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Childhood Astrocytomas Treatment (PDQ®)

Health Professional Version

PDQ Pediatric Treatment Editorial Board.

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This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of childhood astrocytomas. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

This summary is reviewed regularly and updated as necessary by the PDQ Pediatric Treatment Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

General Information About Childhood Astrocytomas

Primary brain tumors, including astrocytomas, are a diverse group of diseases that together constitute the most common solid tumors of childhood. Brain tumors are classified according to histology and molecular features, but tumor location and extent of spread are also important factors that affect treatment and prognosis. Immunohistochemical analysis, cytogenetic and molecular genetic findings, and measures of mitotic activity are used in tumor diagnosis and classification.

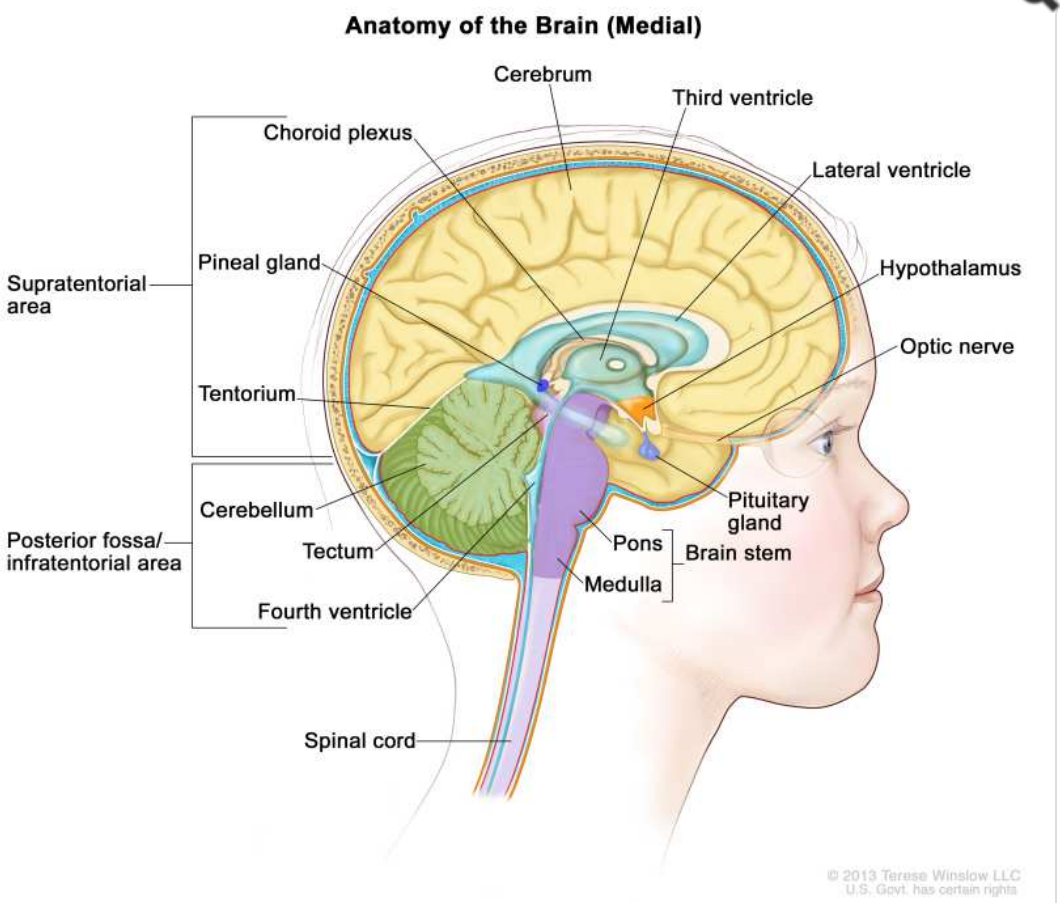
Gliomas are thought to arise from glial precursor cells that are present in the brain and spinal cord. Gliomas are named according to their presumed clinicopathologic and histologic subtype. Astrocytoma is the most commonly diagnosed type of glioma in children.

According to the World Health Organization (WHO) classification of brain tumors, gliomas are classified further as low-grade (grades I and II) or high-grade (grades III and IV) tumors. Children with low-grade tumors have a relatively favorable prognosis, especially when the tumors can be completely resected. Children with high-grade tumors generally have a less favorable prognosis, but this is somewhat dependent on subtype.

The PDQ childhood brain tumor treatment summaries are organized primarily according to the WHO classification of nervous system tumors.[1,2] For a full description of the classification of nervous system tumors and a link to the corresponding treatment summary for each type of brain tumor, refer to the PDQ summary on Childhood Brain and Spinal Cord Tumors Treatment Overview.

Anatomy

Childhood astrocytomas can occur anywhere in the central nervous system (CNS) (refer to the Figure). Refer to Table 3 for the most common CNS location for each tumor type.



Anatomy of the inside of the brain, showing the cerebrum, cerebellum, brain stem, spinal cord, optic nerve, hypothalamus, and other parts of the brain.

Clinical Features

Presenting symptoms for childhood astrocytomas depend on the following:

- CNS location.
- Size of the tumor.
- Rate of tumor growth.
- Chronologic and developmental age of the child.

In infants and young children, low-grade astrocytomas presenting in the hypothalamus may result in diencephalic syndrome, which is manifested by failure to thrive in an emaciated, seemingly euphoric child. Such children may have little in the way of other neurologic findings, but can have macrocephaly, intermittent lethargy, and visual impairment.[3]

Diagnostic Evaluation

The diagnostic evaluation for astrocytoma includes magnetic resonance imaging (MRI) of the brain or spine. For brain primary tumors, spinal MRI is usually performed in conjunction with the initial brain MRI to exclude neuraxis metastases.

Lumbar punctures examining the cerebrospinal fluid for circulating tumor cells are not commonly performed in children with this disease.

Clinicopathologic Classification of Childhood Astrocytomas and Other Tumors of Glial Origin

The pathologic classification of pediatric brain tumors is a specialized area that is evolving. Examination of the diagnostic tissue by a neuropathologist who has particular expertise in this area is strongly recommended.

Tumor types are based on the putative glial cell type of origin, as follows:

- Astrocytomas (astrocytes).
- Oligodendroglial tumors (oligodendrocytes).
- Mixed gliomas (cell types of origin include oligodendrocytes, astrocytes, and ependymal cells).
- Mixed neuronal-glial tumors.

WHO histologic grade for astrocytic tumors

According to the WHO histologic typing of CNS tumors, childhood astrocytomas and other tumors of glial origin are classified according to clinicopathologic and histologic subtype and are graded (grade I to IV).[1]

WHO histologic grades are commonly referred to as low-grade gliomas or high-grade gliomas (refer to Table 1).

Table 1. World Health Organization (WHO) Histologic Grade and Corresponding Classification for Tumors of the Central Nervous System

WHO Histologic Grade	Grade Classification
I	Low grade
II	Low grade
III	High grade
IV	High grade

The 2016 WHO criteria began to utilize molecular data in the diagnosis of some tumors because of the accumulation of published evidence that tumor behavior is typically driven by common biological alterations (refer to Table 2). Within glial CNS tumors, this was most evident in changes in the classification of the diffuse gliomas, which were grouped together based on genetic driver mutations rather than histopathological similarities.[2] Two types of diffuse gliomas are no longer considered distinct entities: fibrillary astrocytoma and protoplasmic astrocytoma. Epithelioid glioblastoma is a new, provisionally included variant that is categorized as one subtype of *IDH*–wild-type glioblastoma.

Table 2. 2016 World Health Organization (WHO) Classification and Histologic Grade of Astrocytic Tumors[a]

Type	WHO Histologic Grade
Diffuse Astrocytic Tumors:	
—Diffuse astrocytoma, *IDH*-mutant	II
—Anaplastic astrocytoma, *IDH*-mutant	III
—Glioblastoma, *IDH*–wild-type	IV
—Glioblastoma, *IDH*-mutant	IV
—Diffuse midline glioma, H3 K27M-mutant	IV
Other Astrocytic Tumors:	
—Pilocytic astrocytoma	I

Type	WHO Histologic Grade
—Pilomyxoid astrocytoma	Grade uncertain[b]
—Pleomorphic xanthoastrocytoma	II
—Anaplastic pleomorphic xanthoastrocytoma	III
—Subependymal giant cell astrocytoma	I
Other Gliomas:	
—Angiocentric glioma	I
—Choroid glioma of the third ventricle	II
—Astroblastoma	Grade uncertain

[a]Adapted from Louis et al.[2]

[b]In 2007, the WHO determined that the pilomyxoid variant of pilocytic astrocytoma may be an aggressive variant that is more likely to disseminate, and it was reclassified as a grade II tumor.[1,2,4,5] In 2016, the WHO suggested not grading the pilomyxoid variant until further studies clarify its behavior.[1,2]

CNS location

Childhood astrocytomas and other tumors of glial origin can occur anywhere in the CNS, although each tumor type tends to have common CNS locations (refer to Table 3).

Table 3. Common Central Nervous System (CNS) Locations for Childhood Astrocytomas and Other Tumors of Glial Origin

Tumor Type	Common CNS Location
Pilocytic astrocytoma	Optic nerve, optic chiasm/hypothalamus, thalamus and basal ganglia, cerebral hemispheres, cerebellum, and brain stem; and spinal cord (rare)
Pleomorphic xanthoastrocytoma	Superficial location in cerebrum (temporal lobe preferentially)
Diffuse astrocytoma	Cerebrum (frontal and temporal lobes), brain stem, spinal cord, optic nerve, optic chiasm, optic pathway, hypothalamus, and thalamus
Anaplastic astrocytoma, glioblastoma	Cerebrum; occasionally cerebellum, brain stem, and spinal cord
Diffuse midline glioma, H3 K27M-mutant	Pons, thalamus, spinal cord, and other midline structures

Cerebellum: More than 80% of astrocytomas located in the cerebellum are low grade (pilocytic grade I) and often cystic; most of the remainder are diffuse grade II astrocytomas. Malignant astrocytomas in the cerebellum are rare.[1,2] The presence of certain histologic features (e.g., MIB-1 rate, anaplasia) has been used retrospectively to predict event-free survival for pilocytic astrocytomas arising in the cerebellum or other locations.[6-8]

Brain stem: Astrocytomas arising in the brain stem may be either high grade or low grade, with the frequency of either type being highly dependent on the location of the tumor within the brain stem.[9,10] Tumors not involving the pons are overwhelmingly low-grade gliomas (e.g., tectal gliomas of the midbrain), whereas tumors located exclusively in the pons without exophytic components are largely diffuse midline gliomas (e.g., diffuse intrinsic pontine gliomas with the H3 K27M-mutant genotype).[9,10] (Refer to the PDQ summary on Childhood Brain Stem Glioma Treatment for more information.)

