Gliomas in Children

Jane E. Minturn, MD, PhD [1,2]
Michael J. Fisher, MD [1,2,*]

Address
*,[1]Division of Oncology and Center for Childhood Cancer Research,
Children's Hospital of Philadelphia, 3501 Civic Center Boulevard, CTRB 4028,
Philadelphia, PA 19104, USA
Email: fisherm@email.chop.edu
[2]Department of Pediatrics, Perelman School of Medicine at the University
of Pennsylvania, Philadelphia, PA, USA

Opinion statement

Gliomas are the most common brain tumor in children and represent nearly 50 % of all pediatric central nervous system (CNS) tumors. They are a heterogeneous group of diseases, ranging from highly malignant and frequently fatal to histologically benign and curable by surgery alone. A uniform treatment approach to these tumors is not practical, due to their histological and biological heterogeneity. Low-grade gliomas (LGGs) are best treated with maximally safe surgical resection, generally achievable for hemispheric or cerebellar locations. Patients with deep midline, optic pathway/hypothalamic, and brain stem locations should undergo subtotal resection or biopsy only. If a complete resection is not feasible, subtotal resection followed by adjuvant chemotherapy or radiotherapy is the standard approach; however, observation alone with serial neuroimaging is used in some asymptomatic, surgically inaccessible lesions. Chemotherapy is used first-line in cases of residual or progressive disease, to avoid or delay radiation therapy and its associated side effects. Regimens demonstrating objective responses and increased progression free survival (PFS) include carboplatin and vincristine (CV), thioguanine/procarbazine/CCNU/vincristine (TPCV), or weekly vinblastine. High-grade gliomas (HGGs) are less common in children than in adults, though are similar in their aggressive clinical behavior, resistance to therapy, and dismal outcomes. There is not a single "standard of care" therapy for non-metastatic HGGs, but generally accepted is an aggressive attempt at a complete surgical resection, followed by multimodality therapy with focal radiation and chemotherapy. The use of temozolomide (TMZ) during and following radiotherapy is common, though it appeared not to improve the outcome in a cooperative group clinical trial when compared to an historical control cohort. The angiogenesis inhibitor bevacizumab, used alone or in combination with irinotecan, is also commonly used as maintenance therapy after radiation. Current trials are prospectively comparing TMZ to newer agents (vorinostat, bevacizumab) in a randomized phase II trial. Brainstem gliomas are a unique category of childhood gliomas. Approximately 80 % of childhood brainstem gliomas arise within the pons as diffuse intrinsic pontine gliomas (DIPG). When biopsied, these are usually HGGs and carry

a dismal prognosis. Standard therapy is focal radiation (54–58 Gy), preferably on a clinical trial testing concurrent chemotherapy or biologic agent. No standard chemotherapy agent has impacted survival. The remaining 20 % of brainstem gliomas are low-grade, arise in the midbrain, dorsal medulla, or cervicomedullary junction, and are indolent in nature with a much better prognosis. Improvement in the outcome of all childhood gliomas will require increased knowledge of the underlying biology of these tumors, in order to treat with more biologically based and precise therapies.

Introduction

Tumors of the central nervous system (CNS) are the leading cause of cancer-related morbidity and mortality, and are the most common solid malignancy in childhood. Past therapeutic approaches have relied on data from adult glioma biology and clinical trials; however, recent molecular studies of childhood gliomas reveal distinct differences that should translate into pediatric-specific glioma therapies. While there has been substantial improvement in our treatment approaches, including proton radiation therapy, minimally invasive surgical approaches, and molecularly guided targeted agents, the backbone of treatment remains surgery, radiotherapy and cytotoxic chemotherapy.

Low-grade gliomas (LGG) are the most common childhood brain tumor, representing over 30 % of all primary brain tumors in pediatric patients [1]. There is histologic heterogeneity even within the LGG subclass of gliomas. Most commonly seen in children are pilocytic astrocytomas (PAs) and diffuse (fibrillary) astrocytomas, but oligodendroglioma, ganglioglioma, pilomyxoid astrocytomas, and pleomorphic xanthoastrocytomas are also among the LGGs of childhood. These are currently treated in a similar fashion, though they have varying prognoses, and recently discovered molecular distinctions may soon have an impact on therapeutic decisions. Pilocytic astrocytomas are World Health Organization (WHO) grade I tumors that arise sporadically or in children with neurofibromatosis type 1 (NF1). In sporadic PAs, tandem duplications of the *BRAF* kinase gene have been identified as the most frequent genetic alteration, creating a novel fusion protein (KIAA1549:BRAF) with constitutively active BRAF activity [2, 3]. PAs arising in children with NF1 have allelic loss of the *NF1* gene, resulting in loss of *NF1* protein (neurofibromin) and hyperactivated signaling through the RAS pathway [4, 5]. The common end result of both mutations is increased mitogen-activated protein kinase (MAPK) pathway activity, promoting tumorigenesis and serving as tractable targets for anti-glioma therapy.

