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Pediatric CNS tumors: Overview and treatment paradigms

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ABSTRACT

Central nervous system (CNS) tumors represent the most common solid tumors occurring in children, with gliomas, medulloblastomas and ependymomas being the most frequently diagnosed. The most recent 2021 World Health Organization (WHO) Classification of Tumors of the CNS (CNS5) has integrated molecular genetics with traditional histopathology leading to more accurate diagnosis and risk stratification/prognostication with subsequent development of personalized treatment paradigms. Pediatric gliomas are traditionally subdivided into low-grade (pLGG) or high-grade gliomas (pHGG). pLGG tend to have excellent overall survival, however, the disease course maybe characterized by multiple recurrences resulting in significant morbidity. Surgical resection is standard with medical therapy (chemotherapy or oral molecular targeted therapy) reserved in the event of radiographic/symptomatic progression. pHGG have poor overall survival despite intensive multimodality therapy. Ependymomas occur in the infratentorial and supratentorial brain as well as in the spine, with the standard treatment including maximal safe resection with involved field radiation therapy that is curative in two-thirds of patients overall. Medulloblastomas are the most common malignant embryonal CNS tumor arising in the cerebellum and are biologically heterogeneous. Given the risk of CSF dissemination, medulloblastomas require surgery, craniospinal radiation as well as multi agent chemotherapy, an approach that is curative in the majority of patients with non-metastatic disease. The field of pediatric neuro-oncology has made robust strides in the past few decades and the role of molecular diagnostics has continued to improve our understanding of pediatric tumor biology and offer more personalized treatment paradigms.

Introduction

Central nervous system (CNS) tumors represent the most common solid tumors occurring in children with an age-standardized incidence rate of 5.61 and 7.26 per 100,000 persons during childhood and adolescence, respectively. CNS tumors are one of the leading causes of cancer related mortality in children as well as adolescents and young adults (AYAs).[1] Pediatric CNS tumor survivors develop unique long-term sequelae including neurological deficits that impact their quality of life. [2-5]

Fortunately, in the last two decades we have witnessed several important advances in pediatric neuro-oncology leading to improved understanding of tumor biology as well as identification of biomarkers leading to more accurate diagnosis, prognosis, and risk stratification. This is reflected in the 2021World Health Organization's (WHO) Classification of Tumors of the CNS (CNS5) that integrate histologic and molecular features into a combined diagnosis. Coupled with the development of novel therapeutics, this has enabled personalization of treatment regimens to maximize survival while minimizing long term morbidities. [6]

In this review, we will focus on an overview of the most frequently encountered primary pediatric CNS tumors (gliomas, ependymomas and medulloblastomas) along with the general approach to diagnosis and management.

Glioma

Gliomas are the most common type of CNS tumors representing 51.2% and 30.6% of all pediatric CNS tumors occurring in children aged 0-14 years and adolescents aged 15-19 years, respectively. [7,8,9] Gliomas encompass a wide range of glial neoplasms which differ in anatomical location, histomorphology, degree of infiltration, molecular features and clinical course. Gliomas are traditionally subdivided into low-grade gliomas (WHO grade I-II) and high-grade gliomas (WHO grades III-IV) that are predictive of patient survival. Overall, pediatric low-grade gliomas (pLGGs) and pediatric high-grade gliomas (pHGGs) comprise

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~30% and 10% of all pediatric CNS tumors, respectively.[9, 10]

Pediatric low-grade glioma

pLGGs are the most common type of CNS tumors occurring in children with an excellent 20-year overall survival (OS) of approximately 87%. However, the clinical course may be characterized by multiple recurrences depending on age at diagnosis, extent of resection and molecular phenotype necessitating several lines of treatment. Those factors result in neurologic, endocrinologic, ophthalmologic and cognitive morbidities that impact the patient's quality of life[11-13]. pLGGs can arise anywhere in the brain or spinal cord, and the presenting symptoms vary according to tumor location.

The CNS5 now classifies pLGG into 3 different families: (1) Pediatric type diffuse low-grade gliomas, (2) circumscribed astrocytic gliomas and (3) glioneuronal and neuronal tumors. Several tumor subtypes are recognized in each category that differ in histological appearance and underlying molecular drivers. The prognosis is determined by anatomical location, extent of resection, and histopathological as well as molecular markers.[8] A subset of pLGGs arise in the setting of genetic predisposition syndromes such as Neurofibromatosis Type I (NF1), Tuberous Sclerosis Complex (TSC) or RASopathies like Noonan Syndrome. NF1 patients develop optic pathway gliomas (OPG) or brainstem low-grade gliomas, which are predominantly pilocytic astrocytomas by histopathology while patients with TSC develop subependymal giant cell astrocytomas (SEGA). [14-16]

The vast majority of sporadic pLGGs have genetic alterations associated with the RAS/mitogen activated protein kinase (RAS/MAPK) pathway, including BRAF fusion, BRAF V600E mutation, and less commonly, alterations in fibroblast growth factor receptor 1-3 (FGFR1-3), neutrophic tropomyosin receptor kinase (NTRK), MYB, or MYBL1 genes. [10, 17, 18,19, 20] Mutations in MAPK pathway component genes can trigger cellular senescence which likely accounts for the relative growth slowing/arrest post puberty and lack of transformation to higher-grade gliomas (with specific exceptions such as BRAFV600E) in the absence of additional cooperating alterations. [13, 21]

Table 1
Common Pediatric Low-grade Gliomas (pLGG) & glioneuronal tumors with associated molecular alterations based on 2021 WHO CNS5. [10, 13]

2021 WHO CNS5 classification	Common molecular alterations
Pediatric Low-grade Gliomas (pLGG)	
Pilocytic Astrocytoma	KIAA1549-BRAF (70-80%)
	FGFR1-TACC1 (3-5%)
	FGFR1 SNV (3-5%)
	BRAF p.V600E (3-5%)
	Other BRAF Fusions (2-5%)
	CRAF Fusions (2-5%)
	PTPN11 SNV (2-5%)
	KRAS/HRAS SNV (2-5%)
Subependymal Giant Cell Astrocytoma (SEGA)	TSC1/2 SNV (85-95%)
Diffuse Astrocytoma	BRAF p.V600E (20-40%)
	MYBL1 alteration (5-10%)
	KIAA1549-BRAF (5-10%)
	FGFR1 SNV (2-5%)
	H3.3 p.K27M (2-5%)
	IDH1 p.R132H (2-5%)
	Other RTK SNV/Fusions (2-3%)
Pleomorphic Xanthoastrocytoma	BRAF p.V600E (80-90%)
Mixed Glioneuronal Tumors	
Ganglioglioma	BRAF p.V600E (40-50%)
	KIAA1549-BRAF (10-15%)
Dysembryoplastic Neuroepithelial Tumor (DNET)	FGFR1-TKD duplication (20-30%)
	FGFR1 SNV (20-30%)
	FGFR1-TACC1 (10-15%)
	Other RTK SNV/Fusions (5-10%)
	BRAF p.V600E (5-10)
Chordoid Glioma of Third Ventricle	PRKCA SNV (80-90%)
Angiocentric Glioma	MYB (80-90%)

Table 1 represents commonly encountered pLGGs and mixed glioneuronal tumors with their associated common molecular alternations. [10, 13,22,7]

Treatment for pediatric low-grade glioma

Treatment strategies for pLGG have significantly improved with our understanding of the heterogeneity of their histologic, clinical and molecular characteristics leading to more individualized treatment approaches. Given their excellent OS, the goal of treatment is focused on optimizing overall functional outcomes and minimizing long-term sequalae and comorbidities to maintain a good quality of life. [23] Developing an appropriate treatment plan requires multidisciplinary input from neurosurgery, radiation oncology, neuroradiology and pediatric neuro-oncology. These specialists should carefully weigh the risks and benefits of tumor directed interventions against tumor related morbidity. The mainstay of pLGG treatment includes surgical resection and maximal safe excision with an intent to cure. However, feasibility may be limited by location, infiltrative nature, or molecular phenotype of the lesion and surgical indications in these situations include tissue sampling for diagnosis and molecular classification and debulking in the setting of mass effect and hydrocephalus. Large cohort studies have demonstrated that up to 50% patients have residual tumor burden with 30% requiring medical treatment.[16, 24]. Medical therapy is indicated only in the event of incompletely resected tumors with clinical progression or unequivocal evidence of radiographic progression with likelihood of significant morbidity. Radiation therapy, while an extremely effective approach, is often reserved in pLGGs due to the associated long-term sequalae including risk of secondary malignancies, vasculopathies, stroke, endocrinopathies as well as long-term cognitive deficits.[23]

Frequently used chemotherapy regimens in newly-diagnosed pLGG achieve 3-year progression free survival (PFS) between 50–80% which include: i) carboplatin alone or in combination with vincristine (CV); ii) thioguanine, procarbazine, CCNU and vincristine (TPCV) (less preferred given risks of secondary malignancy and infertility): and iii) vinblastine alone. Bevacizumab, a vascular endothelial growth factor inhibitor (VEGF) may be used to rescue rapidly progressive vision loss in patients with progressive optic pathway gliomas. [16, 25-27].