Cerebrum: High-grade astrocytomas are often locally invasive and extensive and tend to occur

above the tentorium in the cerebrum.[11] Spread via the subarachnoid space may occur. Metastasis outside of the CNS has been reported but is extremely infrequent until multiple local relapses have occurred.

Gliomatosis cerebri is no longer considered a distinct entity, but rather to be a growth pattern found in some diffuse astrocytic tumors and, occasionally, oligodendroglial tumors. The growth pattern encompasses widespread involvement of the cerebral hemispheres, often extending caudally to affect the brain stem, cerebellum, and/or spinal cord.[1] This pattern rarely arises in the cerebellum and spreads rostrally.[12] Patients with gliomatosis cerebri may respond to treatment initially, but overall have a poor prognosis.[13]

Neurofibromatosis type 1 (NF1)

Children with NF1 have an increased propensity to develop WHO grade I and grade II astrocytomas in the visual (optic) pathway; as many as 20% of all patients with NF1 will develop an optic pathway glioma. In these patients, the tumor may be found on screening evaluations when the child is asymptomatic or has apparent static neurologic and/or visual deficits.

Pathologic confirmation is frequently not obtained in asymptomatic patients; when biopsies have been performed, these tumors have been found to be predominantly pilocytic (grade I) rather than diffuse astrocytic tumors.[2,5,14]

In general, treatment is not required for incidental tumors found with surveillance neuroimaging. Symptomatic lesions, often causing vision impairment, or those that have radiographically progressed may require treatment.[15]

Tuberous sclerosis

Patients with tuberous sclerosis have a predilection for low-grade glioma development, especially subependymal giant cell astrocytomas. Mutations in either *TSC1* or *TSC2* cause pathway alterations that impact the mammalian target of rapamycin (mTOR) pathway, leading to increases in proliferation. Subependymal giant cell astrocytomas have been sensitive to targeted approaches via inhibition of the mTOR pathway.[16]

Genomic Alterations

Molecular features of low-grade gliomas

Pilocytic and diffuse astrocytomas

Genomic alterations involving activation of *BRAF* and the ERK/MAPK pathway are very common in sporadic cases of pilocytic astrocytoma, a type of low-grade glioma.

BRAF-KIAA1549 alterations

BRAF activation in pilocytic astrocytoma occurs most commonly through a *BRAF-KIAA1549* gene fusion, producing a fusion protein that lacks the BRAF regulatory domain.[17-21] This fusion is seen in most infratentorial and midline pilocytic astrocytomas, but is present at lower frequency in supratentorial (hemispheric) tumors.[17,18,22-27]

Presence of the *BRAF-KIAA1549* fusion predicted a better clinical outcome (progression-free survival [PFS] and overall survival [OS]) in one report that described children with incompletely resected low-grade gliomas.[26] However, other factors such as *CDKN2A* deletion, whole chromosome 7 gain, and tumor location may modify the impact of the *BRAF* mutation on outcome.[28]; [29][Level of evidence: 3iiiDiii] Progression to high-grade glioma is rare for pediatric low-grade glioma with the *BRAF-KIAA1549* fusion.[30]

BRAF activation through the *BRAF-KIAA1549* fusion has also been described in other pediatric low-grade gliomas (e.g., pilomyxoid astrocytoma).[25,26] Other genomic alterations in pilocytic

astrocytomas that can activate the ERK/MAPK pathway (e.g., alternative *BRAF* gene fusions, *RAF1* rearrangements, *RAS* mutations, and *BRAF* V600E point mutations) are less commonly observed.[18,20,21,31]

BRAF V600E mutations

BRAF V600E point mutations are occasionally observed in pilocytic astrocytoma; the mutations are also observed in nonpilocytic pediatric low-grade gliomas, including gangliogliomа,[32] desmoplastic infantile ganglioglioma, and approximately two-thirds of pleomorphic xanthoastrocytomas.[33-35]

Studies have observed the following:

- In a retrospective series of more than 400 children with low-grade gliomas, 17% of tumors were *BRAF* V600E mutant. The 10-year PFS rate was 27% for *BRAF* V600E–mutant cases, compared with 60% for cases whose tumors did not harbor that mutation. Additional factors associated with this poor prognosis included subtotal resection and *CDKN2A* deletion.[36] Even in patients who underwent a gross-total resection, recurrence was noted in one-third of these cases, suggesting that *BRAF* V600E tumors have a more invasive phenotype than do other low-grade glioma variants.
- In a similar analysis, children with diencephalic low-grade astrocytomas with a *BRAF* V600E mutation had a 5-year PFS rate of 22%, compared with a PFS rate of 52% in children who were *BRAF* wild-type.[37][Level of evidence: 3iiiDiii]
- The frequency of the *BRAF* V600E mutation was significantly higher in pediatric low-grade glioma that transformed to high-grade glioma (8 of 18 cases) than was the frequency of the mutation in cases that did not transform to high-grade glioma (10 of 167 cases).[30]

Other mutations

Activating mutations in *FGFR1*, *PTPN11*, and *NTRK2* fusion genes have also been identified in noncerebellar pilocytic astrocytomas.[38] In pediatric grade II diffuse astrocytomas, the most common alterations reported (up to 53% of tumors) are rearrangements in the MYB family of transcription factors.[39,40]

Angiocentric gliomas

Angiocentric gliomas typically arise in children and young adults as cerebral tumors presenting with seizures.[2]

Two reports in 2016 identified *MYB* gene alterations as being present in almost all cases diagnosed as angiocentric glioma, with *QKI* being the primary fusion partner in cases where fusion-partner testing was possible.[41,42] While angiocentric gliomas most commonly occur supratentorially, brain stem angiocentric gliomas with *MYB-QKI* fusions have also been reported.[43,44]

Astroblastomas

Astroblastomas are defined histologically as glial neoplasms composed of GFAP-positive cells and contain astroblastic pseudorosettes that often demonstrate sclerosis. Astroblastomas are diagnosed primarily in childhood through young adulthood.[2]

The following studies have described genomic alterations associated with astroblastoma:

- A report describing a molecular classification of CNS primitive neuroectodermal tumors (PNETs) identified an entity termed *CNS high-grade neuroepithelial tumor with MN1 alteration* (CNS HGNET-MN1) that was characterized by gene fusions involving *MN1*.[45] Most tumors with a histologic diagnosis of astroblastoma (16 of 23) belonged to this

molecularly defined entity.

- A report of 27 histologically defined astroblastomas found that 10 cases had *MN1* rearrangements, 7 cases had *BRAF* rearrangements, and 2 cases had *RELA* rearrangements.[46] Methylation array analysis showed that the cases with *MN1* rearrangements clustered with CNS HGNET-MN1, the *BRAF*-mutated cases clustered with pleomorphic xanthoastrocytomas, and the *RELA* cases clustered with ependymomas.
- Genomic evaluation of eight cases of astroblastoma identified four with *MN1* alterations. Of the remaining four cases, two had genomic alterations consistent with high-grade glioma and two cases could not be classified on the basis of their molecular characteristics.[47]
- A study described eight cases of astroblastoma. All five cases that underwent fluorescence *in situ* hybridization analysis showed *MN1* rearrangements.[48]

These reports suggest that the histologic diagnosis of astroblastoma encompasses a heterogeneous group of genomically defined entities; astroblastomas with *MN1* fusions represent a distinctive subset of histologically diagnosed cases.[49]

Neurofibromatosis type 1 (NF1)

Children with NF1-associated low-grade gliomas often have tumors in the optic pathway that are not biopsied. In a series of pediatric patients (n = 17; median age, 10 years) with NF1-associated low-grade gliomas in which tissue was collected and subjected to whole-exome sequencing, the number of mutations was very low (median, 6 per case).[50] Germline *NF1* mutations were observed in 88% of patients, and the most common somatic alteration was loss of heterozygosity for *NF1*, with a smaller number of cases showing inactivating mutations in the second *NF1* allele. *CDKN2A* loss was observed in 1 of 17 patients (6%). Alterations in *TP53* and *ATRX* were not observed among the 17 pediatric patients with NF1-associated low-grade gliomas. Activating *BRAF* genomic alterations are uncommon in pilocytic astrocytoma and other low-grade gliomas occurring in children with NF1.[24,50]

Tuberous sclerosis

Most children with tuberous sclerosis have a germline mutation in one of two tuberous sclerosis genes (*TSC1* or *TSC2*). Either of these mutations results in activation of the mammalian target of rapamycin (mTOR) complex 1. These children are at risk of developing subependymal giant cell astrocytomas, cortical tubers, and subependymal nodules. Because subependymal giant cell astrocytomas are driven by mTOR activation, mTOR inhibitors are active agents that can induce tumor regression in children with these tumors.[51]

Molecular features of high-grade gliomas

Pediatric high-grade gliomas, especially glioblastoma multiforme, are biologically distinct from those arising in adults.[52-55]

Subgroups identified using DNA methylation patterns

Pediatric high-grade gliomas can be separated into distinct subgroups on the basis of epigenetic patterns (DNA methylation), and these subgroups show distinguishing chromosome copy number gains/losses and gene mutations in the tumor.[56-58] Particularly distinctive subtypes of pediatric high-grade gliomas are those with recurring mutations at specific amino acids in histone genes, and together these account for approximately one-half of pediatric high-grade gliomas.[58]

The following pediatric high-grade glioma subgroups were identified on the basis of their DNA methylation patterns, and they show distinctive molecular and clinical characteristics:[58]

1. **The histone K27 mutations: H3.3 (*H3F3A*) and H3.1 (*HIST1H3B* and, rarely,**

***HIST1H3C*) mutations at K27:** The histone K27–mutated cases occur predominantly in middle childhood (median age, approximately 10 years), are almost exclusively midline (thalamus, brain stem, and spinal cord), and carry a very poor prognosis. The 2016 WHO classification groups these cancers into a single entity—diffuse midline glioma, H3 K27M–mutant—although there are clinical and biological distinctions between cases with H3.3 and H3.1 mutations, as described below.[2] These cases can be diagnosed using immunohistochemistry to identify the presence of K27M.