High-grade gliomas (HGG) comprise 8–12 % of pediatric brain tumors. Unfortunately, there has been little improvement in survival outcomes for this tumor in over 20 years of prospective randomized trials [6, 7•, 8]. Histologically, childhood anaplastic astrocytoma (AA, WHO grade III) and glioblastoma multiforme (GBM, WHO grade IV) appear similar to their adult counterparts, but increasingly, molecular distinctions between childhood and adult HGGs are being defined [9–13]. Recent analyses of DNA copy number, gene expression signatures, and sequencing of childhood HGGs revealed differences in expression of platelet-derived growth factor receptor (*PDGFRA*, overexpressed) and epidermal growth factor receptor (*EGFR*, repressed), as well as mutations in chromatin remodeling pathways regulating gene expression that clearly distinguish childhood from adult HGG [9, 13, 14] and have implications for future targeted therapies. Interestingly, infant HGGs (younger than 3 years old) have different genetic profiles, which may account for their better prognosis [15••, 16]. Expression of the DNA-repair enzyme, MGMT, a known prognostic factor in adult HGGs treated with temozolomide (TMZ), is also strongly correlated with outcome in pediatric HGG [7•, 17–19].

Brainstem gliomas account for 10–20 % of pediatric CNS tumors, and the majority are of the diffuse intrinsic pontine gliomas (DIPG) subtype. The latter have a peak age of onset in middle childhood (6–7 years) and are rare in adults. DIPG has a dismal prognosis, with a median survival of less than 1 year and fewer than 20 % of patients alive at 2 years. There have been minimal treatment advances over the past decades [20, Class III]. Improvements are hampered by the limited knowledge of DIPG biology, as historically this was a diagnosis made radiographically. Recently, there has been increased interest in performing stereotactic biopsy of DIPG [21]. This has been dem-

onstrated to be safe and feasible by experienced pediatric neurosurgeons at high-volume academic centers (primarily in Europe) [22]. The ability to acquire tissue prior to therapy has yielded valuable data toward improving our understanding of the biology of DIPG and to help define genetic targets with therapeutic relevance [14, 15••, 21, 23, 24].

The ongoing challenges in treating childhood gliomas are currently being addressed by advances in diagnostic imaging, radiotherapy, and surgical techniques; however, future advances and improvements in outcomes are dependent on increasing participation in cooperative group studies in which tissue submission and biological correlates are incorporated into trial design.

Treatment

Diagnostic procedures

- Magnetic resonance imaging (MRI) is the modality of choice for the diagnostic evaluation of childhood gliomas. It is important in disease staging, preoperative navigation, radiation planning, and in monitoring treatment response. LGGs are typically hypo-intense on T1-weighted, and hyper-intense on T2-weighted imaging. Pilocytic astrocytomas have a characteristic well-circumscribed cystic component with a contrast-enhancing mural nodule, while diffuse fibrillary astrocytomas have little enhancement and often have indistinct borders. HGGs tend to have a more heterogeneous appearance and are hypo-/iso-intense on T1 weighted imaging, hyper-intense on T2 sequences, and often show contrast enhancement with or without evidence of necrosis. Advanced imaging of gliomas can aid in preoperative diagnosis and may be prognostic. In comparison to LGGs, HGGs have increased choline peaks and elevated choline:N-acetylaspartate ratio on MR spectroscopy (MRS). They also show restricted diffusion and increased blood flow on diffusion/perfusion-weighted sequences [25, 26]. DIPGs have a classic MRI appearance of an expansile lesion centered in the pons that is hypo-/iso-intense on T1-weighted, hyper-intense on T2-weighted, and variably enhancing on post-contrast imaging. Specific MRI sequences, including multi-voxel MRS and dynamic susceptibility contrast (DSC) MRI of DIPG can predict short or long survival interval from diagnosis, though have yet to impact treatment decisions [27]. Metastatic disease is not uncommon for HGG; therefore, imaging of the entire neuraxis is indicated at diagnosis. In contrast, low grade and brainstem gliomas rarely spread, so spine imaging is not typically indicated unless multi-focal disease is seen in the brain [28].