Given that pLGGs represent single molecularly driven entities that almost universally result in the activation of the RAS/MAPK pathway, targeted therapies blocking MAPK signaling are being used as novel therapeutics. Up to 40% of pLGG harbor focal gains at 7q34 due to a tandem duplication leading to the formation of a novel oncogenic fusion, KIAA1549-BRAF, which represents the most frequently encountered molecular alteration. KIAA1549-BRAF is enriched in specific histologies like pilocytic astrocytomas that frequently arise in the posterior fossa/cerebellum and have a highly circumscribed growth pattern that renders them amenable to gross total resection resulting in excellent PFS and OS. 15-20% of pLGGs harbor BRAFV600 mutations which are enriched in specific histologies including ganglioglioma and pleomorphic xanthoastrocytoma (PXA).

Current targeted therapies for pLGG include MEK inhibitors (e.g., selumetinib, trametinib), BRAF inhibitors (e.g., dabrafenib) and pan-RAF inhibitors (e.g., tovorarafenib). [20, 22] These therapies have demonstrated impressive responses and are increasingly preferred for treatment of relapsed pLGGs. Dabrafenib (BRAF inhibitor) and trametinib (MEK 1-2 inhibitor) combination is now FDA approved for the treatment of newly diagnosed patients with BRAFV600E mutant LGGs in lieu of chemotherapy given higher objective response rates, longer PFS and favorable safety profile demonstrated in a pivotal randomized trial. [28] Larotrectinib and entrectinib are FDA approved for the treatment of NTRK altered and NTRK/ROS/ALK altered pLGGs respectively. Everolimus, an mTOR inhibitor, is FDA approved for the treatment of patients with TSC associated SEGA and is also associated with improved seizure control. Fortunately, these targeted therapies tend to have more

manageable and limited systemic toxicities without specific neurotoxicities described to date, although the long-term sequelae remain unclear.

Pediatric low-grade glioma in neurofibromatosis type I

NF1 is the most common cancer predisposition syndrome of the nervous system and occurs 1 in 3000 live births. Of all pLGGs, 20% of are associated with NF1[10].

The most common pLGG seen in patients with NF1 are optic pathway gliomas (OPG), which are pilocytic astrocytomas histopathologically, representing 65-75% of all CNS tumors in these children. [29] OPG can affect any section of the optic pathway. Depending on their location, OPG can present with visual acuity deterioration, visual field defects, pendular movement nystagmus (often in patients < 2 years), proptosis or endocrine disturbances (precocious puberty or increased growth velocity). [30] Diencephalic syndrome — characterized by severe failure to thrive, emaciation, hyperalertness, and visual or endocrine disturbances — may be present if there is hypothalamic involvement or obstructive hydrocephalus. [31]

OPG tend to be more commonly diagnosed in patients less than 8-years-old. [32] In general, two-thirds of pediatric patients with NF1 with an OPG tend not to require intervention, often only requiring surveillance with ophthalmologic exam. Some OPGs spontaneously regress over time. [32, 33]

Treatment is indicated in the event of radiographic progression or visual deterioration, with treatment for NF1 associated pLGG including either chemotherapy or molecularly targeted therapy. Ongoing clinical trials aim to randomize newly diagnosed patients to receive either traditional chemotherapy or targeted therapy with a MEK inhibitor (selumetinib) and will evaluate response rates, functional outcomes as well as toxicity profiles.[23]

Routine surveillance neuroimaging for NF1 is not recommended unless there are concerns about new neurological or systemic symptoms, new pain, or focal deficits that could prompt re-evaluation of both pLGGs and pHGGs.[31] Of note, neuroimaging for patients with NF1 can frequently have Focal Areas of Signal Intensity (FASI), usually characterized by non-enhancing, small areas without mass effect or edema; they are usually found in 70% of NF1 pediatric cases and must be differentiated from gliomas. [29]

Pediatric high-grade glioma

pHGG are diffusely infiltrative, aggressive tumors that carry a poor prognosis and account for approximately 40% of childhood brain tumor related deaths. [1, 9] pHGG tend to present with a short prodrome of signs and symptoms such as increased intracranial pressure including headaches with nausea/vomiting, papilledema or diplopia, developmental regression, seizures, and focal neurologic deficits like hemiplegia, dysmetria, pyramidal tract signs and cranial neuropathies. [34]

As is commonly used in the adult population, the term “glioblastoma” has been abandoned in the pediatric oncological population. The new CNS5 defines four subtypes of pHGG: Grade 4 Diffuse midline glioma (DMG) H3K27-altered, Grade 4 Diffuse hemispheric gliomas H3G34-mutant, Grade 4 pediatric-type high-grade gliomas H3-wildtype and IDH-wildtype, and infant-type hemispheric gliomas [35, 36] Diffuse midline glioma (DMG) includes malignant (WHO grade 4) tumors of the thalamus, brainstem, and spinal cord. DMGs are called diffuse intrinsic pontine glioma (DIPG) when they arise from the pons, with the average age of diagnosis at 8 and represent nearly 75% of all pediatric brainstem tumors.

Diffuse hemispheric glioma, H3 G34-mutant are aggressive infiltrating gliomas involving the cerebral hemispheres typically occurring in adolescents and young adults (AYAs). Infant-type hemispheric gliomas are often diagnosed in the first year of life, and the majority are characterized by receptor tyrosine kinase (RTK) fusions including NTRK1/2/3, ROS1, ALK or MET. There are several cancer predisposition syndromes linked to an increased risk of HGGs including but not limited to Neurofibromatosis Type I (NF1), Li-Fraumeni syndrome (LFS) and Constitutional Mismatch Repair Deficiency (CMMRD).

Despite advances in the understanding of molecular features of pHGGs over the past decade, there continue to be limited therapeutic approaches that have proven to be effective and survival remains poor.

Treatment for pediatric high-grade glioma

Most treatment modalities for pHGGs have incorporated the use surgery, radiation therapy and chemotherapy, but unfortunately the 5-year OS for these patients is less than 20%. [15]

The goals of surgery include obtaining tissue for pathologic diagnosis and achieving a maximal safe resection. Depending on tumor location, the extent of the surgery must be balanced with preservation of neurologic function. Biopsy alone is preferrable where the lesion is not amenable to resection, e.g. deeper midline location pHGG like a thalamic diffuse midline glioma (DMG) or tumors that infiltrate into eloquent cortex. Localized field irradiation post-surgery is standard therapy given the infiltrative nature of these tumors. pHGG patients typically receive a total radiation dose of 54-60 Gy equivalent in daily fractions of 1.8 or 2 Gy over 6 weeks.

There is no “standard” adjuvant chemotherapy regimen. Although alkylator chemotherapy including temozolomide (TMZ) and/or lomustine (CCNU) appears to benefit at least a subset of pHGG patients, a standard of care has not been established and children are enrolled in clinical trials whenever possible. There are some tumor-specific considerations worth noting. For diffuse intrinsic pontine glioma (DIPG), the diagnosis is based on neuroimaging with surgical biopsy reserved in the event of atypical presentation, imaging or for determining clinical trial eligibility. No chemotherapy or biological therapy has demonstrated benefit for the treatment of DIPG, and these along with non-pontine diffuse midlines gliomas, H3K27 altered are treated with radiation therapy only. Interestingly, pHGGs occurring in patients <3 years of age are associated with improved outcomes and are typically treated with chemotherapy regimens, such as carboplatin/etoposide; radiation therapy is generally avoided due to significant age associated morbidities.

Targeted therapy based on tumor molecular genetics has been employed for recurrent or progressive pHGG, however, benefit has been noted only in small subsets. For pHGGs harboring BRAFV600E mutations, BRAF and MEK inhibitor combination such as dabrafenib and trametinib can be administered post radiation therapy or at the time of first progression with good responses to treatment noted. Oncogenic gene fusions that are almost exclusively found in infant pHGG include: *NTRK1/2/3* (neurotrophic tropomyosin-related kinase), *ROS* (protein tyrosine kinase encoded by the ROS1 gene), or *ALK* (anaplastic lymphoma kinase). [37, 38] Larotrectinib and Entrectinib are FDA approved therapies targeting NTRK altered and NTRK/ROS/ALK altered pHGGs respectively. [39]

Immunotherapy for pediatric CNS tumors is currently being studied and implemented to decrease mortality and limit morbidity. However, the unique microenvironment of the CNS limits its delivery. Examples of immunotherapy that have been employed include checkpoint inhibitors, vaccine therapy, adoptive immunotherapy like chimeric antigen receptor T cell therapy (CAR-T cell therapy), and viral therapy.[40] Immune checkpoint inhibitors have demonstrated benefit in a subset of patients with replication repair deficient (RRD) pHGGs that are characterized by hypermutation, often resulting from germline defects in mismatch repair genes as seen in patients with CMMRD. It is important to note that tumor-targeting immunotherapy can cause local inflammation and edema that can worsen and/or cause focal neurological deficits and seizures. As such, it is difficult to differentiate between immune-related pseudoprogression versus true tumor progression based on clinical presentation alone. A trial of steroids can be administered, and

significant improvement is often suggestive of pseudoprogression. [40, 41]

Ependymoma

Ependymomas are glial tumors that arise from radial glia (the progenitors that give rise to ependymal cells) within or adjacent to the ependymal lining of the ventricular system or the central canal of the spinal cord. Overall, ependymomas account for 10-12% of childhood CNS tumors. Ninety percent of pediatric ependymomas are intracranial, $2/3^{rds}$ of which arise in the posterior fossa (PF) and $1/3^{rd}$ are supratentorial (ST). Ten percent of ependymomas are spinal. However, an increased incidence of spinal ependymomas is observed in patients with neurofibromatosis type 2 (NF2) associated schwannomatosis, another cancer predisposition syndrome. Ependymomas are typically locally invasive tumors, with disseminated disease occurring in approximately 10% of patients.