- **H3.3K27M:** H3.3K27M cases occur throughout the midline and pons, account for approximately 60% of cases in these locations, and commonly present between the ages of 5 and 10 years.[58] The prognosis for H3.3K27M patients is especially poor, with a median survival of less than 1 year; the 2-year survival is less than 5%.[58]
- **H3.1K27M:** H3.1K27M cases are approximately fivefold less common than H3.3K27M cases. They occur primarily in the pons and present at a younger age than other H3.3K27M cases (median age, 5 years vs. 6–10 years). These cases have a slightly more favorable prognosis than do H3.3K27M cases (median survival, 15 months vs. 11 months). Mutations in *ACVR1*, which is also the mutation observed in the genetic condition fibrodysplasia ossificans progressiva, are present in a high proportion of H3.1K27M cases.[58-60]
- **H3.2K27M:** Rarely, K27M mutations are also identified in H3.2 (*HIST2H3C*) cases.[58]

2. **H3.3 (*H3F3A*) mutation at G34:** The H3.3G34 subtype presents in older children and young adults (median age, 14–18 years) and arises exclusively in the cerebral cortex.[56,57] H3.3G34 cases commonly have mutations in *TP53* and *ATRX* and show widespread hypomethylation across the whole genome. Patients with *H3F3A* mutations are at high risk of treatment failure,[61] but the prognosis is not as poor as that of patients with histone 3.1 or 3.3 K27M mutations.[57] O-6-methylguanine-DNA methyltransferase (MGMT) methylation is observed in approximately two-thirds of cases, and aside from the *IDH1*-mutated subtype (see below), the H3.3G34 subtype is the only pediatric high-grade glioma subtype that demonstrates MGMT methylation rates exceeding 20%.[58]
3. ***IDH1* mutation:** *IDH1*-mutated cases represent a small percentage of pediatric high-grade gliomas (approximately 5%), and pediatric high-grade glioma patients whose tumors have *IDH1* mutations are almost exclusively older adolescents (median age in a pediatric population, 16 years) with hemispheric tumors.[58] *IDH1*-mutated cases often show *TP53* mutations, MGMT promoter methylation, and a glioma-CpG island methylator phenotype (G-CIMP).[56,57] Pediatric patients with *IDH1* mutations show a more favorable prognosis than do other pediatric glioblastoma multiforme patients; 5-year overall survival (OS) rates exceed 60% for pediatric patients with *IDH1* mutations, compared with 5-year OS rates of less than 20% for patients with wild-type *IDH1*.[58]
4. **Pleomorphic xanthoastrocytoma (PXA)–like:** Approximately 10% of pediatric high-grade gliomas have DNA methylation patterns that are PXA-like.[57] PXA-like cases commonly have *BRAF* V600E mutations and a relatively favorable outcome (approximately 50% survival at 5 years).[58,61]
5. **Low-grade glioma–like:** A small subset of pediatric brain tumors with the histologic appearance of high-grade gliomas show DNA methylation patterns like those of low-grade gliomas.[57,58] These cases are primarily observed in young patients (median age, 4 years); 10 of 16 infants with a glioblastoma multiforme diagnosis were in the low-grade glioma–like group.[58] The prognosis for these patients is much more favorable than for other pediatric high-grade glioma subtypes.[61] Refer below for additional discussion of glioblastoma multiforme in infants.

Other mutations

Pediatric glioblastoma multiforme high-grade glioma patients whose tumors lack both histone mutations and *IDH1* mutations represent approximately 40% of pediatric glioblastoma multiforme cases.[58,62] This is a heterogeneous group, with higher rates of gene amplifications than other pediatric high-grade glioma subtypes. The most commonly amplified genes are *PDGFRA*, *EGFR*, *CCND/CDK*, and *MYC/MYCN*;[56,57] MGMT promoter methylation rates are low in this group.[62] One report divided this group into three subtypes. The subtype characterized by high rates of *MYCN* amplification showed the poorest prognosis, while the subtype characterized by *TERT* promoter mutations and *EGFR* amplification showed the most favorable prognosis. The third group was characterized by *PDGFRA* amplification.[62]

High-grade gliomas in infants

Infants and young children with high-grade gliomas appear to have tumors with distinctive molecular characteristics when compared with tumors of older children and adults with high-grade gliomas. An indication of this difference was noted with the application of DNA methylation analysis to pediatric high-grade tumors, which found that approximately 7% of pediatric patients with a histologic diagnosis of high-grade glioma had tumors with methylation patterns more closely resembling those of low-grade gliomas.[58] Ten of 16 infants (younger than 1 year) with a high-grade glioma diagnosis were in this methylation array–defined group.[58] The 5-year survival rate for patients in this report diagnosed at younger than 1 year exceeded 60%, while the 5-year survival rate for patients aged 1 to 3 years and older was less than 20%.

Two studies of the molecular characteristics of high-grade gliomas in infants and young children have further defined the distinctive nature of tumors arising in children younger than 1 year. A key finding from both studies is the importance of gene fusions involving tyrosine kinases (e.g., *ALK*, *NTRK1, NTRK2, NTRK3*, and *ROS1*) in patients in this age group. Both studies also found that infants with high-grade gliomas whose tumors have these gene fusions have survival rates much higher than those of older children with high-grade gliomas.[63,64]

The first study presented data for 118 children younger than 1 year with a low-grade or high-grade glioma diagnosis who had tumor tissue available for genomic characterization.[63] Approximately 75% of the cases were classified as low grade, but the diminished utility of histologic classification in this age group was illustrated by the relatively low OS rate for the low-grade cohort (71%) and the relatively favorable survival for the high-grade cohort (55%). Rates of surgical resection were higher for patients with high-grade tumors, a result of many of the low-grade tumors occurring in midline locations while the high-grade tumors were found in supratentorial locations; this finding may also help to explain the relative outcomes for the two groups. Genomic characterization divided the infant glioma population into the following three groups, the first of which included patients with high-grade gliomas:

- Group 1 tumors were receptor tyrosine kinase driven and primarily high grade (83%). These tumors harbored lesions in *ALK*, *ROS1*, *NTRK*, and *MET*. Median age at diagnosis was 3 months, and OS rates were approximately 60%.
- Group 2 tumors were RAS/MAPK driven and were all hemispheric low-grade gliomas, representing one-fourth of hemispheric gliomas in infants. *BRAF* V600E was the most common alteration, followed by *FGFR1* alterations and *BRAF* fusions. This group had a median age at presentation of 8 months and had the most favorable outcome (10-year OS rate, 93%).
- Group 3 tumors were RAS/MAPK driven with low-grade histology and midline presentation (approximately 80% optic pathway/hypothalamic gliomas). Most group 3 tumors showed either *BRAF* fusions or *BRAF* V600E. Median age at diagnosis was 7.5 months. The progression-free survival (PFS) rate at 5-years was approximately 20%, and the OS rate at 10 years was approximately 50% (far inferior to that of optic

pathway/hypothalamic gliomas in children aged >1 year).

The second study focused on tumors from children younger than 4 years with a pathological diagnosis of WHO grades II, III, and IV gliomas, astrocytomas, or glioneuronal tumors. Among the 191 tumors studied that met inclusion criteria, 61 had methylation profiles consistent with glioma subtypes that occur in older children (e.g., *IDH1*, diffuse midline glioma K27M-mutant, subependymal giant cell astrocytoma, pleomorphic xanthoastrocytoma, etc.). The remaining 130 cases were termed the *intrinsic set* and were the focus of additional molecular characterization:[64]

- The *intrinsic set* contained most of the patients diagnosed before age 1 year (49 of 63 patients, 78%) and had a median age of 7.2 months. Tumors were frequently in a superficial hemispheric location, often involving the meninges, and had a well-defined border with adjacent normal brain.
- The methylation classifier placed most of these cases in either the desmoplastic infantile ganglioglioma/astrocytoma (DIGG/DIA) subgroup or in the infantile hemispheric glioma subgroup.
- For 41 tumors from the *intrinsic set* in which tissue was available for gene panel and RNA sequencing, 25 tumors had fusions involving either *ALK* (n = 10), *NTRK1* (n = 2), *NTRK2* (n = 2), *NTRK3* (n = 8), *ROS1* (n = 2), or *MET* (n = 1). *BRAF* mutations (n = 3) were observed in cases that were high scoring by methylation array for the DIGG/DIA or DIGG/DIA-like subgroups.
- For patients in the *intrinsic set*, the 5-year survival rate appeared higher for patients whose tumors had gene fusions when compared with patients whose tumors lacked fusions (approximately 80% vs. 60%, respectively); however, both of these groups of patients had much higher survival rates than did other children with high-grade gliomas.