Interventional procedures

Surgery

Surgery plays a critical role in the management of childhood gliomas by establishing a tissue diagnosis, decreasing compression of surrounding structures to alleviate symptoms and relieving obstruction of cerebrospinal fluid (CSF) flow. Surgery alone is essentially curative for LGGs

when a complete resection can be achieved [29, Class III]. In addition to extent of resection, tumor grade is a prognostic factor for overall survival (OS) and progression free survival (PFS) [30, Class I]. Many LGGs, however, are located in deep midline structures and inaccessible for a complete resection. The surgical management of these tumors has greatly benefitted from new, minimally invasive neurosurgical techniques that include stereotactic biopsy for diagnosis and endoscopic third ventriculostomy for CSF diversion [31, 32]. Once diagnosis has been established appropriate adjuvant therapy can be delivered. The degree of surgical resection for HGGs is a critical component of therapy and predictive of improved event free survival. Specifically, patients achieving a gross total resection have a significantly better outcome than those with residual tumor [7•, Class III, 33, Class I]. The role for surgery in DIPGs is evolving. In the recent past, the diagnosis was made solely on imaging, and neuro-oncologists and radiation oncologists were comfortable treating without tissue. However, as survival has not improved despite multiple clinical trials, there is a push to biopsy tumors in order to provide tissue for biology, target identification, and treatment stratification [15••, 22].

Complications	General neurosurgical complications include the risk of bleeding, infection, stroke, brain edema, and permanent neurological dysfunction. Depending on location, additional risks of vision loss, posterior fossa syndrome (mutism, oropharyngeal dyspraxia, emotional lability, ataxia, truncal hypotonia) [34], cerebral salt wasting, transient diabetes insipidus, and syndrome of inappropriate antidiuretic hormone secretion (SIADH) exist.
Special points	The one exception in which surgery does not play much of a role is optic pathway/hypothalamic gliomas in patients with NF-1. These tumors have classic imaging features, a fairly reliable clinical course, and can be treated without a tissue diagnosis [35].

Radiation

Radiation therapy for childhood gliomas is a critical treatment modality for HGG and DIPG, but should be used judiciously in LGG, and requires a careful weighing of its risks to the developing brain. As long-term survival among children with CNS malignancies increases, the emergence of late morbidity related to radiotherapy is more apparent (see Survivorship and Surveillance) [36]. New developments in radiation treatment planning and techniques, including proton radiation therapy, should significantly decrease these late effects by limiting dose to developing normal tissues [37, 38]. In general, focal radiation with 54 Gy is standard dosing for glioma (boosted to 59.4 Gy for residual/unresectable HGG). The treatment margin beyond the resection cavity varies from 1 cm (for LGG) to 2 cm (for HGG) for treating marginal microscopic residual disease. The use of radiotherapy for LGG is discouraged upfront, and chemotherapy is often used to delay or avoid radiation, taking into account the age of the child, prior therapy, location of the tumor, and the presence of NF-1 [39–41, Class III]. When needed however, it is an effective therapy and results in long-term disease control [42]. Radiation therapy for HGG even after a complete surgical resection is standard

practice and part of a multimodality treatment plan in children older than 3 years. The addition of chemotherapy to radiation has been accepted practice for many years; however, a "standard regimen" has not been identified and studies of new drug combinations are ongoing. In infants with HGG, chemotherapy alone is frequently employed to defer radiation until tumor progression or an older age is reached [43, Class III, 44]. For DIPG, radiation is the only therapeutic modality consistently demonstrating clinical and radiographic response, though without long-term disease control. Approximately 70 % of children have neurologic improvement and 40–60 % objective tumor response after conventional radiotherapy (54 Gy over 30 daily 180 cGy fractions) [20, Class III]. Higher dose, hyperfractionated (twice daily doses) RT to 64.8–78 Gy or hypofractionated (larger daily dose given over fewer days) has not demonstrated improved survival (reviewed in [45]). Additional radiation-based therapies, such as concurrent chemo-radiotherapy and radiation sensitizers, have no proven benefit [46–48, Class III], with the past 30 years of published clinical trials consistently reporting 2-year OS across studies of < 25 % [20, 45, Class III].

| Complications | Acute complications of radiation include nausea, vomiting, radiation dermatitis, alopecia, and fatigue/somnolence syndrome. Long-term late effects include radiation necrosis, hearing loss, bone hypoplasia, stroke, second malignant neoplasms, endocrine dysfunction and neurocognitive effects (highlighted in Survivorship and Surveillance section). |

| Special points | The advantage of proton radiation therapy over standard techniques is based on the physical characteristics of the proton particle most notably the sharp dose fall-off beyond the target (tumor) along the particle path, substantially sparing normal adjacent tissue from unnecessary radiation exposure [37, 38]. |

