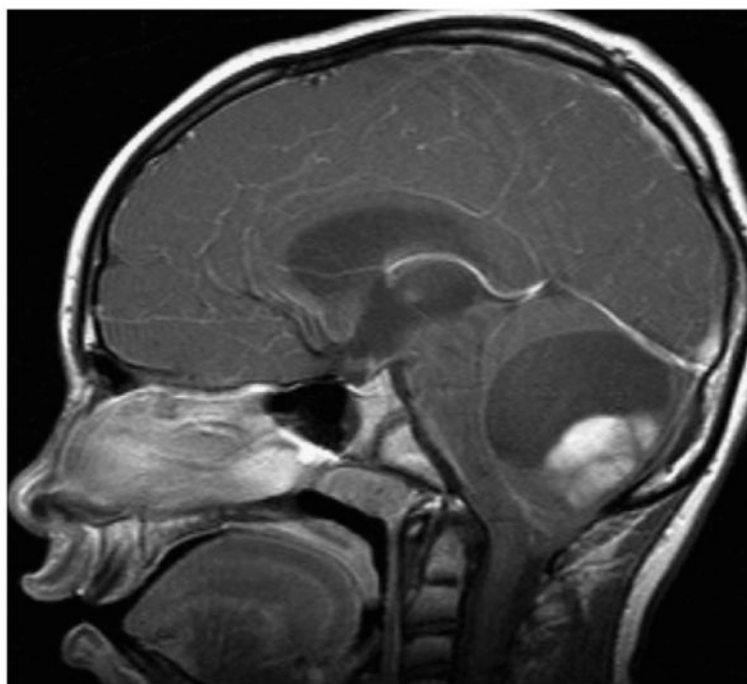


Figure 3. Sagittal postgadolinium magnetic resonance image of a pilocytic astrocytoma of the cerebellum.

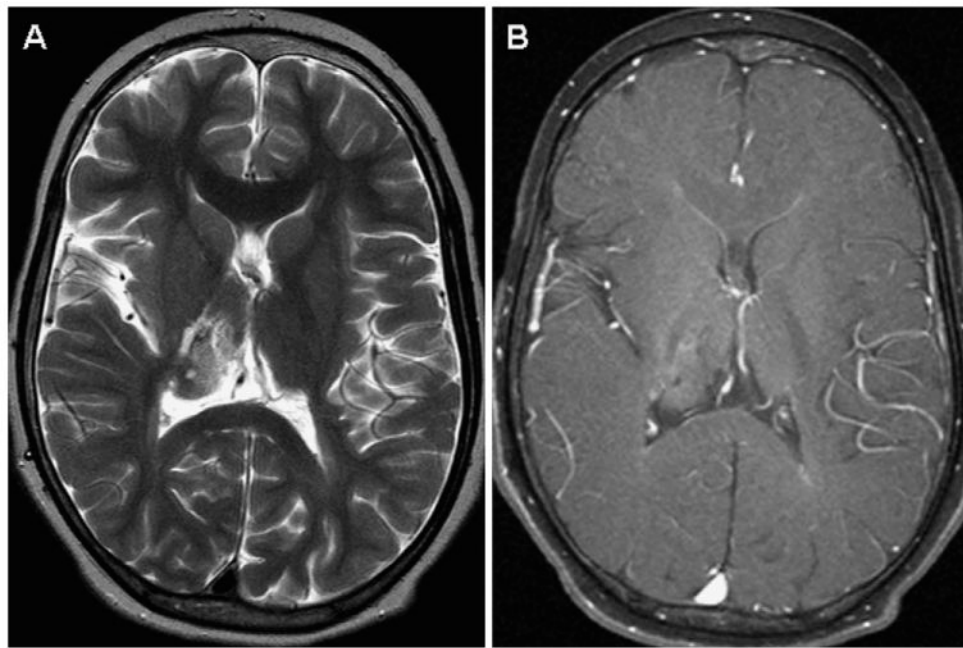


Figure 4. Axial magnetic resonance images of a right thalamic fibrillary astrocytoma status postbiopsy. A, Heterogeneous and hyperintense on T2-weighted images. B, Minimal enhancement on postgadolinium imaging. The patient had left hemiparesis. Because of its location, the tumor was treated with chemotherapy.