Secondary high-grade glioma

Childhood secondary high-grade glioma (high-grade glioma that is preceded by a low-grade glioma) is uncommon (2.9% in a study of 886 patients). No pediatric low-grade gliomas with the *BRAF-KIAA1549* fusion transformed to a high-grade glioma, whereas low-grade gliomas with the *BRAF* V600E mutations were associated with increased risk of transformation. Seven of 18 patients (approximately 40%) with secondary high-grade glioma had *BRAF* V600E mutations, with *CDKN2A* alterations present in 8 of 14 cases (57%).[30]

Neurofibromatosis type 1 (NF1)

High-grade gliomas can arise in children with NF1, although low-grade gliomas are much more common. When a high-grade tumor occurs, it is most often in adulthood. Genomic characterization of 23 patients with NF1-associated high-grade gliomas (median age, 38.8 years; 5 patients younger than 18 years) showed higher rates of mutations compared with NF1 patients who had low-grade gliomas (21.5 vs. 6 mutations, respectively).[50] The vast majority of patients showed *NF1* germline mutations, with either loss of heterozygosity or with an inactivating mutation in the second *NF1* allele. In contrast to NF1-associated low-grade gliomas, genomic alterations associated with high-grade gliomas were common (*CDKN2A* [58%], *ATRX* [38%], and *TP53* [29%]).[50]

Molecular features of neuronal and mixed neuronal-glial tumors

Neuronal and mixed neuronal-glial tumors are generally low-grade tumors, with an exception of the grade III anaplastic gangliogliomas. The histologies recognized by the 2016 WHO classification include the following:[2]

- Dysembryoplastic neuroepithelial tumor.

- Gangliocytoma.
- Ganglioglioma.
- Anaplastic ganglioglioma.
- Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease).
- Desmoplastic infantile astrocytoma and ganglioglioma.
- Papillary glioneuronal tumor.
- Rosette-forming glioneuronal tumor.
- Diffuse leptomeningeal glioneuronal tumor.
- Central neurocytoma.
- Extraventricular neurocytoma.
- Cerebellar liponeurocytoma.
- Paraganglioma.

Dysembryoplastic neuroepithelial tumor (DNET)

DNET presents in children and adults, with the median age at diagnosis in mid-to-late adolescence. It is characterized histopathologically by the presence of columns of oligodendroglial-like cells and cortical ganglion cells floating in mucin.[1] The temporal lobe is the most common location, and it is associated with drug-refractory epilepsy.[65,66]

FGFR1 alterations have been reported in 60% to 80% of DNETs, and include *FGFR1* activating point mutations, internal tandem duplication of the kinase domain, and activating gene fusions.[42,67,68] *BRAF* mutations are uncommon in DNET.

DNET of the septum pellucidum

Septal DNET generally presents with symptoms related to obstructive hydrocephalus.[69,70] Septal DNET has an indolent clinical behavior, with most tumors not requiring treatment other than surgery. In a single-institution series that incorporated other literature-reported cases, the median age at presentation was in the adolescent age range.[71]

Mutations that are common in low-grade gliomas (e.g., *BRAF* V600E) and in cortical DNETs (*FGFR1* mutations) are uncommon in septal DNET.[70-72] Instead, mutations in *PDGFRA* at the K385 residue typify most cases of septal DNET.

A report of the molecular characterization of 18 septal DNETs showed that 14 had a *PDGFRA* mutation, with all but one being a mutation at the K385 residue,[71] which is in the extracellular region of *PDGFRA* that mediates the receptor-receptor interaction required for dimerization and activation upon binding of PDGFs. Among the remaining four cases, three had *FGFR1* mutations in line with those observed in cortical DNET. A second report observed *PDGFRA* mutations at K385 in each of four cases of septal DNET.[72] Combined, the two reports indicate that septal DNET is a distinct entity characterized by a stereotypic anatomic location and, in most cases, a *PDGFRA* mutation. Low-grade glioneuronal tumors with the K385 *PDGFRA* mutation have also been identified as arising in the corpus callosum and periventricular white matter of the lateral ventricle, leading to the proposal that *myxoid glioneuronal tumor, PDGFRA p.K385-mutant* be considered as a distinct central nervous system (CNS) tumor entity.[73]

Ganglioglioma

Ganglioglioma presents during childhood and into adulthood. It most commonly arises in the cerebral cortex and is associated with seizures, but also presents in other sites, including the

spinal cord.[65,74]

The unifying theme for the molecular pathogenesis of ganglioglioma is genomic alterations leading to MAPK pathway activation.[42,75] *BRAF* alterations are observed in approximately 50% of ganglioglioma cases, with V600E being by far the most common alteration; however, other *BRAF* mutations and gene fusions are also observed. Other less commonly altered genes in ganglioglioma include *KRAS*, *FGFR1/2*, *RAF1*, *NTRK2*, and *NF1*.[42,75]

Desmoplastic infantile astrocytomas (DIA) and desmoplastic infantile gangliogliomas (DIG)

DIA and DIG most often present in the first year of life and show a characteristic imaging appearance in which a contrast-enhancing solid nodule accompanies a large cystic component.[76,77] DIG is more common than DIA,[76] and by methylation array analysis, both diagnoses cluster together.[78] Survival outcome is generally favorable with surgical resection.[76]

The most commonly observed genomic alterations in DIA and DIG are *BRAF* mutations involving V600; gene fusions involving kinase genes are observed less frequently.

- Among 16 cases confirmed by histology and DNA methylation profiling to be DIA and DIG, *BRAF* mutations were observed in seven cases (43.8%): four *BRAF* V600E mutations and three *BRAF* V600D mutations. One additional case had an *EML4-ALK* fusion. *BRAF* mutations were present in 4 of 12 (25%) DIG cases (with 3 of 4 mutated cases having *BRAF* V600D) and in 3 of 4 (75%) DIA cases (all 3 mutated cases with *BRAF* V600E).
- A study of seven DIG cases found MAPK pathway alterations in four (57%).[79] Three alterations involved *BRAF* (V600E, V600D, and one deletion/insertion centered at V600) and one was a *TPM3-NTRK1* in-frame fusion. Notably, the variant allele frequency was low (8%–27%), suggesting that DIG is characterized by a prominent nonneoplastic component resulting in low clonal driver mutation allele frequencies.
- Another report also described the *BRAF* V600D mutation in a DIG case.[80] As the V600D mutation is far less common than V600E in other cancers, its detection in multiple DIG cases suggests an association between the mutation and DIG.

Papillary glioneuronal tumor

Papillary glioneuronal tumor is a low-grade biphasic neoplasm with astrocytic and neuronal differentiation that primarily arises in the supratentorial compartment.[2] The median age at presentation is in the early 20s, but it can be observed during childhood through adulthood.

The primary genomic alteration associated with papillary glioneuronal tumor is a gene fusion, *SLC44A1-PRKCA*, that is associated with the t(9:17)(q31;q24) translocation.[81,82] In one study of 28 cases diagnosed histologically as papillary glioneuronal tumor using methylation arrays, 11 of the cases clustered in a distinctive methylation class, while the remaining cases showed methylation profiles typical for other tumor entities. Molecular analysis of the cases in the distinctive methylation cluster showed that all of them had the *SLC44A1-PRKCA* gene fusion except for a single case with a *NOTCH1-PRKCA* gene fusion.[83] This suggests that molecular methods for identifying the presence of a *PRKCA* fusion are less susceptible to misclassification in diagnosing papillary glioneuronal tumor than are morphology-based methods.

Rosette-forming glioneuronal tumor (RGNT)

RGNT presents in adolescents and adults, with tumors generally located infratentorially, although tumors can arise in mesencephalic or diencephalic regions.[84] The typical histological appearance shows both a glial component and a neurocytic component arranged in rosettes or perivascular pseudorosettes.[2] Outcome for patients with RGNT is generally favorable, consistent with the WHO grade I designation.[84]

DNA methylation profiling shows that RGNT has a distinct epigenetic profile that distinguishes it

from other low-grade glial/glioneuronal tumor entities.[84] A study of 30 cases of RGNT observed *FGFR1* hotspot mutations in all analyzed tumors.[84] In addition, *PIK3CA* activating mutations were concurrently observed in 19 of 30 cases (63%). Missense or damaging mutations in *NF1* were identified in 10 of 30 cases (33%), with 7 tumors having mutations in *FGFR1*, *PIK3CA*, and *NF1*. The co-occurrence of mutations that activate both the MAPK pathway and the PI3K pathway makes the mutation profile of RGNT distinctive among astrocytic and glioneuronal tumors.

Diffuse leptomeningeal glioneuronal tumor (DLGNT)

DLGNT is a rare CNS tumor that has been characterized radiographically by leptomeningeal enhancement on magnetic resonance imaging (MRI) that may involve the posterior fossa, brain stem region, and spinal cord.[85] Intraparenchymal lesions, when present, typically involve the spinal cord;[85] localized intramedullary glioneuronal tumors without leptomeningeal dissemination and with histomorphologic, immunophenotypic, and genomic characteristics similar to DLGNT have been reported.[86]

DLGNT showed a distinctive epigenetic profile on DNA methylation arrays, and unsupervised clustering of array data applied to 30 cases defined two subclasses of DLGNT: methylation class (MC)-1 (n = 17) and MC-2 (n = 13).[85] Of note, many of the array-defined cases had originally been diagnosed as other entities (e.g., primitive neuroectodermal tumors, pilocytic astrocytoma, and anaplastic astrocytoma). Patients with DLGNT-MC-1 were diagnosed at an earlier age than were patients with DLGNT-MC-2 (5 years vs. 14 years, respectively). The 5-year overall survival rate was higher for patients with DLGNT-MC-1 than for those with DLGNT-MC-2 (100% vs. 43%, respectively). Genomic findings from the 30 methylation array–defined DLGNT cases are provided below:

- All 30 cases showed loss of chromosome 1p, but only 6 of 17 DLGNT-MC-1 cases showed additional gain of chromosome 1q, compared with all cases of DLGNT-MC-2.[85] A separate report found that chromosome 1q gain was an adverse prognostic factor in patients with DLGNT (including cases with localized disease),[87] which is consistent with the inferior outcome for patients with DLGNT-MC-2.
- Co-deletions of 1p/19q were more frequent in the DLGNT-MC-1 group (7 of 13, 54%) than in the DLGNT-MC-2 group (2 of 13, 15%). In contrast to oligodendroglioma, mutations of *IDH1* and *IDH2* were not identified.[85]
- MAPK pathway activation is common in DLGNT cases.[85] The *KIAA1549-BRAF* fusion was present in 11 of 15 DLGNT-MC-1 cases (65%) and in 9 of 13 DLGNT-MC-2 cases (69%). Fusions involving *NTRK1/2/3* were present in one case each, and another case had a *TRIM33-RAF1* fusion.