Pharmacologic treatment

Chemotherapy

Chemotherapy is the first line of treatment for LGGs that are not amenable to surgical resection without high-risk of neurologic morbidity or for progressive or symptomatic tumors after sub-total resection or observation; especially in younger children or children with NF-1, who are at higher risk for radiation induced morbidity. Typical locations for such LGGs include the deep midline supratentorial region and optic pathway/hypothalamus. In a significant proportion of these cases, chemotherapy will delay or eliminate the need for radiation therapy. The combination of carboplatin and vincristine (CV) is widely used as front-line therapy for LGG, and has demonstrated disease control with objective responses and prolonged PFS [41, Class I]. An alternative regimen of thioguanine, procarbazine, lomustine, and vincristine (TPCV) [49] is also active against LGG, and when compared to CV in a randomized trial, may have superior long-term event-free survival [50••, Class I]. Cisplatin and etoposide has been used as front-line therapy in some European countries with very high response and long-term disease control [51, Class III]; however, many investigators are reluctant to use this combination because of the risk of high-frequency hearing loss, though this

may be avoided with lower dosed regimens [52]. Single-agent weekly vinblastine, initially used as an alternative for patients with allergy to carboplatin [53, Class III], has reasonable response rates in patients who have progressed on first-line therapy and should be considered in advance of radiation for LGGs that have failed CV or TPCV [54, Class III]. Other retrieval regimens for recurrent LGG under study include bevacizumab in combination with irinotecan [55], and TMZ, though no randomized controlled trials have been performed to compare regimens [56]. In the treatment of HGG, early cooperative group trials demonstrated that the addition of chemotherapy (prednisone, lomustine, vincristine) to involved field radiation therapy improved survival over radiation alone [57, Class I]. Unfortunately, a "standard" chemotherapy regimen has not been clearly identified and studies comparing to historical controls may be inaccurate given advances in neuropathology [7•, Class III, 58]. There is a statistically significant improvement in survival with the addition of TMZ to radiation in adult HGGs [59, Class III]; however, the survival benefit of TMZ in childhood HGG was less clear in a recent, pediatric, non-randomized phase II trial [7•, Class III]. Temozolomide is still used as a backbone for HGG therapy; however, it is being studied in combination with targeted agents including bevacizumab, a VEGF inhibitor, and veliparib, a poly(ADP-ribose) polymerase (PARP) inhibitor; both protein biomarkers expressed in aggressive tumors and associated with resistance to therapy [24, 60]. Bevacizumab and irinotecan as a maintenance therapy with or without TMZ is also used frequently in pediatric HGG, though the only controlled studies have been in the relapsed setting, where it has had minimal efficacy compared to published trials in adults [61–64, Class III]. The use of high-dose chemotherapy with autologous stem cell support has been used in HGG to avoid radiation in the very young [43, Class III] and as a salvage regimen for recurrent HGG [65, Class III]. There is evidence of response, but it is unclear if this will translate into prolonged improved survival [44]. The current Children's Oncology Group (COG) clinical trial for newly diagnosed HGG is a phase II randomized "pick the winner" approach, comparing two experimental chemoradiotherapy arms (suberoylanilide hydroxamic acid (SAHA) + radiation versus bevacizumab + radiation) to the standard arm of temozolomide given with local radiation. This is followed by maintenance chemotherapy with bevacizumab and temozolomide given to all subjects. This approach will evaluate whether we can improve upon TMZ+ radiation as the "de facto standard" chemoradiotherapy regimen for HGG. The use of conventional chemotherapy for DIPG is currently not indicated, and multiple clinical trials investigating dose, schedule, and delivery of agents to intensify or modulate the effects of local irradiation have not resulted in improved outcomes. Recent published efforts have focused on the use of radiosensitizers, such as motexafin-gadolinium [66], and rationally chosen molecularly targeted agents against PDGFR, RAS signaling, EGFR and vascular growth factors, but none of these clinical trials has demonstrated clinical benefit over radiation therapy alone [67–70, Class III]. A newer approach involves creating cancer vaccines to induce systemic immunity against tumor-specific or tumor-enriched antigens. Currently enrolling,

	early phase, pediatric DIPG trials utilizing this strategy use peptide-based vaccines against pooled glioma associated antigens [71] or against the mutated EGFR (EGFRvIII), known to be expressed in DIPG [72].
Complications	Nausea, vomiting, hair loss, myelosuppression, immunosuppression with infection risk, allergic reactions (especially with carboplatin), ototoxicity (cisplatin), and risk of secondary malignancy with alkylators (procarbazine, lomustine, temozolomide), which may be higher in patients with NF-1.
Special points	Given the dismal prognosis for both HGG and DIPG despite several decades of clinical trials, the importance of obtaining tissue specimens for biological studies to identify new targets and molecularly stratify patients is imperative.