Clinical symptoms of ependymomas include hydrocephalus secondary to fourth ventricle obstruction, headache, irritability, nausea, vomiting, ataxia, papilledema, and increased head circumference in infants. Tumors extending through the foramina of Luschka and foramen of Magendie infiltrate lower cranial nerves causing hoarseness, dysphagia. and torticollis. Spinal cord ependymomas cause localized pain at the level of the lesion, radicular dysesthesias, progressive spastic quadriparesis, and scoliosis. Myxopapillary ependymomas of the conus medullaris and filum terminale may present with low back pain, radicular pain, saddle anesthesia, and sphincter dysfunction.

Histological characteristics of classic ependymomas are perivascular pseudorosettes and the pathognomonic true ependymal rosettes. The WHO grading system (grade II/classic versus grade III/anaplastic) is of limited value because of interobserver variability, even between experienced neuropathologists. Despite the histological overlap, ST, PF and spinal cord ependymoma represent biologically distinct entities. [42-45] Therefore, molecular characterization is critical for appropriate diagnosis, treatment planning and prognostication.

There are two subtypes of posterior fossa (PF) ependymomas, posterior fossa A (PFA) and posterior fossa B (PFB). PFA ependymomas occur in infants and young children and are characterized by global loss of H3K27me3 by immunohistochemistry which is a robust and cost-effective molecular surrogate for PF-EPN-A. PFB ependymomas occur in older children and adults and have intact H3K27me3.[45-48]

Supratentorial (ST) ependymomas are characterized by recurrent fusions on chromosome 11 involving either the nuclear factor kappa B (NF-κB) co-activator RELA fused to ZFTA (ST-EPN-RELA), or recurrent fusions of *YAP1* and *MAML2* (ST-EPN-YAP). [45, 49, 50] ST ependymomas that do not harbor a fusion of either ZFTA or YAP1 may represent high-grade gliomas or embryonal tumors.

Myxopapillary ependymoma is a variant of spinal ependymomas arising in the region of the conus medullaris and filum terminale with a typically benign course. However, late metastatic recurrences have been reported. A highly aggressive subvariant of spinal ependymoma harboring MYCN and MYC amplicons has been described but is rare in children.[8]

PF-EPN-A with balanced 1q and 6q status and ST ependymomas with a complete surgical resection have excellent 5-year progression-free survival approaching 80%. In PF-EPN-A tumors, 1q gain and 6q loss are markers of poor prognosis.[51, 52]

Treatment for ependymoma

The standard treatment for ependymomas is surgery, with a goal of gross total resection. This is followed by immediate postoperative conformal radiation (tumor plus 1 cm margin), even for patients as young as 12 months old, given the relative preservation of neurocognitive function. Incomplete resection confers poor prognosis and second-look surgery should be considered in these cases. [51] Radiation therapy sparing strategy, i.e., observation alone, may be considered in selected instances of gross totally resected ST ependymoma (non-anaplastic) including YAP1 fused ST ependymoma as well as in spinal myxopapillary ependymomas. This is due to retrospective reports of favorable outcomes in these ependymoma subtypes.

Adjuvant chemotherapy does not provide a survival benefit in these patients. Two instances where chemotherapy has a defined role is with incompletely resected tumors, where it can serve as a bridge to shrink tumors and facilitate second look surgery with the goal of gross total resection. Secondly, in infants, chemotherapy may be used to delay start of RT until 12 months of age given the higher risks of second malignant neoplasms and brainstem necrosis in infants <12 months.[53, 54]

Medulloblastoma

Medulloblastoma is the most common malignant embryonal CNS tumor arising in the cerebellum with an incidence of 6 cases per 1,000,000/year. [55, 56] Genomic studies have demonstrated that medulloblastomas, although morphologically similar, have extensive biological heterogeneity. The CNS5 recognizes five distinct molecular subgroups of medulloblastoma that differ in their cells of origin, driver alterations, and clinical behavior, necessitating distinct treatment approaches (Table 2) [8]: 1) Wingless-activated (WNT), 2) SHH-activated TP53 wild-type (SHH-TP53WT), 3) SHH-activated TP53 mutant (SHH-TP53 mutant), 4) Group 3 (non-WNT/non-SHH) and 5) Group 4 (non-WNT/non-SHH). [57-62]

The most common initial presenting symptoms of medulloblastoma can include increased intracranial pressure (ICP) due to obstructive hydrocephalus, headache, vomiting, and ataxia, usually preceding the diagnosis by 2–8 weeks. Other associated symptoms with presentation can include changes in personality, academic regression, irritability, lethargy, diplopia, head tilt, and/or truncal ataxia.

On T1-weighted images of an MRI of the brain, medulloblastomas are often isointense or hypointense to surrounding normal brain. Diffusion restriction is observed in almost all tumors as a result of uniform hypercellularity. Medulloblastoma subgroups have distinct imaging characteristics. SHH tumors tend to be located in the cerebellar hemispheres. Group 3 (avidly enhancing) and group 4 (non-enhancing) tumors tend to occupy the midline fourth ventricle. WNT tumors invade the lateral recess in 40%–50% of cases. Neuroaxis staging with spine imaging and lumbar CSF cytology (performed ≥2 weeks after surgical resection to avoid false positivity) is essential given that leptomeningeal metastases at diagnosis is detected in 20%–30% of patients, many who are often asymptomatic.

Risk stratification (i.e., risk of relapse) (Table 3) is currently based on clinical staging, and neuropathological and molecular features. The major determinants of clinical risk stratification include age (pts <3 years given inability to use craniospinal irradiation without severe neurocognitive consequences), metastasis (M stage), residual post-operative disease assessed by post-op MRI performed within 48 hours of surgery and histology (large-cell, anaplastic, medulloblastoma with extensive nodularity, desmoplastic/nodular).

Table 2
Molecular subgroups of medulloblastoma.

Molecular subgroup	WNT (10%)	SHH (30%)	Group 3 (25%)	Group 4 (35%)
Age	Child/AYA	Infancy/AYA	Early childhood	Childhood
Metastasis at dx	5%	15%	40%	35%
5-year OS	95%	75% (lower if TP53 mutant)	50%	75%
Genetic driver	*CTNNB1 DDX3X*	*PTCH1, SUFU TP53*	*MYC/ MYCN PVT*	*KDM6A SNCAIP*
Syndrome	FAP	Gorlin, GPR16 ELP1, Li Fraumeni	*BRCA1/2 PALB2*	*BRCA1/2 PALB2*

Table 3
Clinical risk stratification of medulloblastoma.

Average Risk/Standard Risk: ≥3 yrs	<1.5cm^3 residual tumor	M0	no anaplasia
High Risk: ≥3 yrs	≥1.5cm^3 residual tumor	M1-M4	anaplasia (focal/ diffuse)
Infant: <3 y	any M stage	+/- residual tumor	any histology

Molecular features that have prognostic implications include WNT subgroup patients that are considered low-risk while MYC amplified group 3 and *TP53* mutant SHH medulloblastoma comprise very-high risk patients. [59]

Treatment of medulloblastoma

The mainstay of treatment for medulloblastoma is surgery, radiation therapy, and chemotherapy. The goals of surgery are to control increased intracranial pressure, achieve a maximal safe surgical resection and establish a molecular diagnosis prior to protocoled therapy. Potential complications of posterior fossa surgery include posterior fossa syndrome(PFS)/cerebellar mutism that is reported in up to 40% of children. [63] PFS symptoms include mutism or severe dysarthria, personality changes or emotional lability, hypotonia, ataxia, oral motor apraxia, and/or reduced oral intake. Symptoms frequently start 1–2 days after surgery and may last for several months, with varying degrees of recovery with intensive rehabilitation and therapy. A higher incidence has been described among patients with midline Group 4 medulloblastoma. A lower incidence has been reported among patients with laterally located SHH tumors, presumable due to relative sparing of cerebellar outflow tracts through the superior cerebellar peduncle.