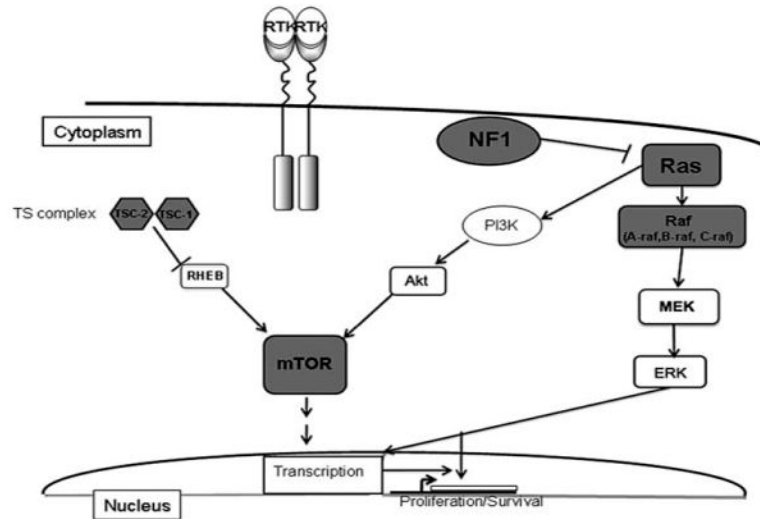


Figure 5. Pediatric low-grade glioma tumorigenesis. *BRAF*, an oncogene implicated in malignant melanoma and other carcinomas, may be involved in the tumorigenesis of sporadic low-grade gliomas. A *BRAF* fusion gene with increased kinase activity upregulates the downstream MEK/ERK pathway and results in increased transcriptional activity and cellular proliferation. Low-grade gliomas in children with susceptibility syndromes also reveal some of the pathways leading to tumorigenesis; inactivation of the tumor suppressor neurofibromin in neurofibromatosis type 1 results in RAS activation and upregulation of the RAS/RAF/MEK pathway; in tuberous sclerosis, mutation in 1 of 2 tumor suppressor genes, *TSC1* or *TSC2*, can lead to direct activation of the mammalian target of rapamycin pathway. Neurofibromatosis type 1 tumors also reveal increased mammalian target of rapamycin expression, albeit by different mechanisms.

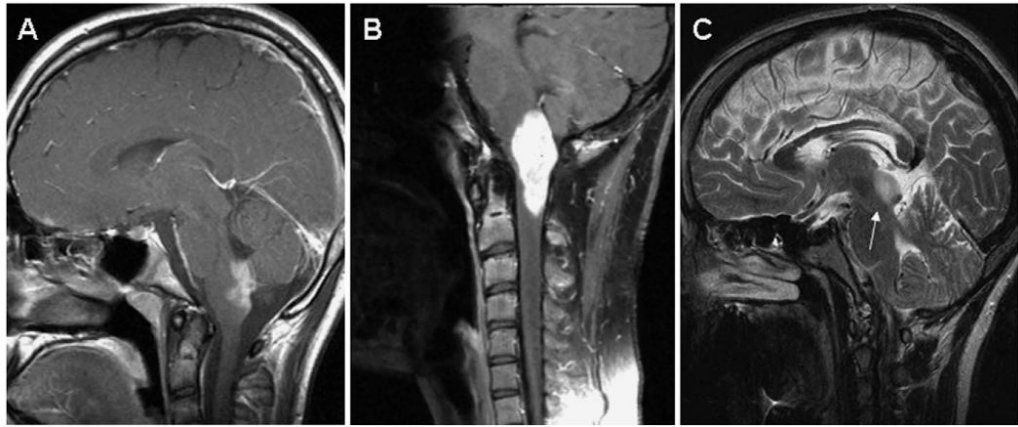


Figure 6. Magnetic resonance (MR) images of low-grade gliomas of the brain stem. A, Postgadolinium sagittal image of a dorsally exophytic glioma. B, Postgadolinium sagittal image of a cervicomedullary glioma. C, T2-weighted sagittal image of a tectal glioma.

Table 1**Key Histological Features of Pediatric Low-Grade Gliomas^a**

Astrocytic tumors
Grade 1
Pilocytic astrocytoma—biphasic pattern, rosenthal fibers, microcysts, eosinophilic granular bodies
Subependymal giant cell astrocytoma—large gangliod astrocytes
Grade 2
Diffuse astrocytoma (fibrillary, ^b gemistocytic, or protoplasmic)—nuclear atypia with very rare or absent mitoses, microcysts containing mucinous fluid
Pilomyxoid astrocytoma—prominent mucoid matrix, angiocentric arrangement of monomorphous, bipolar tumor cells, rosenthal fibers, eosinophilic granular bodies
Pleomorphic xanthoastrocytoma—pleomorphic and lipidized cells, surrounding reticulin network, eosinophilic granular bodies
Oligodendroglial tumors
Grade 2
Oligodendroglial—monomorphic cells, uniform round nuclei, perinuclear halos, microcalcifications, mucoid/cystic degeneration, dense network of branching capillaries
Neuronal and mixed neuronal-glia tumors
Grade 1
Ganglioglioma—combination of neoplastic, mature ganglion cells, and neoplastic glial cells
Gangliocytoma—irregular groups of large, multipolar neurons with dysplastic features
Desmoplastic infantile ganglioglioma—prominent desmoplastic stroma, poorly differentiated neuroepithelial cells, deeply basophilic nuclei
Dysembryoplastic neuroepithelial tumor—hallmark “specific glioneuronal element”

^aWHO *Classification of Tumors of the CNS*. 3rd ed.³

^bMost diffuse astrocytomas in children are fibrillary.