Emerging therapies

Newer approaches to glioma treatment are needed for children with re-current/refractory LGGs, or newly diagnosed HGG and DIPG, and rely on understanding and identifying biologically relevant targets to allow ratio-nale, tumor-specific therapy. Tumor targets currently under investigation in the field of glioma biology include cell-signaling pathway receptors, effec-tors, and regulators of gene expression. In treating recurrent LGG, co-tar-geting mTOR and EGFR, both of which are highly expressed in LGG, resulted in prolonged stable disease in preliminary studies [73]. Oncogenic BRAF signaling, defined by the novel KIAA1549:BRAF fusion gene in LGG [3] provides multiple targets for inhibition, including BRAF and MEK (agents currently in clinical trial), Biologically relevant targets currently under pre-clinical or early clinical investigation in HGG and/or DIPG in-clude EGFR (Erlotinib), PDGFRb/VEGFR/c-kit (sunitinib), c-MET (crizoti-nib), PDGFR (crenolanib) [15••, 24], and aurora kinase B [23].

Pediatric considerations

Survivorship and surveillance

Neurological deficits

- Children with gliomas are at risk for neurological deficits as a conse-quence of multiple factors, including the presence of tumor in a specific location, prolonged hydrocephalus, surgical resection, and the effects of therapy. These may include sensory or motor deficits, vision loss, diffi-culty with speech and coordination. Physical, occupational, and speech therapies should be coordinated and tailored to individual needs.

Neurocognitive deficits

- As treatment for pediatric gliomas advances and becomes more tar-geted and precise, the risk of damage to the developing normal brain should be lessened. However, studies of long term survivors of childhood glioma, including a population of children treated from 1985 to 1992 for HGG (median follow-up of 15.1 years), demonstrate impaired neuropsychological functioning, including low average mean intellectual function, and below average or impaired executive func-tioning, visual learning and memory, and psychomotor processing speed [74]. In this study, independent risk factors for lower neuropsychological

functioning included midline or infratentorial tumor location, female sex, and young age at treatment [74]. Similarly, several studies of children with cerebral hemisphere and midline (optic pathway/hypothalamic) LGGs treated with radiotherapy demonstrate significant long-term intellectual impairment [75–77]. Patients who underwent radiotherapy at very young ages (median age 4 years in one study, mean age 5.7 years in another) had the most significant decline in cognitive function [75, 77, Class IV]. A recent study examining the intellectual outcomes in children with LGG (without NF-1) treated first-line with chemotherapy and subsequent radiotherapy at relapse, demonstrated normal range neurocognitive testing in those who avoided radiotherapy at a young age [78]; highlighting the important approach of deferring or delaying radiotherapy in the youngest children. Neuropsychologists are a critical part of the treatment team, and prospective longitudinal testing is essential in order to better understand the impact of disease and treatment on neurocognitive development, and to timely target remedial interventions to improve outcomes. Systematic longitudinal assessment of the neurocognitive functioning of survivors of childhood gliomas should be a standard part of long-term follow-up care [36].

Neurovascular events

- Cranial radiation increases the risk of vascular injury including large-vessel stenosis, atherosclerosis, and vascular insufficiency. The rate of neurovascular events (stroke or transient ischemic attack) is 100-fold higher in children radiated for brain tumors compared with the general pediatric population [79]; the highest risk for stroke occurs in patients who receive radiation to the circle of Willis, common for inoperable midline gliomas [79]. The occurrence of stroke continues to increase over time among brain tumor survivors, with a mean time of 13.9 years from brain tumor diagnosis to "late occurring stroke" [80]. This wide range of events emphasizes the need for long-term follow-up in a multi-disciplinary survivorship program, and justifies the importance of continued neuro-imaging surveillance [81].

Endocrine dysfunction

- Precocious or delayed growth or pubertal development may be a presenting sign of a hypothalamic glioma. Anterior pituitary dysfunction resulting in deficits in thyroid, growth, cortisol, and sex hormones are frequent after cranial radiation. Concerns that growth hormone replacement may increase the risk of tumor growth or recurrence are not borne out by large studies (reviewed in [82]).

Disclosure

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Dolecek TA, Propp JM, Stroup NE, et al. Central brain tumor registry of the United States. 2012. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005–2009. Neuro Oncol. 2012;14(sup 5):v1–49.

2. 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):8673–7.

3. Sievert AJ, Jackson EM, 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):449–58.

4. Kluwe L, Hagel C, Tatagiba M, et al. Loss of NF1 alleles distinguish sporadic from NF1-associated pilocytic astrocytomas. J Neuropathol Exp Neurol. 2001;60(9):917–20.

5. Lau N, Feldkamp MM, Roncari L, et al. Loss of neurofibromin is associated with activation of RAS/MAPK and PI3-K/AKT signaling in a neurofibromatosis 1 astrocytoma. J Neuropathol Exp Neurol. 2000;59(9):759–67.

6. Broniscer A. Past, present, and future strategies in the treatment of high-grade glioma in children. Cancer Invest. 2006;24(1):77–81.