Risk adjusted craniospinal irradiation (CSI) is administered along with a boost to the primary tumor bed. the currently recommended radiation therapy for standard-risk patients includes CSI of 23.4 Gy, with a tumor bed boost of 55.8 Gy.

Adjuvant chemotherapy allows for reduction of CSI dose in patients with average risk medulloblastoma. Following radiation therapy, 4–8 cycles of cisplatin-based chemotherapy are administered, with either cisplatin, lomustine, and vincristine or cisplatin, cyclophosphamide, and vincristine—both with similar survival. WNT medulloblastoma patients have an excellent prognosis and those with average risk disease based on clinical risk stratification maybe treated with 15-18 Gy of CSI with lower alkylator cumulative chemotherapy doses. Medulloblastoma patients with metastatic dissemination or residual disease over 1.5 cm2 are treated with 36–39 Gy of craniospinal irradiation with a boost to the tumor bed of 55.8 Gy. This is followed by 6 cycles of cisplatin, cyclophosphamide, and vincristine-based chemotherapy, although the additional benefit of chemotherapy is unclear. Infants are treated with radiation-sparing approaches given the devastating neurocognitive sequelae with CSI. Treatment strategies include administration of intraventricular methotrexate with standard dose cytotoxic chemotherapy or administration of high dose chemotherapy with autologous stem cell transplant. [64, 65] SHH medulloblastoma have excellent radiation-free survival of nearly 90% while group 3 infants have a poor prognosis with radiation sparing strategies. [65-67]

Standard-risk medulloblastoma patients have a 5-year survival of approximately 80%; 5-year survival in high-risk medulloblastoma patients is approximately 50%–60%. [56, 68-71] For the majority of survivors, long-term functional and cognitive outcomes are relatively poor. Patients who received CSI at a young age are generally unable to live independently. [72, 73] In addition to neurocognitive sequelae and hearing loss, medulloblastoma survivors are burdened with a high incidence of stroke and multiple medical co-morbidities.[72]

Conclusion

Despite advances in pediatric cancer with respect to survival outcomes and therapeutics, pediatric CNS tumors continue to be a significant cause of morbidity and mortality. Fortunately, due to the advent of molecular diagnostics, the overall classification, prognostication as well as treatment and management of pediatric CNS tumors has significantly improved. Additionally, there has been development of novel therapeutics, including targeted therapy that have decreased treatment related toxicity and sequalae. There are multiple ongoing clinical trials that are focused on more effective treatment paradigms by concentrating on tumor biology, de-escalation of therapy and reduction of associated treatment related morbidity to better ensure improved quality of life and survival in this patient population.

CRediT authorship contribution statement

Karishma Parikh: Conceptualization, Data curation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sameer Farouk Sait:** Conceptualization, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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References

1. Ostrom QT, Price M, Ryan K, Edelson J, Neff C, Cioffi G, Waite KA, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: pediatric brain tumor foundation childhood and adolescent primary brain and other central nervous system tumors diagnosed in the United States in 2014-2018. *Neuro Oncol*. 2022;24(Suppl 3). https://doi.org/10.1093/neuonc/noac161. iii1-iii38PubMed PMID: 36066969; PMCID: PMC9447434.
2. Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, Green DM, Armstrong GT, Nottage KA, Jones KE, Sklar CA, Srivastava DK, Robison LL. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA*. 2013;309(22):2371–2381. https://doi.org/10.1001/jama.2013.6296. PubMed PMID: 23757085; PMCID: PMC3771083.
3. Neil EC, Hanmantgad S, Khakoo Y. Neurological complications of pediatric cancer. *J Child Neurol*. 2016;31(12):1412–1420. https://doi.org/10.1177/0883073815620673.
4. Wells EM, Ullrich NJ, Seidel K, Leisenring W, Sklar CA, Armstrong GT, Diller L, King A, Krull KR, Neglia JP, Stovall M, Whelan K, Oeffinger KC, Robison LL, Packer RJ. Longitudinal assessment of late-onset neurologic conditions in survivors of childhood central nervous system tumors: a Childhood Cancer Survivor Study report. *Neuro Oncol*. 2018;20(1):132–142. https://doi.org/10.1093/neuonc/nox148.
5. Parasole R, Petruzziello F, Menna G, Mangione A, Cianciulli E, Buffardi S, Marchese L, Nastro A, Misuraca A, Poggi V. Central nervous system complications during treatment of acute lymphoblastic leukemia in a single pediatric institution. *Leukemia & Lymphoma*. 2010;51(6):1063–1071. https://doi.org/10.3109/10428191003754608.
6. Torp SH, Solheim O, Skjulsvik AJ. The WHO 2021 Classification of Central Nervous System tumours: a practical update on what neurosurgeons need to know-a minireview. *Acta Neurochir (Wien)*. 2022;164(9):2453–2464. https://doi.org/10.1007/s00701-022-05301-y. Epub 20220726PubMed PMID: 35879477; PMCID: PMC9427889.