Extraventricular neurocytoma

Extraventricular neurocytoma is histologically similar to central neurocytoma, consisting of small uniform cells that demonstrate neuronal differentiation, but it arises in the brain parenchyma rather than in association with the ventricular system.[2] It presents during childhood through adulthood.

In a study of 40 tumors histologically classified as extraventricular neurocytoma and subjected to methylation array analysis, only 26 formed a separate cluster distinctive from reference tumors of other histologies.[88] Among cases with an extraventricular neurocytoma methylation array classification for which genomic characterization could be performed, 11 of 15 (73%) showed rearrangements affecting members of the FGFR family, with *FGFR1-TACC1* being the most common alteration.[88]

Prognosis

Low-grade astrocytomas

Low-grade astrocytomas (grade I [pilocytic] and grade II) have a relatively favorable prognosis, particularly for well-circumscribed lesions where complete excision may be possible.[11,89-92] Tumor spread, when it occurs, is usually by contiguous extension; dissemination to other CNS sites is uncommon, but does occur.[93,94] Although metastasis is uncommon, tumors may be of multifocal origin, especially when associated with NF1.

Unfavorable prognostic features for childhood low-grade astrocytomas include the following:[95-98]

- Young age.[98]
- Diffuse histology, especially *IDH* mutant.
- Inability to obtain a complete resection.
- Diencephalic syndrome.[98]
- Metastases. When metastasis does occur, it is associated with a poorer long-term outcome.[99] However, it is increasingly evident that prognosis is largely dependent on specific molecular features integrated with standard pathological grouping.

In patients with pilocytic astrocytoma, elevated MIB-1 labeling index, a marker of cellular proliferative activity, is associated with shortened PFS.[8] A *BRAF-KIAA1549* fusion, found in pilocytic tumors, confers a better clinical outcome.[26]

In children with tumors of the visual pathway, outcome is not only assessed by radiographic disease control or survival but also by visual outcome. Children with isolated optic nerve tumors have a better prognosis than do children with lesions that involve the chiasm or that extend along the optic pathway.[100,101]; [102][Level of evidence: 3iiC] Children with NF1 also have a better prognosis, especially when the tumor is found in asymptomatic patients at the time of screening.[103] Better visual acuity at diagnosis, older age at diagnosis, and presence of NF1 are associated with better visual outcomes.[104]

High-grade astrocytomas

Although high-grade astrocytomas generally carry a poor prognosis in younger patients, those with anaplastic astrocytomas in whom a gross-total resection is possible may fare better,[90,105,106] as well as those with non-H3 K27M–mutant tumors.

Molecular subtypes of pediatric glioblastoma multiforme show prognostic significance.[57] Patients whose tumors have histone K27M mutations have the poorest prognosis, with 3-year survival rates below 5%. In the thalamus, wild-type high-grade gliomas have a somewhat better prognosis than do those harboring an H3.3 mutation. For high-grade gliomas in the thalamus, patients with H3 wild-type tumors have a somewhat better prognosis (2-year overall survival [OS], 71%) than do patients who harbor H3 K27M mutations (2-year OS, 13%).[107] Patients whose tumors have *IDH1* mutations appear to have the most favorable prognosis among pediatric glioblastoma multiforme cases, while those with histone G34 mutations and those lacking both histone and *IDH1* mutations have an intermediate prognosis (3-year OS, approximately 30%). In a multivariate analysis that included both molecular and clinical factors, the presence of gene amplifications and K27M mutations were associated with a poorer prognosis, while the presence of *IDH1* mutations was associated with a more favorable prognosis.[57]

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Stage Information for Childhood Astrocytomas

There is no recognized staging system for childhood astrocytomas. For the purposes of this summary, the treatment of childhood astrocytomas will be described using the following classifications:

- Low-grade astrocytoma—grades I and II (e.g., pilocytic astrocytomas and diffuse astrocytomas).
  - Newly diagnosed.
  - Progressive/recurrent.
- High-grade astrocytoma—grades III and IV (anaplastic astrocytomas and glioblastoma).
  - Newly diagnosed.
  - Recurrent.

Treatment Option Overview for Childhood Astrocytomas

Dramatic improvements in survival have been achieved for children and adolescents with cancer. Between 1975 and 2010, childhood cancer mortality decreased by more than 50%.[1] Many of the improvements in survival in childhood cancer have been made as a result of clinical trials that have attempted to improve on the best available, accepted therapy. Clinical trials in pediatrics are designed to compare new therapy with therapy that is currently accepted as standard. This comparison may be done in a randomized study of two treatment arms or by evaluating a single new treatment and comparing the results with previously obtained results that assessed an existing therapy. Because of the relative rarity of cancer in children, all patients with brain tumors should be considered for entry into a clinical trial. Information about ongoing National Cancer Institute (NCI)–supported clinical trials is available from the NCI website.

To determine and implement optimal treatment, planning by a multidisciplinary team of cancer specialists who have experience treating childhood brain tumors is required. Irradiation of pediatric brain tumors is technically very demanding and should be carried out in centers that have experience in that area to ensure optimal results.

Long-term management of patients with brain tumors is complex and requires a multidisciplinary approach. (Refer to the PDQ summary on Late Effects of Treatment for Childhood Cancer for specific information about the incidence, type, and monitoring of late effects in childhood and adolescent cancer survivors.)

Table 4 describes the standard treatment options for low-grade and high-grade childhood astrocytomas.

Table 4. Standard Treatment Options for Childhood Astrocytomas

Treatment Group	Standard Treatment Options
Childhood low-grade astrocytomas:	
Newly diagnosed childhood low-grade astrocytomas	Observation without intervention
	Surgery
	Adjuvant therapy (for tumors that are incompletely resected):
	—Observation after surgery
	—Chemotherapy
	—Radiation therapy
	—Targeted therapy
Progressive/recurrent childhood low-grade astrocytomas	Second surgery
	Radiation therapy
	Chemotherapy
	Targeted therapy with or without chemotherapy
Childhood high-grade astrocytomas:	
Newly diagnosed childhood high-grade astrocytomas	Surgery
	Adjuvant therapy:
	—Radiation therapy
	—Chemotherapy
Recurrent childhood high-grade astrocytomas	Surgery (not considered standard treatment)
	High-dose chemotherapy with stem cell transplant (SCT) (not considered standard treatment)
	Radiation therapy (not considered standard treatment)
	Targeted therapy with a BRAF inhibitor, for patients with a *BRAF* V600E mutation (not considered standard treatment)

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Treatment of Childhood Low-Grade Astrocytomas

To determine and implement optimal management, treatment is often guided by a multidisciplinary team of cancer specialists who have experience treating childhood brain tumors.

For children with low-grade optic pathway astrocytomas, treatment options should be considered not only to improve survival but also to stabilize visual function.[1,2]

Standard treatment options for newly diagnosed childhood low-grade astrocytomas include the following:

1. Observation without intervention.

2. Surgery.
3. Adjuvant therapy (for tumors that are incompletely resected).
    - Observation after surgery.
    - Chemotherapy.
    - Radiation therapy.
    - Targeted therapy.

Observation without intervention

Observation, in the absence of any intervention, is an option for patients with neurofibromatosis type 1 (NF1) or incidentally found, asymptomatic masses.[3] Spontaneous regressions of optic pathway gliomas have been reported in children with and without NF1.[4,5]

Surgery

Surgical resection is the primary treatment for childhood low-grade astrocytoma [6,7] and surgical feasibility is determined by tumor location. In infants and young children, low-grade astrocytomas presenting in the optic chiasm/hypothalamus make surgery difficult; consequently, biopsies are not always done. This is especially true in patients with NF1.[6] When associated with NF1, tumors may be of multifocal origin. Diffuse astrocytomas (World Health Organization [WHO] grade II) may be less amenable to total resection, and this may contribute to a poorer outcome in these patients.

- **Cerebellum:** Complete or near-complete removal can be obtained in 90% to 95% of patients with pilocytic tumors that occur in the cerebellum.[7]
- **Optic nerve:** For children with isolated optic nerve lesions and progressive symptoms, complete surgical resection, while curative, generally results in blindness in the affected eye. In the absence of retained vision in the affected eye, complete surgical resection may be considered when cosmesis related to proptosis is of concern.
- **Midline structures (hypothalamus, thalamus, brain stem, and spinal cord):** Low-grade astrocytomas that occur in midline structures can sometimes be aggressively resected, with resultant long-term disease control.[4,8,9]; [10][Level of evidence: 3iiiA] Despite the increasing surgical accessibility of these tumors, such resection may result in significant neurologic sequelae, especially in children younger than 2 years at diagnosis.[11][Level of evidence: 3iC] Because of the infiltrative nature of some deep-seated lesions, extensive surgical resection may not be appropriate and biopsy only should be considered.[12][Level of evidence: 3iiiDiii]
- **Cerebrum:** Circumscribed, grade I hemispheric tumors are often amenable to complete surgical resection.

After resection, immediate (within 48 hours of resection per Children's Oncology Group [COG] criteria) postoperative magnetic resonance imaging is obtained. Surveillance scans are then obtained periodically for completely resected tumors, although the value following the initial 3- to 6-month postoperative period is uncertain.[13]; [14][Level of evidence: 3iiDiii]

Factors related to outcome for children with low-grade gliomas treated with surgery followed by observation were identified in a COG study that included 518 evaluable patients.[7] Overall outcome for the entire group was a 78% progression-free survival (PFS) rate at 8 years and 96% overall survival (OS) rate at 8 years. The following factors were related to prognosis:[7]

- **Tumor location:** Children with cerebellar and cerebral tumors showed a higher PFS rate at 8 years compared with patients with midline and chiasmatic tumors (84% ± 1.9% vs. 51%

± 5.9%, respectively).