7.• Cohen KJ, Pollack IF, Zhou T, et al. Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. Neuro Oncol. 2011;13(3):317–23.
This non-randomized trial examined the use of temozolomide with radiation for newly diagnosed HGG. Major findings of this trial include that temozolomide may not be as efficacious in childhood HGG as it is in adult HGG and underscores the differences. It also highlighted the perils of using historical controls.

8. Fangusaro J. Pediatric high grade glioma: a review and update on tumor clinical characteristics and biology. Front Oncol. 2012;2:105.

9. Paugh BS, Qu C, Jones C, et al. Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. J Clin Oncol. 2010;28(18):3061–8.

10. Pollack IF, Hamilton RL, James CD, et al. Rarity of PTEN deletions and EGFR amplification in malignant gliomas of childhood: results from the Children's Cancer Group 945 cohort. J Neurosurg. 2006;105(5 Suppl):418–24.

11. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008;321(5897):1807–12.

12. Liang ML, Ma J, Ho M, et al. Tyrosine kinase expression in pediatric high grade astrocytoma. J Neurooncol. 2008;87(3):247–53.

13. Schwartzentruber J, Korshunov A, Liu XY, et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature. 2012;482(7384):226–31.

14. Wu G, Broniscer A, McEachron TA, et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. Nat Genet. 2012;44(3):251–3.

15.•• Paugh BS, Broniscer A, Qu C, et al. Genome-wide analyses identify recurrent amplifications of receptor tyrosine kinases and cell-cycle regulatory genes in diffuse intrinsic pontine glioma. J Clin Oncol. 2011;29(30):3999–4006.
This paper on genome-wide studies in a large cohort of DIPG samples identifies relevant genomic alterations likely important in tumorigenesis and highlights the distinct biology of DIPG compared to HGG. This study also raises awareness of the importance of collecting tumor tissue for DIPG.

16. Sanders RP, Kocak M, Burger PC, et al. High-grade astrocytoma in very young children. Pediatr Blood Cancer. 2007;49(7):888–93.

17. Pollack IF, Hamilton RL, Sobol RW, et al. O6-methylguanine-DNA methyltransferase expression strongly correlates with outcome in childhood malignant gliomas: results from the CCG-945 Cohort. J Clin Oncol. 2006;24(21):3431–7.

18. Pollack IF, Hamilton RL, Sobol RW, et al. Mismatch repair deficiency is an uncommon mechanism of alkylator resistance in pediatric malignant gliomas: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2010;55(6):1066–71.

19. Esteller M, Garcia-Foncillas J, Andion E, et al. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. N Engl J Med. 2000;343(19):1350–4.

20. Jansen MH, van Vuurden DG, Vandertop WP, et al. Diffuse intrinsic pontine gliomas: a systematic update on clinical trials and biology. Cancer Treat Rev. 2012;38(1):27–35.

21. Grill J, Puget S, Andreiuolo F, et al. Critical oncogenic mutations in newly diagnosed pediatric diffuse in-

trinsic pontine glioma. Pediatr Blood Cancer. 2012;58(4):489–91.

22. Roujeau T, Machado G, Garnett MR, et al. Stereotactic biopsy of diffuse pontine lesions in children. J Neurosurg. 2007;107(1 Suppl):1–4.

23. Buczkowicz P, Zarghooni M, Bartels U, et al. Aurora Kinase B. Is a Potential Therapeutic Target in Pediatric Diffuse Intrinsic Pontine Glioma. Brain Pathol. 2012.

24. Zarghooni M, Bartels U, Lee E, et al. Whole-genome profiling of pediatric diffuse intrinsic pontine gliomas highlights platelet-derived growth factor receptor alpha and poly (ADP-ribose) polymerase as potential therapeutic targets. J Clin Oncol. 2010;28(8):1337–44.

25. Morita N, Harada M, Otsuka H, et al. Clinical application of MR spectroscopy and imaging of brain tumor. Magn Reson Med Sci. 2010;9(4):167–75.

26. Lev MH, Ozsunar Y, Henson JW, et al. Glial tumor grading and outcome prediction using dynamic spin-echo MR susceptibility mapping compared with conventional contrast-enhanced MR: confounding effect of elevated rCBV of oligodendrogliomas [corrected]. AJNR Am J Neuroradiol. 2004;25(2):214–21.

27. Hipp SJ, Steffen-Smith E, Hammoud D, et al. Predicting outcome of children with diffuse intrinsic pontine gliomas using multiparametric imaging. Neuro Oncol. 2011;13(8):904–9.

28. Perilongo G, Garre ML, Giangaspero F. Low-grade gliomas and leptomeningeal dissemination: a poorly understood phenomenon. Childs Nerv Syst. 2003;19(4):197–203.