7. Hauser P. Classification and treatment of pediatric gliomas in the molecular era. *Children (Basel)*. 2021;8(9), 20210827. https://doi.org/10.3390/children8090739. EpubPubMed PMID: 34572171; PMCID: PMC8464723.
8. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021;23(8):1231–1251. https://doi.org/10.1093/neuonc/noab106. PubMed PMID: 34185076; PMCID: PMC8328013.
9. Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2016-2020. *Neuro Oncol*. 2023;25(12 Suppl 2). https://doi.org/10.1093/neuonc/noad149. iv1-iv99PubMed PMID: 37793125; PMCID: PMC10550277.
10. Ryall S, Tabori U, Hawkins C. Pediatric low-grade glioma in the era of molecular diagnostics. *Acta Neuropathol Commun*. 2020;8(1). https://doi.org/10.1186/s40478-020-00902-z.
11. Bandopadhayay P, Bergthold G, London WB, Goumnerova LC, Morales La, Madrid A, Marcus KJ, Guo D, Ullrich NJ, Robison NJ, Chi SN, Beroukhim R, Kieran MW, Manley PE. Long-term outcome of 4,040 children diagnosed with pediatric low-grade gliomas: an analysis of the Surveillance Epidemiology and End Results (SEER) database. *Pediatr Blood Cancer*. 2014;61(7):1173–1179. https://doi.org/10.1002/pbc.24958. Epub 20140130PubMed PMID: 24482038; PMCID: PMC4657506.
12. Krishnatry R, Zhukova N, Guerreiro Stucklin AS, Pole JD, Mistry M, Fried I, Ramaswamy V, Bartels U, Huang A, Laperriere N, Dirks P, Nathan PC, Greenberg M, Malkin D, Hawkins C, Bandopadhayay P, Kieran MW, Manley PE, Bouffet E, Tabori U. Clinical and treatment factors determining long-term outcomes for adult survivors of childhood low-grade glioma: a population-based study. *Cancer*. 2016;122(8):1261–1269. https://doi.org/10.1002/cncr.29907. Epub 20160310PubMed PMID: 26970559.
13. Ryall S, Zapotocky M, Fukuoka K, Nobre L, Guerreiro Stucklin A, Bennett J, Siddaway R, Li C, Pajovic S, Arnoldo A, Kowalski PE, Johnson M, Sheth J, Lassaletta A, Tatevossian RG, Orisme W, Qaddoumi I, Surrey LF, Li MM, Waanders AJ, Gilheeney S, Rosenblum M, Bale T, Tsang DS, Laperriere N, Kulkarni A, Ibrahim GM, Drake J, Dirks P, Taylor MD, Rutka JT, Laughlin S, Shroff M, Shago M, Hazrati LN, D'Arcy C, Ramaswamy V, Bartels U, Huang A, Bouffet E, Karajannis MA, Santi M, Ellison DW, Tabori U, Hawkins C. Integrated molecular and clinical analysis of 1,000 pediatric low-grade gliomas. *Cancer Cell*. 2020;37(4):569–583. https://doi.org/10.1016/j.ccell.2020.03.011. e5PubMed PMID: 32289278; PMCID: PMC7169997.
14. Sturm D, Pfister SM, Jones DTW. Pediatric gliomas: current concepts on diagnosis, biology, and clinical management. *J Clin Oncol*. 2017;35(21):2370–2377. https://doi.org/10.1200/JCO.2017.73.0242. Epub 20170622PubMed PMID: 28640698.
15. Ceglie G, Del Baldo G, Agolini E, Rinelli M, Cacchione A, Del Bufalo F, Vinci M, Carta R, Boccuto L, Miele E, Mastronuzzi A, Locatelli F, Carai A. Cancer predisposition syndromes associated with pediatric high-grade gliomas. *Front Pediatr*. 2020;8, 561487. https://doi.org/10.3389/fped.2020.561487. Epub 20201112PubMed PMID: 33282797; PMCID: PMC7690624.
16. Demaliaj D, Gardner SL. Novel therapies for pediatric low grade glioma. *Curr Opin Neurol*. 2024;37(6):702–707. https://doi.org/10.1097/WCO.0000000000001319. Epub 20240926PubMed PMID: 39324939.
17. Haizel-Cobbina J, Thakkar R, Richard K, Du L, Levine A, Bennett J, Hawkins C, Tabori U, Dewan MC. Clinical and molecular features of disseminated pediatric low-grade glioma and glioneuronal tumors: a systematic review and survival analysis. *Neurooncol Adv*. 2022;4(1):vdac122. https://doi.org/10.1093/noajnl/vdac122. Epub 20220805PubMed PMID: 36382112; PMCID: PMC9639355.
18. Yaman Bajin I, Bouffet E. Advances in the treatment of pediatric low-grade gliomas. *Curr Neurol Neurosci Rep*. 2024;24(10):527–535. https://doi.org/10.1007/s11910-024-01369-4. Epub 20240815PubMed PMID: 39143379.
19. Packer RJ, Pfister S, Bouffet E, Avery R, Bandopadhayay P, Bornhorst M, Bowers DC, Ellison D, Fangusaro J, Foreman N, Fouladi M, Gajjar A, Haas-Kogan D, Hawkins C, Ho CY, Hwang E, Jabado N, Kilburn LB, Lassaletta A, Ligon KL, Massimino M, Meeteren SV, Mueller S, Nicolaides T, Perilongo G, Tabori U, Vezina G, Warren K, Witt O, Zhu Y, Jones DT, Kieran M. Pediatric low-grade gliomas: implications of the biologic era. *Neuro Oncol*. 2017;19(6):750–761. https://doi.org/10.1093/neuonc/now209. PubMed PMID: 27683733; PMCID: PMC5464436.
20. Sheikh SR, Klesse LJ, Mangum R, Bui A, Siegel BI, Abdelbaki MS, Patel NJ. The role of MEK inhibition in pediatric low-grade gliomas. *Front Oncol*. 2024;14, 1503894. https://doi.org/10.3389/fonc.2024.1503894. Epub 20241220PubMed PMID: 39759151; PMCID: PMC11695311.
21. Zaazoue MA, Manley PE, Mehdar MA, Ullrich NJ, Dasenbrock HH, Chordas CA, Goumnerova LC. Optimizing postoperative surveillance of pediatric low-grade glioma using tumor behavior patterns. *Neurosurgery*. 2020;86(2):288–297. https://doi.org/10.1093/neuros/nyz072. PubMed PMID: 30892635.
22. de Blank P, Bandopadhayay P, Haas-Kogan D, Fouladi M, Fangusaro J. Management of pediatric low-grade glioma. *Curr Opin Pediatr*. 2019;31(1):21–27. https://doi.org/10.1097/MOP.0000000000000717. PubMed PMID: 30531227; PMCID: PMC6664811.
23. Lassaletta A, Zapotocky M, Bouffet E. Chemotherapy in pediatric low-grade gliomas (PLGG). *Childs Nerv Syst*. 2024;40(10):3229–3239. https://doi.org/10.1007/s00381-024-06458-w. Epub 20240531PubMed PMID: 38819670.
24. Thomale UW, Gnekow AK, Kandels D, Bison B, Hernaiz Driever P, Witt O, Pietsch T, Koch A, Capper D, Kortmann RD, Timmermann B, Harrabi S, Simon M, El Damaty A, Krauss J, Schuhmann MU, Aigner A. Long-term follow-up of surgical intervention pattern in pediatric low-grade gliomas: report from the German SIOP-LGG 2004 cohort. *J Neurosurg Pediatr*. 2022;30(3):316–329. https://doi.org/10.3171/2022.6.PEDS22108. Epub 20220722PubMed PMID: 35901673.
25. Sridhar S, Paul MR, Yeh-Nayre L, Khanna PC, Elster J, Aristizabal P, Crawford JR. Single-agent bevacizumab in the treatment of symptomatic newly diagnosed and recurrent/refractory pediatric cervicomedullary brainstem low-grade gliomas: a single institutional experience. *J Pediatr Hematol Oncol*. 2023;45(1). https://doi.org/10.1097/MPH.0000000000002462. e21-e5Epub 20220413PubMed PMID: 35426868.
26. Siegel BI, Nelson D, Peragallo JH, MacDonald TJ, Wolf DS. Visual outcomes after bevacizumab-based therapy for optic pathway glioma. *Pediatr Blood Cancer*. 2023;70(12):e30668. https://doi.org/10.1002/pbc.30668. Epub 20230914PubMed PMID: 37707323.
27. Bennebroek CAM, van Zwol J, Porro GL, Oostenbrink R, Dittrich ATM, Groot ALW, Pott JW, Janssen EJM, Bauer NJ, van Genderen MM, Saeed P, Lequin MH, de Graaf P, Schouten-van Meeteren AYN. Impact of bevacizumab on visual function, tumor size, and toxicity in pediatric progressive optic pathway glioma: a retrospective nationwide multicentre study. *Cancers (Basel)*. 2022;14(24). https://doi.org/10.3390/cancers14246087. Epub 20221210PubMed PMID: 36551572; PMCID: PMC9776082.
28. Bouffet E, Hansford JR, Garre ML, Hara J, Plant-Fox A, Aerts I, Locatelli F, van der Lugt J, Papusha L, Sahm F, Tabori U, Cohen KJ, Packer RJ, Witt O, Sandalic L, Bento Pereira da Silva A, Russo M, Hargrave DR. Dabrafenib plus trametinib in pediatric glioma with BRAF V600 mutations. *N Engl J Med*. 2023;389(12):1108–1120. https://doi.org/10.1056/NEJMoa2303815. PubMed PMID: 37733309.
29. Khatua S, Gutmann DH, Packer RJ. Neurofibromatosis type 1 and optic pathway glioma: molecular interplay and therapeutic insights. *Pediatr Blood Cancer*. 2018;65(3). https://doi.org/10.1002/pbc.26838. Epub 20171019PubMed PMID: 29049847.
30. Guillamo JS, Creange A, Kalifa C, Grill J, Rodriguez D, Doz F, Barbarot S, Zerah M, Sanson M, Bastuji-Garin S, Wolkenstein P, Reseau NFF. Prognostic factors of CNS tumours in Neurofibromatosis 1 (NF1): a retrospective study of 104 patients. *Brain*. 2003;126(Pt 1):152–160. https://doi.org/10.1093/brain/awg016. PubMed PMID: 12477702.
31. Evans DGR, Salvador H, Chang VY, Erez A, Voss SD, Schneider KW, Scott HS, Plon SE, Tabori U. Cancer and Central Nervous System Tumor Surveillance in Pediatric Neurofibromatosis 1. *Clin Cancer Res*. 2017;23(12):e46–e53. https://doi.org/10.1158/1078-0432.CCR-17-0589. PubMed PMID: 28620004.
32. Fisher MJ, Loguidice M, Gutmann DH, Listernick R, Ferner RE, Ullrich NJ, Packer RJ, Tabori U, Hoffman RO, Ardern-Holmes SL, Hummel TR, Hargrave DR, Bouffet E, Charrow J, Bilaniuk LT, Balcer LJ, Liu GT. Visual outcomes in children with neurofibromatosis type 1-associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. *Neuro Oncol*. 2012;14(6):790–797. https://doi.org/10.1093/neuonc/nos076. Epub 20120403PubMed PMID: 22474213; PMCID: PMC3367846.
33. Perilongo et al. 1999-Spontaneous-partial-regression-of-low-grade-glioma-in-children-with-neurofibromatosis-1-a-real.pdf.
34. Fangusaro 2009 Pediatric-high-grade-gliomas-and-diffuse-intrinsic-pontine-gliomas.pdf.
35. Komori T. The 2021 WHO classification of tumors, 5th edition, central nervous system tumors: the 10 basic principles. *Brain Tumor Pathol*. 2022;39(2):47–50. https://doi.org/10.1007/s10014-022-00428-3. PubMed PMID: 35316415.
36. Sejda A, Grajkowska W, Trubicka J, Szutowicz E, Wojdacz T, Kloc W, Izycka-Swieszewska E. WHO CNS5 2021 classification of gliomas: a practical review and road signs for diagnosing pathologists and proper patho-clinical and neuro-oncological cooperation. *Folia Neuropathol*. 2022;60(2):137–152. https://doi.org/10.5114/fn.2022.118183. PubMed PMID: 35950467.
37. Stücklin AG, Ryall S, Fukuoka K, Zapotocky M, Lassaletta A, Arnoldo A, Zhong Y, Kowalski P, Li C, Taylor M, Tabori U, Hawkins C. HGG-19. Molecular analysis uncovers 3 distinct subgroups and multiple targetable gene fusions in infant gliomas. *Neuro Oncol*. 2019;21(Suppl 2). https://doi.org/10.1093/neuonc/noz036.113. ii90-ii1. Epub 2019/04/23PubMed PMID: PMC6477307.
38. Clarke MT, Jones DTW, Mackay A, Carvalho D, Izquierdo E, Hiddingh L, Temelso S, Burford A, Molinari V, Boult JKR, Virasami A, Carceller F, Marshall LV, Zebian B, Chandler C, Al-Sarraj S, Lowis S, Knipstein J, Bailey S, Crosier S, Mastronuzzi A, Carai A, Ellison DW, Baker SJ, Capper D, Maybury M, Moore AS, Vinci M, Hargrave D, Popov S, Jacques TS, Jones C. HGG-25. Infant gliomas comprise multiple biological and clinicopathological subgroups. *Neuro Oncol*. 2018;20(suppl_2). https://doi.org/10.1093/neuonc/noy059.297. i94-i.
39. Robinson G, Desai A, Gauvain K, Basu E, Dorris K, Maese L, Sabnis A, Foster J, Shusterman S, Yoon J, Weiss B, Abdelbaki M, Farid-Kapadia M, Meneses-Lorente G, Cardenas A, Hutchinson K, Bergthold G, Chow Maneval E, Fox E, Gajjar A. PDCT-13. Entrectinib in children and adolescents with recurrent or refractory solid tumors including primary CNS tumors. *Neuro Oncol*. 2019;21(Supplement_6). https://doi.org/10.1093/neuonc/noz175.774. vi186-vi.
40. Finch EA, Duke E, Hwang EI, Packer RJ. Immunotherapy approaches for pediatric CNS tumors and associated neurotoxicity. *Pediatr Neurol*. 2020;107:7–15. https://doi.org/10.1016/j.pediatrneurol.2020.01.004. Epub 20200127PubMed PMID: 32113728.
41. Shalabi H, Nellan A, Shah NN, Gust J. Immunotherapy associated neurotoxicity in pediatric oncology. *Front Oncol*. 2022;12, 836452. https://doi.org/10.3389/fonc.2022.836452. Epub 20220221PubMed PMID: 35265526; PMCID: PMC8899040.
42. Johnson RA, Wright KD, Poppleton H, Mohankumar KM, Finkelstein D, Pounds SB, Rand V, Leary SE, White E, Eden C, Hogg T, Northcott P, Mack S, Neale G, Wang YD, Coyle B, Atkinson J, DeWire M, Kranenburg TA, Gillespie Y, Allen JC, Merchant T, Boop FA, Sanford RA, Gajjar A, Ellison DW, Taylor MD, Grundy RG, Gilbertson RJ. Cross-species genomics matches driver mutations and cell compartments to model