- **Histology:** Approximately three-fourths of patients had pilocytic astrocytoma; PFS and OS were superior for these patients when compared with children with nonpilocytic tumors.
- **Extent of resection:** Patients with gross-total resection had 8-year PFS rates exceeding 90% and OS rates of 99%. By comparison, approximately one-half of patients with any degree of residual tumor (as assessed by operative report and by postoperative imaging) showed disease progression by 8 years, although OS rates exceeded 90%.[7]

  The extent of resection necessary for cure is unknown because patients with microscopic and even gross residual tumor after surgery may experience long-term PFS without postoperative therapy.[6,7]
- **Age:** Younger children (age <5 years) showed higher rates of tumor progression but there was no significant age effect for OS in multivariate analysis. In a retrospective review of a different series of pediatric patients, children younger than 1 year with low-grade glioma demonstrated an inferior PFS compared with children aged 1 year and older.[15]

The long-term functional outcome of cerebellar pilocytic astrocytomas is relatively favorable. Full-scale mean intelligence quotients (IQs) of patients with low-grade gliomas treated with surgery alone are close to the normative population. However, long-term medical, psychological, and educational deficits may be present in these patients.[16]; [17,18][Level of evidence: 3iiiC]

Adjuvant therapy

Adjuvant therapy following complete resection of a low-grade glioma is generally not required unless there is a subsequent recurrence of disease. Treatment options for patients with incompletely resected tumor must be individualized and may include one or more of the following:

- Observation after surgery.
- Chemotherapy.
- Radiation therapy.
- Targeted therapy (for subependymal giant cell astrocytomas).

A shunt or other cerebrospinal fluid diversion procedure may be needed.

Observation after surgery

In patients in whom a portion of the tumor has been resected, the patient may be observed without further disease-directed treatment, particularly if the pace of tumor regrowth is anticipated to be very slow. Approximately 50% of patients with less-than-gross total resection may have disease that remains progression-free at 5 to 8 years, supporting the observation strategy in selected patients.[7]

Chemotherapy

Given the long-term side effects associated with radiation therapy, postoperative chemotherapy may be initially recommended.

Chemotherapy may result in objective tumor shrinkage and delay the need for radiation therapy in most patients.[19-22] Chemotherapy is also an option that may delay or avoid radiation therapy in adolescents with optic nerve pathway gliomas.[23][Level of evidence: 3iiDii] Chemotherapy has been shown to shrink tumors in children with hypothalamic gliomas and the diencephalic syndrome, resulting in weight gain in those who respond to treatment.[24]

The most widely used regimens to treat tumor progression or symptomatic nonresectable, low-

grade gliomas are the following:

- Carboplatin with or without vincristine.[19,20,25]; [26][Level of evidence: 3iiiDiii]
- Combination of thioguanine, procarbazine, lomustine, and vincristine (TPCV).[22]; [27][Level of evidence: 1iiA]

The COG reported the results of a randomized phase III trial (COG-A9952) that treated children younger than 10 years with low-grade chiasmatic/hypothalamic gliomas without NF1 using one of two regimens: carboplatin and vincristine (CV) or TPCV. The 5-year event-free survival (EFS) rate was 39% (± 4%) for the CV regimen and 52% (± 5%) for the TPCV regimen. Toxicity rates between the two regimens were relatively comparable.[27] In the same study, children with NF1 were nonrandomly assigned to receive treatment with CV. The 5-year EFS rate for children with NF1 was markedly better, at 69% (± 4%), than it was for children without NF1 who received CV. In multivariate analysis, NF1 was an independent predictor of better EFS but not OS.[28]

A multicenter, prospective, randomized trial that compared treatment with vincristine/carboplatin with vincristine/carboplatin plus etoposide in children with low-grade glioma failed to demonstrate a difference in PFS and OS between the two regimens.[29][Level of evidence: 1iiD]

Other chemotherapy approaches have been employed to treat children with progressive or symptomatic nonresectable, low-grade astrocytomas, including the following:

- Multiagent, platinum-based regimens.[20,21,30]; [31][Level of evidence: 2Diii]; [32][Level of evidence: 3iiiB] Reported 5-year PFS rates have ranged from approximately 35% to 60% for children receiving platinum-based chemotherapy for optic pathway gliomas,[20,21] but most patients ultimately require further treatment. This is particularly true for children who initially present with hypothalamic/chiasmatic gliomas that have neuraxis dissemination.[33][Level of evidence: 3iiiDiii]
- Vinblastine.[34,35]
- Temozolomide.[36,37]

Among children receiving chemotherapy for optic pathway gliomas, those without NF1 have higher rates of disease progression than those with NF1, and infants have higher rates of disease progression than do children older than 1 year.[20,21,30,35] Visual status (including acuity and field) is an important measure of outcome and response to treatment. Vision function can be impaired; it is variable even in patients with radiographic responses and is often less than optimal. More than one-third of patients *successfully* treated with chemotherapy have poor vision in one or both eyes, and some patients lose vision despite radiographic evidence of tumor control (response or stability). In most series, children with sporadic visual pathway gliomas have poorer visual outcomes than do children with NF1.[35]; [38,39][Level of evidence: 3iiiC] Better initial visual acuity, older age, and absence of postchiasmatic involvement are associated with improved or stable vision after chemotherapy.[40,41]

Radiation therapy

Radiation therapy is usually reserved until progressive disease is documented [42,43] and may be further delayed through the use of chemotherapy.[19,20]

For children with low-grade gliomas for whom radiation therapy is indicated, approaches that contour the radiation distribution to the tumor and avoid normal brain tissue (3-D conformal radiation therapy, intensity-modulated radiation therapy, stereotactic radiation therapy, and proton radiation therapy [charged-particle radiation therapy]) all appear effective and may potentially reduce the acute and long-term toxicities associated with these modalities.[44,45]; [46][Level of evidence: 3iDiii] Radiation doses of 54 Gy in 1.8 Gy fractions are typically used.[47,48] In a prospective study of 174 patients treated with proton therapy, the 5-year actuarial rate of local

control was 85% (95% confidence interval [CI], 78%–90%), the PFS rate was 84% (95% CI, 77%–89%), and the OS rate was 92% (95% CI, 85%–95%). Brain stem and spinal cord tumor locations and a dose of 54 Gy relative biological effectiveness (RBE) or less were associated with inferior local control ($P < .01$ for both).[49]

Subsequent to radiation therapy administration, care must be taken in distinguishing radiation-induced imaging changes from disease progression, which usually occurs during the first year after radiation, but may occur even after the first year, especially in patients with pilocytic astrocytomas.[50-53]; [54][Level of evidence: 2A]; [55][Level of evidence: 2C]; [56][Level of evidence: 3iiiDi]; [57][Level of evidence: 3iiiDii]; [12,58][Level of evidence: 3iiiDiii]

Radiation therapy results in long-term disease control for most children with chiasmatic and posterior pathway chiasmatic gliomas, but may also result in substantial intellectual and endocrinologic sequelae, cerebrovascular damage, late death, and possibly an increased risk of secondary tumors.[59-61]; [55][Level of evidence: 2C] A population-based study identified radiation therapy as the most significant risk factor associated with late mortality, although the patients who required radiation therapy may have reflected a higher-risk population.[61]

Children with NF1 may be at higher risk of radiation-associated secondary tumors and morbidity resulting from vascular changes. Radiation therapy and alkylating agents are used as last resorts for these patients, given the theoretically heightened risk of inducing neurologic toxic effects and second malignancy.[62]

Targeted therapy

For children with symptomatic subependymal giant cell astrocytomas (SEGAs), agents that inhibit mammalian target of rapamycin (mTOR) (e.g., everolimus and sirolimus) have been studied.

Evidence (treatment of SEGA with an mTOR inhibitor):

1. Small series have shown significant reductions in the size of these tumors after administration of everolimus or sirolimus, often eliminating the need for surgery.[63]; [64][Level of evidence: 2C]; [65][Level of evidence: 3iiDiv]; [66][Level of evidence: 3iiiC]
2. A multicenter, phase III, placebo-controlled trial of 117 patients confirmed these earlier findings.[67][Level of evidence: 1iDiv]
    - 35% of the patients in the everolimus group had at least a 50% reduction in the size of the SEGA, versus no reduction in the placebo group.
3. In a study of patients who were treated with everolimus for 5 years, the following results were observed:[68]
    - A reduction in the size of the mass was observed in about 50% of patients; in many cases, the reduction was sustained.
    - These patients also had a reduction in seizure frequency.

Treatment options under clinical evaluation

Early-phase therapeutic trials may be available for selected patients. These trials may be available via the COG, the Pediatric Brain Tumor Consortium, or other entities. Information about National Cancer Institute (NCI)–supported clinical trials can be found on the NCI website. For information about clinical trials sponsored by other organizations, refer to the ClinicalTrials.gov website.

The following are examples of national and/or institutional clinical trials that are currently being conducted:

- **NCT02684058** (Phase II Pediatric Study With Dabrafenib in Combination With Trametinib in Patients With High-Grade Gliomas and Low-Grade Gliomas)**:** The purpose of this study is to investigate the activity of dabrafenib in combination with trametinib in children and adolescent patients with *BRAF* V600 mutation–positive low-grade gliomas or relapsed or refractory high-grade gliomas.
- **NCT03871257** (A Study of the Drugs Selumetinib Versus Carboplatin/Vincristine in Patients With NF1 and Low-Grade Glioma)**:** This phase III trial investigates the use of selumetinib compared with the standard treatment of CV for treating patients with NF1-associated low-grade gliomas, and improving vision in patients with low-grade gliomas of the optic pathway (vision nerves).

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Progressive/Recurrent Childhood Low-Grade Astrocytomas

To determine and implement optimal management, treatment is often guided by a multidisciplinary team of cancer specialists who have experience treating childhood brain tumors.

For children with low-grade optic pathway astrocytomas, treatment options should be considered not only to improve survival but also to stabilize visual function.[1,2]

Childhood low-grade astrocytomas may progress or recur many years after initial presentation and treatment.

An individual plan needs to be tailored on the basis of the following:

- Patient age.
- Tumor location.
- Prior treatment.