29. Sutton LN, Cnaan A, Klatt L, et al. Postoperative surveillance imaging in children with cerebellar astrocytomas. J Neurosurg. 1996;84(5):721–5.

30. Shaw EG, Wisoff JH. Prospective clinical trials of intracranial low-grade glioma in adults and children. Neuro Oncol. 2003;5(3):153–60.

31. Selvapandian S. Endoscopic management of thalamic gliomas. Minim Invasive Neurosurg. 2006;49(4):194–6.

32. Li KW, Roonprapunt C, Lawson HC, et al. Endoscopic third ventriculostomy for hydrocephalus associated with tectal gliomas. Neurosurg Focus. 2005;18(6A):E2.

33. Finlay JL, Boyett JM, Yates AJ, et al. Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen. Childrens cancer group. J Clin Oncol. 1995;13(1):112–23.

34. Doxey D, Bruce D, Sklar F, et al. Posterior fossa syndrome: identifiable risk factors and irreversible complications. Pediatr Neurosurg. 1999;31(3):131–6.

35. Listernick R, Ferner RE, Liu GT, et al. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. Ann Neurol. 2007;61(3):189–98.

36. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2009;101(13):946–58.

37. Cotter SE, McBride SM, Yock TI. Proton radiotherapy for solid tumors of childhood. Technol Cancer Res Treat. 2012;11(3):267–78.

38. Hug EB, Muenter MW, Archambeau JO, et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. Strahlenther Onkol. 2002;178(1):10–7.

39. Gnekow AK, Kortmann RD, 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;216(6):331–42.

40. Gnekow AK, Falkenstein F, von Hornstein S, et al. Long-term follow-up of the multicenter, multidisciplinary treatment study HIT-LGG-1996 for low-grade glioma in children and adolescents of the German Speaking Society of Pediatric Oncology and Hematology. Neuro Oncol. 2012;14(10):1265–84.

41. 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):747–54.

42. Merchant TE, Kun LE, Wu S, et al. Phase II trial of conformal radiation therapy for pediatric low-grade glioma. J Clin Oncol. 2009;27(22):3598–604.

43. Dufour C, Grill J, Lellouch-Tubiana A, et al. High-grade glioma in children under 5 years of age: a chemotherapy only approach with the BBSFOP protocol. Eur J Cancer. 2006;42(17):2939–45.

44. Massimino M, Cohen KJ, Finlay JL. Is there a role for myeloablative chemotherapy with autologous hematopoietic cell rescue in the management of childhood high-grade astrocytomas? Pediatr Blood Cancer. 2010;54(4):641–3.

45. Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: critical review of clinical trials. Lancet Oncol. 2006;7(3):241–8.

46. Packer RJ, Krailo M, Mehta M, et al. A Phase I study of concurrent RMP-7 and carboplatin with radiation therapy for children with newly diagnosed brainstem gliomas. Cancer. 2005;104(9):1968–74.

47. Prados MD, Wara WM, Edwards MS, et al. The treatment of brain stem and thalamic gliomas with 78 Gy of hyperfractionated radiation therapy. Int J Radiat Oncol Biol Phys. 1995;32(1):85–91.

48. Sanghavi SN, Needle MN, Krailo MD, et al. A phase I study of topotecan as a radiosensitizer for brainstem

glioma of childhood: first report of the Children's Cancer Group-0952. Neuro Oncol. 2003;5(1):8–13.

49. Prados MD, Edwards MS, Rabbitt J, et al. Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen. J Neuro-oncol. 1997;32(3):235–41.

50.•• Ater JL, Zhou T, Holmes E, et al. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. J Clin Oncol. 2012;30(21):2641–7.
This large, prospective randomized trial compares the use of carboplatin/vincristine and TPCV for treating LGG in children under 10 years of age, and validates the use of chemotherapy to delay or defer RT.

51. 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):4209–16.

52. Massimino M, Spreafico F, Riva D, et al. A lower-dose, lower-toxicity cisplatin-etoposide regimen for childhood progressive low-grade glioma. J Neuro-oncol. 2010;100(1):65–71.

53. 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):2636–42.

54. Bouffet E, Jakacki R, Goldman S, et al. Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. J Clin Oncol. 2012;30(12):1358–63.

55. Hwang EI, Jakacki RI, Fisher MJ, et al. Long-term efficacy and toxicity of bevacizumab-based therapy in children with recurrent low-grade gliomas. Pediatr Blood Cancer. 2012. doi:10.1002/pbc.24297.

56. Lashkari HP, Saso S, Moreno L, et al. Using different schedules of Temozolomide to treat low grade gliomas: systematic review of their efficacy and toxicity. J Neurooncol. 2011;105(2):135–47.

57. Sposto R, Ertel IJ, Jenkin RD, et al. The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial. A report from the Childrens Cancer Study Group. J Neurooncol. 1989;7(2):165–77.