ependymoma. *Nature*. 2010;466(7306):632–636. https://doi.org/10.1038/nature09173. Epub 20100718PubMed PMID: 20639864; PMCID: PMC2912966.
43. Taylor MD, Poppleton H, Fuller C, Su X, Liu Y, Jensen P, Magdaleno S, Dalton J, Calabrese C, Board J, Macdonald T, Rutka J, Guha A, Gajjar A, Curran T, Gilbertson RJ. Radial glia cells are candidate stem cells of ependymoma. *Cancer Cell*. 2005;8(4):323–335. https://doi.org/10.1016/j.ccr.2005.09.001. PubMed PMID: 16226707.
44. Pajtler KW, Mack SC, Ramaswamy V, Smith CA, Witt H, Smith A, Hansford JR, von Hoff K, Wright KD, Hwang E, Frappaz D, Kanemura Y, Massimino M, Faure-Conter C, Modena P, Tabori U, Warren KE, Holland EC, Ichimura K, Giangaspero F, Castel D, von Deimling A, Kool M, Dirks PB, Grundy RG, Foreman NK, Gajjar A, Korshunov A, Finlay J, Gilbertson RJ, Ellison DW, Aldape KD, Merchant TE, Bouffet E, Pfister SM, Taylor MD. The current consensus on the clinical management of intracranial ependymoma and its distinct molecular variants. *Acta Neuropathol*. 2017;133(1):5–12. https://doi.org/10.1007/s00401-016-1643-0. Epub 20161117PubMed PMID: 27858204; PMCID: PMC5209402.
45. Pajtler KW, Witt H, Sill M, Jones DT, Hovestadt V, Kratochwil F, Wani K, Tatevossian R, Punchihewa C, Johann P, Reimand J, Warnatz HJ, Ryzhova M, Mack S, Ramaswamy V, Capper D, Schweizer L, Sieber L, Wittmann A, Huang Z, van Sluis P, Volckmann R, Koster J, Versteeg R, Fults D, Toledano H, Avigad S, Hoffman LM, Donson AM, Foreman N, Hewer E, Zitterbart K, Gilbert M, Armstrong TS, Gupta N, Allen JC, Karajannis MA, Zagzag D, Hasselblatt M, Kulozik AE, Witt O, Collins VP, von Hoff K, Rutkowski S, Pietsch T, Bader G, Yaspo ML, von Deimling A, Lichter P, Taylor MD, Gilbertson R, Ellison DW, Aldape K, Korshunov A, Kool M, Pfister SM. Molecular classification of ependymal tumors across all CNS compartments, histopathological grades, and age groups. *Cancer Cell*. 2015;27(5):728–743. https://doi.org/10.1016/j.ccell.2015.04.002. PubMed PMID: 25965575; PMCID: PMC4712639.
46. Ramaswamy V, Hielscher T, Mack SC, Lassaletta A, Lin T, Pajtler KW, Jones DT, Luu B, Cavalli FM, Aldape K, Remke M, Mynarek M, Rutkowski S, Gururangan S, McLendon RE, Lipp ES, Dunham C, Hukin J, Eisenstat DD, Fulton D, van Landeghem FK, Santi M, van Veelen ML, Van Meir EG, Osuka S, Fan X, Muraszko KM, Tirapelli DP, Oba-Shinjo SM, Marie SK, Carlotti CG, Lee JY, Rao AA, Giannini C, Faria CC, Nunes S, Mora J, Hamilton RL, Hauser P, Jabado N, Petrecca K, Jung S, Massimi L, Zollo M, Cinalli G, Bognar L, Klekner A, Hortobagyi T, Leary S, Ermoian RP, Olson JM, Leonard JR, Gardner C, Grajkowska WA, Chambless LB, Cain J, Eberhart CG, Ahsan S, Massimino M, Giangaspero F, Buttarelli FR, Packer RJ, Emery L, Yong WH, Soto H, Liau LM, Everson R, Grossbach A, Shalaby T, Grotzer M, Karajannis MA, Zagzag D, Wheeler H, von Hoff K, Alonso MM, Tunon T, Schuller U, Zitterbart K, Sterba J, Chan JA, Guzman M, Elbabaa SK, Colman H, Dhall G, Fisher PG, Fouladi M, Gajjar A, Goldman S, Hwang E, Kool M, Ladha H, Vera-Bolanos E, Wani K, Lieberman F, Mikkelsen T, Omuro AM, Pollack IF, Prados M, Robins HI, Soffietti R, Wu J, Metellus P, Tabori U, Bartels U, Bouffet E, Hawkins CE, Rutka JT, Dirks P, Pfister SM, Merchant TE, Gilbert MR, Armstrong TS, Korshunov A, Ellison DW, Taylor MD. Therapeutic impact of cytoreductive surgery and irradiation of posterior fossa ependymoma in the molecular era: a retrospective multicohort analysis. *J Clin Oncol*. 2016;34(21):2468–2477. https://doi.org/10.1200/JCO.2015.65.7825. Epub 20160606PubMed PMID: 27269943; PMCID: PMC4962737.
47. Ramaswamy V, Taylor MD. Treatment implications of posterior fossa ependymoma subgroups. *Chin J Cancer*. 2016;35(1):93. https://doi.org/10.1186/s40880-016-0155-6. Epub 20161115PubMed PMID: 27846874; PMCID: PMC5111181.
48. Witt H, Mack SC, Ryzhova M, Bender S, Sill M, Isserlin R, Benner A, Hielscher T, Milde T, Remke M, Jones DT, Northcott PA, Garzia L, Bertrand KC, Wittmann A, Yao Y, Roberts SS, Massimi L, Van Meter T, Weiss WA, Gupta N, Grajkowska W, Lach B, Cho YJ, von Deimling A, Kulozik AE, Witt O, Bader GD, Hawkins CE, Tabori U, Guha A, Rutka JT, Lichter P, Korshunov A, Taylor MD, Pfister SM. Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma. *Cancer Cell*. 2011;20(2):143–157. https://doi.org/10.1016/j.ccr.2011.07.007. PubMed PMID: 21840481; PMCID: PMC4154494.
49. Parker M, Mohankumar KM, Punchihewa C, Weinlich R, Dalton JD, Li Y, Lee R, Tatevossian RG, Phoenix TN, Thiruvenkatam R, White E, Tang B, Orisme W, Gupta K, Rusch M, Chen X, Li Y, Nagahawhatte P, Hedlund E, Finkelstein D, Wu G, Shurtleff S, Easton J, Boggs K, Yergeau D, Vadodaria B, Mulder HL, Becksfort J, Gupta P, Huether R, Ma J, Song G, Gajjar A, Merchant T, Boop F, Smith AA, Ding L, Lu C, Ochoa K, Zhao D, Fulton RS, Fulton LL, Mardis ER, Wilson RK, Downing JR, Green DR, Zhang J, Ellison DW, Gilbertson RJ. C11orf95-RELA fusions drive oncogenic NF-kappaB signalling in ependymoma. *Nature*. 2014;506(7489):451–455. https://doi.org/10.1038/nature13109. Epub 20140219PubMed PMID: 24553141; PMCID: PMC4050669.
50. Zheng T, Ghasemi DR, Okonechnikov K, Korshunov A, Sill M, Maass KK, Benites Goncalves da Silva P, Ryzhova M, Gojo J, Stichel D, Arabzade A, Kupp R, Benzel J, Taya S, Adachi T, Shiraishi R, Gerber NU, Sturm D, Ecker J, Sievers P, Selt F, Chapman R, Haberler C, Figarella-Branger D, Reifenberger G, Fleischhack G, Rutkowski S, Donson AM, Ramaswamy V, Capper D, Ellison DW, Herold-Mende CC, Schuller U, Brandner S, Driever PH, Kros JM, Snuderl M, Milde T, Grundy RG, Hoshino M, Mack SC, Gilbertson RJ, Jones DTW, Kool M, von Deimling A, Pfister SM, Sahm F, Kawauchi D, Pajtler KW. Cross-species genomics reveals oncogenic dependencies in ZFTA/C11orf95 fusion-positive supratentorial ependymomas. *Cancer Discov*. 2021;11(9):2230–2247. https://doi.org/10.1158/2159-8290.CD-20-0963. Epub 20210420PubMed PMID: 33879448.