Recurrent disease is usually at the primary tumor site, although multifocal or widely disseminated disease to other intracranial sites and to the spinal leptomeninges has been documented.[3,4] Most children whose low-grade diffuse fibrillary astrocytomas recur will harbor low-grade lesions; however, transformation into a higher grade tumor is possible. Surveillance imaging will frequently identify asymptomatic recurrences.[5] At the time of recurrence, a complete evaluation to determine the extent of the relapse is indicated.

Standard treatment options for progressive/recurrent childhood low-grade astrocytomas include the following:

1. Second surgery.
2. Radiation therapy.
3. Chemotherapy.
4. Targeted therapy with or without chemotherapy.

Second surgery

Patients with low-grade astrocytomas who relapse after being treated with surgery alone may be candidates for another surgical resection.[6] The need for surgical intervention must be individualized on the basis of the following:

- Initial tumor type.
- Length of time between initial treatment and the reappearance of the mass lesion.
- Clinical picture.

Utility of second surgery is impacted by site of recurrence and the probability of obtaining a near-

total resection/gross-total resection without significant neurologic injury.[7]

Radiation therapy

The rationale for the use of radiation therapy is essentially the same when utilized as first-line therapy or at the time of recurrence (refer to the Radiation therapy subsection of the Treatment of Childhood Low-Grade Astrocytomas section of this summary). If the child has never received radiation therapy, local radiation therapy may be a treatment option, although chemotherapy in lieu of radiation may be considered, depending on the child's age and the extent and location of the tumor.[8][Level of evidence: 3iA]; [9][Level of evidence: 3iiiDi]

For children with low-grade gliomas for whom radiation therapy is indicated, conformal radiation therapy approaches appear effective and offer the potential for reducing the acute and long-term toxicities associated with this modality.[10-13]

Chemotherapy

If there is recurrence at an unresectable site, chemotherapy should be considered.

Chemotherapy may result in relatively long-term disease control.[14,15] The choice of regimen depends on whether previous chemotherapy has been utilized. Numerous options can be considered, including carboplatin and vincristine (CV); thioguanine, procarbazine, lomustine, and vincristine (TPCV); vinblastine alone; temozolomide alone; or temozolomide in combination with carboplatin and vincristine.[14-17]

Targeted therapy with or without chemotherapy

Antitumor activity has also been observed for bevacizumab given in combination with irinotecan, which, in some cases, also results in clinical or visual improvement.[18]

Evidence (targeted therapy [bevacizumab]):

1. In a phase II study of bevacizumab plus irinotecan for children with recurrent low-grade gliomas, the following results were observed:[19]
    - Sustained partial responses were observed in only two patients (5.7%).
    - The 6-month progression-free survival (PFS) rate was 85.4% (standard error [SE] ± 5.96%).
    - The 2-year PFS rate was 47.8% (SE ± 9.27%).
2. A pilot study of 14 patients with recurrent low-grade gliomas also evaluated bevacizumab-based therapies and observed the following:[20][Level of evidence: 3iiDi]; [21][Level of evidence: 3iiiDiv]
    - Objective responses were seen in 12 patients (86%).
    - No patients progressed on therapy (median treatment duration, 12 months), but 13 of 14 progressed after stopping bevacizumab at a median of 5 months.
3. Bevacizumab has also been employed for children with low-grade gliomas and symptomatic radiation-induced tumor enlargement.[22,23]
    - Treatment with bevacizumab produced radiographic improvement (five of five patients) and allowed weaning off steroids (four of four patients).

With the identification of *BRAF* mutations driving a significant proportion of low-grade gliomas, inhibition of various elements of this molecular pathway (e.g., MEK and BRAF) are actively being tested in ongoing clinical trials, with early reports suggesting substantial activity. While first-generation BRAF inhibitors like vemurafenib and dabrafenib are active against *BRAF*

V600E–mutated tumors, they are contraindicated for tumors with *BRAF* gene fusions because of the potential for paradoxical activation of the MAPK pathway.[24,25]

Studies of BRAF and MEK inhibitors include the following:

1. For patients whose tumors have *BRAF* V600E mutations, the focus of clinical research efforts is on the evaluation of BRAF inhibitors in combination with MEK inhibitors. Such combinations are approved for the treatment of adult cancers with *BRAF* V600E mutations and are more effective than either BRAF inhibitors or MEK inhibitors used as single agents.[26]
    - Results on the use of the BRAF V600E inhibitor dabrafenib demonstrated a 44% overall response rate (1 complete response and 13 partial responses) by central review in children with *BRAF* V600–mutated relapsed or refractory low-grade gliomas. The median duration of response was 26 months. Disease control (complete response plus partial response plus stable disease) was 78%. The therapy was well tolerated, although 91% of patients had some side effects such as fatigue (34%), rash (31%), and pyrexia (28%). Nine of 32 patients had grade 3 to grade 4 toxicities, 10 patients required dose modifications, and 2 patients discontinued treatment, including 1 child who had disseminated intravascular coagulation with hypertension. In this pediatric study, no cases of squamous cell carcinoma of the skin or keratoacanthoma were encountered.[27]
    - Case reports have also documented activity for BRAF inhibitors such as vemurafenib and for BRAF inhibitors in combination with MEK inhibitors for children, adolescents, and young adults with *BRAF* V600–mutated low-grade gliomas.[28-32]
2. The MEK inhibitor selumetinib has been studied in a phase I/II clinical trial for children with low-grade gliomas (PBTC-029 [NCT01089101]).
    a. The phase I component of the PBTC-029 trial showed the following results:[33]
        - Selumetinib was tolerated at a daily dose of 25 mg/m^2.
        - The most common adverse events leading to patient discontinuation of treatment were rash, paronychia, and asymptomatic creatine phosphokinase (CPK) elevation.
    b. Stratum 1 of the phase II component of this trial was for patients with *BRAF* genomic alterations.[34,35]
        - Nine of 25 patients (36%) achieved a partial response, with responses occurring for both *BRAF* V600E patients and for patients with *BRAF* gene fusions.
        - The 2-year PFS rate was 70% for stratum 1 patients.
    c. Stratum 3 of the phase II component of this trial was for patients with NF1-associated low-grade gliomas.[35]
        - The 2-year event-free survival rate for this group was 96%.
        - 10 of 25 patients (40%) achieved partial responses.

    The most common toxicities across all strata were grade 1 and grade 2 CPK elevation, diarrhea, hypoalbuminemia, elevated aspartate aminotransferase (AST), and rash. Rare grade 3 and grade 4 toxicities included elevated CPK, rash, neutropenia, emesis, and paronychia.

Treatment options under clinical evaluation

Early-phase therapeutic trials may be available for selected patients. These trials may be available via the COG, the Pediatric Brain Tumor Consortium, or other entities. Information about National Cancer Institute (NCI)–supported clinical trials can be found on the NCI website. For information about clinical trials sponsored by other organizations, refer to the ClinicalTrials.gov website.

The following are examples of national and/or institutional clinical trials that are currently being conducted:

- **APEC1621 (NCT03155620)** (Pediatric MATCH: Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients with Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphomas, or Histiocytic Disorders)**:** NCI-COG Pediatric Molecular Analysis for Therapeutic Choice (MATCH), referred to as Pediatric MATCH, will match targeted agents with specific molecular changes identified using a next-generation sequencing targeted assay of more than 4,000 different mutations across more than 160 genes in refractory and recurrent solid tumors. Children and adolescents aged 1 to 21 years are eligible for the trial.

  Tumor tissue from progressive or recurrent disease must be available for molecular characterization. Patients with tumors that have molecular variants addressed by treatment arms included in the trial will be offered treatment on Pediatric MATCH. Additional information can be obtained on the NCI website and ClinicalTrials.gov website.

- **PBTC-029B (NCT01089101)** (Selumetinib in Treating Young Patients With Recurrent or Refractory Low-Grade Glioma)**:** This is a clinical trial to determine the side effects and the best dose of the MEK inhibitor selumetinib in children with low-grade astrocytoma (phase I component). Based on activity observed in the phase I component (now completed), the study has been modified to include phase II expansion cohorts for patients with pilocytic astrocytoma and other low-grade astrocytomas with *BRAF* genomic alterations and for NF1 patients with recurrent low-grade astrocytomas.

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Childhood High-Grade Astrocytomas

To determine and implement optimal management, treatment of childhood high-grade astrocytomas should be guided by a multidisciplinary team of cancer specialists who have experience treating childhood brain tumors.

Outcomes in high-grade gliomas occurring in childhood are often more favorable than that in adults. It is not clear whether this difference is caused by biologic variations in tumor characteristics, therapies used, tumor resectability, or other factors.

The therapy for both children and adults with supratentorial high-grade astrocytoma includes surgery, radiation therapy, and chemotherapy.

Standard treatment options for newly diagnosed childhood high-grade astrocytomas include the

following:

1. Surgery.
2. Adjuvant therapy.
    - Radiation therapy.
    - Chemotherapy.

Surgery

The ability to obtain a complete resection is associated with a better prognosis.[1,2] Among patients treated with surgery, radiation therapy, and nitrosourea (lomustine)-based chemotherapy, the 5-year progression-free survival rate was 19% (± 3%); the survival rate was 40% in those who had total resections.[3] Similarly, in a trial of multiagent chemoradiation therapy and adjuvant chemotherapy in addition to valproic acid, the overall 5-year event-free survival (EFS) rate was 13%, but for children with a complete resection of their tumor, the EFS rate was 48%.[4][Level of evidence: 2A]

Adjuvant therapy

Radiation therapy

Radiation therapy is routinely administered to a field that widely encompasses the entire tumor. The radiation therapy dose to the tumor bed is usually at least 54 Gy. Despite such therapy, overall survival (OS) rates remain poor. Similarly poor survival is seen in children with spinal cord primaries and children with thalamic high-grade gliomas (i.e., diffuse midline gliomas, H3 K27M-mutant tumors) treated with radiation therapy.[5,6]; [7,8][Level of evidence: 3iiiA]

Chemotherapy

In one trial, children with glioblastoma who were treated on a prospective randomized trial with adjuvant lomustine, vincristine, and prednisone fared better than children treated with radiation therapy alone.[9] Furthermore, children who received lomustine in addition to temozolomide for subtotally resected tumors, especially glioblastoma with methylated O-6-methylguanine-DNA-methyltransferase (MGMT) overexpression, had a slightly improved outcome.[10] Patients with *IDH1* mutations had an improved 1-year OS rate (100%) when compared with *IDH1*–wild-type tumors (1-year OS rate, 81%), highlighting the potential importance of underlying biological characteristics.[11]

The use of temozolomide to treat glioblastoma was initially investigated in adults. In this population, the addition of temozolomide during and after radiation therapy resulted in improved 2-year EFS compared with treatment with radiation therapy alone. Adult patients with glioblastoma with an MGMT promoter benefitted from temozolomide, whereas those who did not have a methylated MGMT promoter did not.[12,13] The role of temozolomide given concurrently with radiation therapy for children with supratentorial high-grade glioma appears comparable to the outcome seen in children treated with nitrosourea-based therapy [14] and again demonstrated an EFS advantage for those children without MGMT overexpression.