58. Boyett J, Yates A, Gilles FH, et al. When is a high-grade astrocytoma (HGA) not a HGA? Results of a central review of 226 cases of anaplastic astrocytoma (AA), glioblastoma multiforme (GBM), and other-HGA (OTH-HGA) by five neuropathologists. Proc Am Soc Clin Oncol. 1998;17:526a.

59. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–96.

60. Soffietti R, Trevisan E, Bertero L, et al. Anti-angiogenic approaches to malignant gliomas. Curr Cancer Drug Targets. 2012;12(3):279–88.

61. Gururangan S, Chi SN, Young Poussaint T, et al. Lack of efficacy of bevacizumab plus irinotecan in children with recurrent malignant glioma and diffuse brainstem glioma: a Pediatric Brain Tumor Consortium study. J Clin Oncol. 2010;28(18):3069–75.

62. Parekh C, Jubran R, Erdreich-Epstein A, et al. Treatment of children with recurrent high grade gliomas with a bevacizumab containing regimen. J Neuro-oncol. 2011;103(3):673–80.

63. Narayana A, Kunnakkat S, Chacko-Mathew J, et al. Bevacizumab in recurrent high-grade pediatric gliomas. Neuro Oncol. 2010;12(9):985–90.

64. Sweet JA, Feinberg ML, Sherman JH. The role of avastin in the management of recurrent glioblastoma. Neurosurg Clin N Am. 2012;23(2):331–41. x.

65. Finlay JL, Dhall G, Boyett JM, et al. Myeloablative chemotherapy with autologous bone marrow rescue in children and adolescents with recurrent malignant astrocytoma: outcome compared with conventional chemotherapy: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2008;51(6):806–11.

66. Bradley KA, Zhou T, McNall-Knapp RY, et al. Motexafin-gadolinium and involved field radiation therapy for intrinsic pontine glioma of childhood: a children's oncology group phase 2 study. Int J Radiat Oncol Biol Phys. 2013;85(1):e55–60.

67. Pollack IF, Jakacki RI, Blaney SM, et al. Phase I trial of imatinib in children with newly diagnosed brainstem and recurrent malignant gliomas: a Pediatric Brain Tumor Consortium report. Neuro Oncol. 2007;9(2):145–60.

68. Haas-Kogan DA, Banerjee A, Poussaint TY, et al. Phase II trial of tipifarnib and radiation in children with newly diagnosed diffuse intrinsic pontine gliomas. Neuro Oncol. 2011;13(3):298–306.

69. Pollack IF, Stewart CF, Kocak M, et al. A phase II study of gefitinib and irradiation in children with newly diagnosed brainstem gliomas: a report from the Pediatric Brain Tumor Consortium. Neuro Oncol. 2011;13(3):290–7.

70. Broniscer A, Baker JN, Tagen M, et al. Phase I study of vandetanib during and after radiotherapy in children with diffuse intrinsic pontine glioma. J Clin Oncol. 2010;28(31):4762–8.

71. Okada H, Low KL, Kohanbash G, et al. Expression of glioma-associated antigens in pediatric brain stem and non-brain stem gliomas. J Neurooncol. 2008;88(3):245–50.

72. Li G, Mitra SS, Monje M, et al. Expression of epidermal growth factor variant III (EGFRvIII) in pediatric diffuse intrinsic pontine gliomas. J Neurooncol. 2012;108(3):395–402.

73. Yalon M, Rood B, Macdonald TJ, et al. A feasibility and efficacy study of rapamycin and erlotinib for recurrent pediatric low-grade glioma (LGG). Pediatr Blood Cancer. 2013;60(1):71–6.

74. Sands SA, Zhou T, O'Neil SH, et al. Long-term follow-up of children treated for high-grade gliomas: children's oncology group L991 final study report. J Clin Oncol. 2012;30(9):943–9.

75. 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):334–8.

76. Pollack IF, Claassen D. al-Shboul Q, et al. Low-grade gliomas of the cerebral hemispheres in children: an analysis of 71 cases. J Neurosurg. 1995;82(4):536–47.

77. 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):583–9.

78. 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):2038–44.

79. Campen CJ, Kranick SM, Kasner SE, et al. Cranial irradiation increases risk of stroke in pediatric brain tumor survivors. Stroke. 2012;43(11):3035–40.

80. Bowers DC, Liu Y, Leisenring W, et al. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2006;24(33):5277–82.

81. Partap S. Stroke and cerebrovascular complications in childhood cancer survivors. Semin Pediatr Neurol. 2012;19(1):18–24.

82. Mostoufi-Moab S, Grimberg A. Pediatric brain tumor treatment: growth consequences and their management. Pediatr Endocrinol Rev. 2010;8(1):6–17.