51. Merchant TE, Bendel AE, Sabin ND, Burger PC, Shaw DW, Chang E, Wu S, Zhou T, Eisenstat DD, Foreman NK, Fuller CE, Anderson ET, Hukin J, Lau CC, Pollack IF, Laningham FH, Lustig RH, Armstrong FD, Handler MH, Williams-Hughes C, Kessel S, Kocak M, Ellison DW, Ramaswamy V. Conformal radiation therapy for pediatric ependymoma, chemotherapy for incompletely resected ependymoma, and observation for completely resected, supratentorial ependymoma. *J Clin Oncol*. 2019;37(12):974–983. https://doi.org/10.1200/JCO.18.01765. Epub 20190227PubMed PMID: 30811284; PMCID: PMC7186586.
52. Baroni LV, Sundaresan L, Heled A, Coltin H, Pajtler KW, Lin T, Merchant TE, McLendon R, Faria C, Buntine M, White CL, Pfister SM, Gilbert MR, Armstrong TS, Bouffet E, Kumar S, Taylor MD, Aldape KD, Ellison DW, Gottardo NG, Kool M, Korshunov A, Hansford JR, Ramaswamy V. Ultra high-risk PFA ependymoma is characterized by loss of chromosome 6q. *Neuro Oncol*. 2021;23(8):1360–1370. https://doi.org/10.1093/neuonc/noab034. PubMed PMID: 33580238; PMCID: PMC8328032.
53. Bouffet E FN. Chemotherapy for intracranial ependymomas. *Childs Nerv Syst*. 1999;15(10):563–570. https://doi.org/10.1007/s003810050544.
54. Siffert J AJ. Chemotherapy in recurrent ependymoma. *Pediatr Neurosurg*. 1998;28(6):314–319. https://doi.org/10.1159/000028669.
55. Price M, Ballard C, Benedetti J, Neff C, Cioffi G, Waite KA, Kruchko C, Barnholtz-Sloan JS, Ostrom QT. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2017-2021. *Neuro Oncol*. 2024;26(Supplement_6). https://doi.org/10.1093/neuonc/noae145. vi1-vi85PubMed PMID: 39371035; PMCID: PMC11456825.
56. Jakacki RI, Burger PC, Zhou T, Holmes EJ, Kocak M, Onar A, Goldwein J, Mehta M, Packer RJ, Tarbell N, Fitz C, Vezina G, Hilden J, Pollack IF. Outcome of children with metastatic medulloblastoma treated with carboplatin during craniospinal radiotherapy: a Children's Oncology Group Phase I/II study. *J Clin Oncol*. 2012;30(21):2648–2653. https://doi.org/10.1200/JCO.2011.40.2792. Epub 20120604PubMed PMID: 22665539; PMCID: PMC4559602.
57. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, Eberhart CG, Parsons DW, Rutkowski S, Gajjar A, Ellison DW, Lichter P, Gilbertson RJ, Pomeroy SL, Kool M, Pfister SM. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol*. 2012;123(4):465–472. https://doi.org/10.1007/s00401-011-0922-z. Epub 20111202PubMed PMID: 22134537; PMCID: PMC3306779.
58. Hovestadt V, Smith KS, Bihannic L, Filbin MG, Shaw ML, Baumgartner A, DeWitt JC, Groves A, Mayr L, Weisman HR, Richman AR, Shore ME, Goumnerova L, Rosencrance C, Carter RA, Phoenix TN, Hadley JL, Tong Y, Houston J, Ashmun RA, DeCuypere M, Sharma T, Flasch D, Silkov A, Ligon KL, Pomeroy SL, Rivera MN, Rozenblatt-Rosen O, Rusert JM, Wechsler-Reya RJ, Li XN, Peyrl A, Gojo J, Kirchhofer D, Lotsch D, Czech T, Dorfer C, Haberler C, Geyeregger R, Halfmann A, Gawad C, Easton J, Pfister SM, Regev A, Gajjar A, Orr BA, Slavc I, Robinson GW, Bernstein BE, Suva ML, Northcott PA. Resolving medulloblastoma cellular architecture by single-cell genomics. *Nature*. 2019;572(7767):74–79. https://doi.org/10.1038/s41586-019-1434-6. Epub 20190724PubMed PMID: 31341285; PMCID: PMC6754173.
59. Ramaswamy V, Remke M, Bouffet E, Bailey S, Clifford SC, Doz F, Kool M, Dufour C, Vassal G, Milde T, Witt O, von Hoff K, Pietsch T, Northcott PA, Gajjar A, Robinson GW, Padovani L, Andre N, Massimino M, Pizer B, Packer R, Rutkowski S, Pfister SM, Taylor MD, Pomeroy SL. Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. *Acta Neuropathol*. 2016;131(6):821–831. https://doi.org/10.1007/s00401-016-1569-6. Epub 20160404PubMed PMID: 27040285; PMCID: PMC4867119.
60. Visvanathan A, Saulnier O, Chen C, Haldipur P, Orisme W, Delaidelli A, Shin S, Millman J, Bryant A, Abeysundara N, Wu X, Hendrikse LD, Patil V, Bashardanesh Z, Golser J, Livingston BG, Nakashima T, Funakoshi Y, Ong W, Rasnitsyn A, Aldinger KA, Richman CM, Van Ommeren R, Lee JJY, Ly M, Vladoiu MC, Kharas K, Balin P, Erickson AW, Fong V, Zhang J, Suarez RA, Wang H, Huang N, Pallota JG, Douglas T, Haapasalo J, Razavi F, Silvestri E, Sirbu O, Worme S, Kameda-Smith MM, Wu X, Daniels C, MichaelRaj AK, Bhaduri A, Schramek D, Suzuki H, Garzia L, Ahmed N, Kleinman CL, Stein LD, Dirks P, Dunham C, Jabado N, Rich JN, Li W, Sorensen PH, Wechsler-Reya RJ, Weiss WA, Millen KJ, Ellison DW, Dimitrov DS, Taylor MD. Early rhombic lip Protogenin(+ve) stem cells in a human-specific neurovascular niche initiate and maintain group 3 medulloblastoma. *Cell*. 2024;187(17):4733–4750. https://doi.org/10.1016/j.cell.2024.06.011. e26. Epub 20240705PubMed PMID: 38971152; PMCID: PMC11707800.
61. Vladoiu MC, El-Hamamy I, Donovan LK, Farooq H, Holgado BL, Sundaravadanam Y, Ramaswamy V, Hendrikse LD, Kumar S, Mack SC, Lee JJY, Fong V, Juraschka K, Przelicki D, Michealraj A, Skowron P, Luu B, Suzuki H, Morrissy AS, Cavalli FMG, Garzia L, Daniels C, Wu X, Qazi MA, Singh SK, Chan JA, Marra MA, Malkin D, Dirks P, Heisler L, Pugh T, Ng K, Notta F, Thompson EM, Kleinman CL, Joyner AL, Jabado N, Stein L, Taylor MD. Childhood cerebellar tumours mirror conserved fetal transcriptional programs. *Nature*. 2019;572(7767):67–73. https://doi.org/10.1038/s41586-019-1158-7. Epub 20190501PubMed PMID: 31043743; PMCID: PMC6675628.
62. Hendrikse LD, Haldipur P, Saulnier O, Millman J, Sjoboen AH, Erickson AW, Ong W, Gordon V, Coudiere-Morrison L, Mercier AL, Shokouhian M, Suarez RA, Ly M, Borlase S, Scott DS, Vladoiu MC, Farooq H, Sirbu O, Nakashima T, Nambu S, Funakoshi Y, Bahcheli A, Diaz-Mejia JJ, Golser J, Bach K, Phuong-Bao T, Skowron P, Wang EY, Kumar SA, Balin P, Visvanathan A, Lee JJY, Ayoub R, Chen X, Chen X, Mungall KL, Luu B, Berube P, Wang YC, Pfister SM, Kim SK, Delattre O, Bourdeaut F, Doz F, Masliah-Planchon J, Grajkowska WA, Loukides J, Dirks P, Fevre-Montange M, Jouvet A, French PJ, Kros JM, Zitterbart K, Bailey SD, Eberhart CG, Rao AAN, Giannini C, Olson JM, Garami M, Hauser P, Phillips JJ, Ra YS, de Torres C, Mora J, Li KKW, Ng HK, Poon WS, Pollack IF, Lopez-Aguilar E, Gillespie GY, Van Meter TE, Shofuda T, Vibhakar R, Thompson RC, Cooper MK, Rubin JB, Kumabe T, Jung S, Lach B, Iolascon A, Ferrucci V, de Antonellis P, Zollo M, Cinalli G, Robinson S, Stearns DS, Van Meir EG, Porrati P, Finocchiaro G, Massimino M, Carlotti CG, Faria CC, Roussel MF, Boop F, Chan JA, Aldinger KA, Razavi F, Silvestri E, McLendon RE, Thompson EM, Ansari M, Garre ML, Chico F, Eguia P, Perezpena M,

Morrissy AS, Cavalli FMG, Wu X, Daniels C, Rich JN, Jones SJM, Moore RA, Marra MA, Huang X, Reimand J, Sorensen PH, Wechsler-Reya RJ, Weiss WA, Pugh TJ, Garzia L, Kleinman CL, Stein LD, Jabado N, Malkin D, Ayrault O, Golden JA, Ellison DW, Doble B, Ramaswamy V, Werbowetski-Ogilvie TE, Suzuki H, Millen KJ, Taylor MD. Failure of human rhombic lip differentiation underlies medulloblastoma formation. *Nature*. 2022;609(7929):1021–1028. https://doi.org/10.1038/s41586-022-05215-w. Epub 20220921PubMed PMID: 36131014; PMCID: PMC10026724.

63. Gudrunardottir T, Sehested A, Juhler M, Schmiegelow K. Cerebellar mutism: review of the literature. *Childs Nerv Syst*. 2011;27(3):355–363. https://doi.org/10.1007/s00381-010-1328-2. PubMed PMID: 21061011.
64. Cohen BH, Geyer JR, Miller DC, Curran JG, Zhou T, Holmes E, Ingles SA, Dunkel IJ, Hilden J, Packer RJ, Pollack IF, Gajjar A, Finlay JL. Children's Oncology G. Pilot study of intensive chemotherapy with peripheral hematopoietic cell support for children less than 3 years of age with malignant brain tumors, the CCG-99703 Phase I/II study. a report from the children's oncology group. *Pediatr Neurol*. 2015;53(1):31–46. https://doi.org/10.1016/j.pediatrneurol.2015.03.019. Epub 20150409PubMed PMID: 26092413; PMCID: PMC5166616.
65. Lafay-Cousin L, Smith A, Chi SN, Wells E, Madden J, Margol A, Ramaswamy V, Finlay J, Taylor MD, Dhall G, Strother D, Kieran MW, Foreman NK, Packer RJ, Bouffet E. Clinical, pathological, and molecular characterization of infant medulloblastomas treated with sequential high-dose chemotherapy. *Pediatr Blood Cancer*. 2016;63(9):1527–1534. https://doi.org/10.1002/pbc.26042. Epub 20160504PubMed PMID: 27145464; PMCID: PMC5031363.
66. Robinson GW, Rudneva VA, Buchhalter I, Billups CA, Waszak SM, Smith KS, Bowers DC, Bendel A, Fisher PG, Partap S, Crawford JR, Hassall T, Indelicato DJ, Boop F, Klimo P, Sabin ND, Patay Z, Merchant TE, Stewart CF, Orr BA, Korbel JO, Jones DTW, Sharma T, Lichter P, Kool M, Korshunov A, Pfister SM, Gilbertson RJ, Sanders RP, Onar-Thomas A, Ellison DW, Gajjar A, Northcott PA. Risk-adapted therapy for young children with medulloblastoma (SJYC07): therapeutic and molecular outcomes from a multicentre, phase 2 trial. *Lancet Oncol*. 2018;19(6):768–784. https://doi.org/10.1016/S1470-2045(18)30204-3. Epub 20180516PubMed PMID: 29778738; PMCID: PMC6078206.
67. Pietsch T, Schmidt R, Remke M, Korshunov A, Hovestadt V, Jones DT, Felsberg J, Kaulich K, Goschzik T, Kool M, Northcott PA, von Hoff K, von Bueren AO, Friedrich C, Mynarek M, Skladny H, Fleischhack G, Taylor MD, Cremer F, Lichter P, Faldum A, Reifenberger G, Rutkowski S, Pfister SM. Prognostic significance of clinical, histopathological, and molecular characteristics of medulloblastomas in the prospective HIT2000 multicenter clinical trial cohort. *Acta Neuropathol*. 2014;128(1):137–149. https://doi.org/10.1007/s00401-014-1276-0. Epub 20140504PubMed PMID: 24791927; PMCID: PMC4059991.
68. Gajjar A, Chintagumpala M, Ashley D, Kellie S, Kun LE, Merchant TE, Woo S, Wheeler G, Ahern V, Krasin MJ, Fouladi M, Broniscer A, Krance R, Hale GA, Stewart CF, Dauser R, Sanford RA, Fuller C, Lau C, Boyett JM, Wallace D, Gilbertson RJ. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol*. 2006;7(10):813–820. https://doi.org/10.1016/S1470-2045(06)70867-1. PubMed PMID: 17012043.
69. Lannering B, Rutkowski S, Doz F, Pizer B, Gustafsson G, Navajas A, Massimino M, Reddingius R, Benesch M, Carrie C, Taylor R, Gandola L, Bjork-Eriksson T, Giralt J, Oldenburger F, Pietsch T, Figarella-Branger D, Robson K, Forni M, Clifford SC, Warmuth-Metz M, von Hoff K, Faldum A, Mosseri V, Kortmann R. Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. *J Clin Oncol*. 2012;30(26):3187–3193. https://doi.org/10.1200/JCO.2011.39.8719. Epub 20120730PubMed PMID: 22851561.
70. Gandola L, Massimino M, Cefalo G, Solero C, Spreafico F, Pecori E, Riva D, Collini P, Pignoli E, Giangaspero F, Luksch R, Berretta S, Poggi G, Biassoni V, Ferrari A, Pollo B, Favre C, Sardi I, Terenziani M, Fossati-Bellani F. Hyperfractionated accelerated radiotherapy in the Milan strategy for metastatic medulloblastoma. *J Clin Oncol*. 2009;27(4):566–571. https://doi.org/10.1200/JCO.2008.18.4176. Epub 20081215PubMed PMID: 19075266.
71. Packer RJ, Gajjar A, Vezina G, Rorke-Adams L, Burger PC, Robertson PL, Bayer L, LaFond D, Donahue BR, Marymont MH, Muraszko K, Langston J, Sposto R. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J Clin Oncol*. 2006;24(25):4202–4208. https://doi.org/10.1200/JCO.2006.06.4980. PubMed PMID: 16943538.
72. Coltin H, Pequeno P, Liu N, Tsang DS, Gupta S, Taylor MD, Bouffet E, Nathan PC, Ramaswamy V. The burden of surviving childhood medulloblastoma: a population-based, matched cohort study in Ontario. *Canada. J Clin Oncol*. 2023;41(13):2372–2381. https://doi.org/10.1200/JCO.22.02466. Epub 20230125PubMed PMID: 36696605; PMCID: PMC10150896.
73. Jabarkheel R, Amayiri N, Yecies D, Huang Y, Toescu S, Nobre L, Mabbott DJ, Sudhakar SV, Malik P, Laughlin S, Swaidan M, Al Hussaini M, Musharbash A, Chacko G, Mathew LG, Fisher PG, Hargrave D, Bartels U, Tabori U, Pfister SM, Aquilina K, Taylor MD, Grant GA, Bouffet E, Mankad K, Yeom KW, Ramaswamy V. Molecular correlates of cerebellar mutism syndrome in medulloblastoma. *Neuro Oncol*. 2020;22(2):290–297. https://doi.org/10.1093/neuonc/noz158. PubMed PMID: 31504816; PMCID: PMC7442348.