The use of adjuvant bevacizumab after radiation therapy did not prolong OS or progression-free survival in pediatric patients with newly diagnosed high-grade gliomas.[15]

Younger children may benefit from chemotherapy or consolidation with high-dose chemotherapy to delay, modify, or, in selected cases, obviate the need for radiation therapy.[16-18]

Treatment options under clinical evaluation

Early-phase therapeutic trials may be available for selected patients. These trials may be available

via the Children's Oncology Group (COG), the Pediatric Brain Tumor Consortium, or other entities. Information about National Cancer Institute (NCI)–supported clinical trials can be found on the NCI website. For information about clinical trials sponsored by other organizations, refer to the ClinicalTrials.gov website.

The following are examples of national and/or institutional clinical trials that are currently being conducted:

- **ACNS1721 (NCT03581292)** (Veliparib, Radiation Therapy, and Temozolomide in Treating Participants With Newly Diagnosed Malignant Glioma Without H3 K27M or *BRAF* V600E Mutations)**:** This phase II trial investigates the use of veliparib, radiation therapy, and temozolomide in treating patients with newly diagnosed malignant glioma without H3 K27M or *BRAF* V600E mutations.
- **ACNS1723 (NCT03919071)** (Dabrafenib Combined With Trametinib After Radiation Therapy in Treating Patients With Newly-Diagnosed High-Grade Glioma)**:** This phase II trial investigates the use of the combination of dabrafenib and trametinib after radiation therapy in children and young adults with high-grade gliomas who have a *BRAF* V600 mutation.

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Recurrent Childhood High-Grade Astrocytomas

To determine and implement optimal management, treatment of childhood high-grade astrocytomas should be guided by a multidisciplinary team of cancer specialists who have experience treating childhood brain tumors.

Most patients with high-grade astrocytomas or gliomas will eventually have tumor recurrence. Recurrences usually occur within 3 years of original diagnosis, but some patients recur many years after initial treatment. Disease may recur at the primary tumor site, at the margin of the resection/radiation bed, or at noncontiguous central nervous system sites. Systemic relapse rarely occurs.

At the time of recurrence, a complete evaluation for extent of relapse is indicated for all malignant tumors. Biopsy or surgical resection may be necessary for confirmation of relapse because other entities, such as secondary tumor and treatment-related brain necrosis, may be clinically indistinguishable from tumor recurrence.

Treatment options for recurrent childhood high-grade astrocytomas include the following:

1. Surgery.
2. High-dose chemotherapy with stem cell transplant (SCT).[1]
3. Radiation therapy.
4. Targeted therapy with a BRAF inhibitor, for patients with a *BRAF* V600E mutation.[2]

Surgery

The utility of surgical intervention must be individualized on the basis of the following:

- Initial tumor type.
- Length of time between initial treatment and the reappearance of the mass lesion.
- Location of the recurrent tumor.
- Consideration of therapeutics based on the requirement for fresh tumor tissue or to deliver therapy to the operative bed.

High-dose chemotherapy with SCT

High-dose, marrow-ablative chemotherapy with hematopoietic SCT may be effective in a highly selected subset of patients with minimal residual disease at time of recurrence.[1][Level of evidence: 3iiiA] However, the results of previous clinical trials that tested various targeted and combination chemotherapies have largely failed to demonstrate convincing benefits for enrolled patients.[3-5]

Radiation therapy

Radiation therapy is appropriate for patients who have not previously been irradiated. Radiation doses and volumes are similar to those used for newly diagnosed patients. Generally, this is limited to young children initially treated with radiation-avoiding strategies.

For previously irradiated patients, reirradiation has been used, although the data demonstrating benefit are sparse. Stereotactic radiosurgery (SRS) or stereotactic radiation therapy (SRT) techniques using either hypofractionated radiation therapy or standard fraction sizes may be considered. For small volume distinct lesions, SRS allows for maximum sparing of normal tissues. For more infiltrative lesions, fractionated radiation therapy may better spare normal tissues.[6]

Targeted therapy

Molecular targets for recurrent high-grade gliomas are limited. *BRAF* V600E mutations are present in a small subset of these patients, and a small number of cases have responded to BRAF inhibitors.

A case report documented a complete response to the BRAF inhibitor vemurafenib in a patient with recurrent *BRAF* V600–mutated glioblastoma.[7] A phase I study reported in an abstract that eight children with progressive *BRAF* V600E high-grade gliomas were treated with dabrafenib and demonstrated three complete responses, three partial responses, and two progressive disease responses.[8]

A small percentage of children with high-grade gliomas have gene fusions involving tyrosine kinases (e.g., *ALK*, *NTRK1*, *NTRK2*, *NTRK3*, *ROS1*, and *MET*).[9,10] Kinase gene fusions account for a high percentage of cases among children younger than 1 year, but they can occur throughout childhood. Case reports have described responses to kinase inhibitors for patients with relapsed or refractory high-grade gliomas who have these gene fusions.[11,12]

Treatment options under clinical evaluation

The role of immune checkpoint inhibition in the treatment of children with recurrent high-grade astrocytoma is currently under study. Children with biallelic mismatch repair deficiency have a very high mutational burden and neoantigen expression and are at risk of developing a variety of cancers, including hematologic malignancies, gastrointestinal cancers, and brain tumors. The high mutation and neoantigen load has been correlated with improved response to immune checkpoint inhibition. Early case reports have demonstrated clinical and radiographic responses in children

who are treated with an anti–programmed death-1 (anti–PD-1) inhibitor.[13]

Patients for whom initial treatment fails may benefit from additional treatment, including entry into clinical trials of novel therapeutic approaches.[14] Early-phase therapeutic trials may be available for selected patients. These trials may be available via the Children's Oncology Group (COG), the Pediatric Brain Tumor Consortium, or other entities. Information about NCI-supported clinical trials can be found on the NCI website. For information about clinical trials sponsored by other organizations, refer to the ClinicalTrials.gov website.

The following are examples of national and/or institutional clinical trials that are currently being conducted:

- **APEC1621 (NCT03155620)** (Pediatric MATCH: Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients with Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphomas, or Histiocytic Disorders)**:** NCI-COG Pediatric Molecular Analysis for Therapeutic Choice (MATCH), referred to as Pediatric MATCH, will match targeted agents with specific molecular changes identified using a next-generation sequencing targeted assay of more than 4,000 different mutations across more than 160 genes in refractory and recurrent solid tumors. Children and adolescents aged 1 to 21 years are eligible for the trial.

  Tumor tissue from progressive or recurrent disease must be available for molecular characterization. Patients with tumors that have molecular variants addressed by treatment arms included in the trial will be offered treatment on Pediatric MATCH. Additional information can be obtained on the NCI website and ClinicalTrials.gov website.

- **NCT02684058** (Phase II Pediatric Study With Dabrafenib in Combination With Trametinib in Patients With High-Grade Gliomas and Low-Grade Gliomas)**:** The purpose of this study is to investigate the activity of dabrafenib in combination with trametinib in children and adolescent patients with *BRAF* V600 mutation–positive low-grade gliomas or relapsed or refractory high-grade gliomas.

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Changes to this Summary (11/25/2020)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

General Information About Childhood Astrocytomas

The High-grade gliomas in infants subsection of the Genomic Alterations section was renamed from Gliomas in infants and extensively revised.

Treatment of Childhood Low-Grade Astrocytomas

Revised text to state that visual status is an important measure of outcome and response to treatment. Vision function can be impaired; it is variable even in patients with radiographic responses and is often less than optimal. Also added text to state that more than one-third of patients *successfully* treated with chemotherapy have poor vision in one or both eyes, and some patients lose vision despite radiographic evidence of tumor control.

Added text to state that in a prospective study of 174 patients treated with proton therapy, the 5-year actuarial rate of local control was 85%, the progression-free survival rate was 84%, and the overall survival rate was 92%. Brain stem and spinal cord tumor locations and a dose of 54 Gy relative biological effectiveness or less were associated with inferior local control (cited Indelicato et al. as reference 49).

Treatment of Progressive/Recurrent Childhood Low-Grade Astrocytomas

Added Zhukova et al. as reference 23.

Revised text to update the results of a study on the use of dabrafenib in children with *BRAF* V600–mutated relapsed or refractory low-grade gliomas, including the overall response rate, median duration of response, disease control rate, and reported side effects (cited Hargrave et al. as reference 27).

Treatment of Recurrent Childhood High-Grade Astrocytomas

Added text to state that a small percentage of children with high-grade gliomas have gene fusions involving tyrosine kinases (cited Torre et al. and Clarke et al. as references 9 and 10, respectively). Also added text to state that kinase gene fusions account for a high percentage of cases among children younger than 1 year, but they can occur throughout childhood. Case reports have described responses to kinase inhibitors for patients with relapsed or refractory high-grade gliomas who have these gene fusions (cited Ziegler et al. and Desai et al. as references 11 and 12, respectively).

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About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of childhood astrocytomas. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

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- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for Childhood Astrocytomas Treatment are:

- Kenneth J. Cohen, MD, MBA (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital)
- Louis S. Constine, MD (James P. Wilmot Cancer Center at University of Rochester

Medical Center)

- Karen J. Marcus, MD, FACR (Dana-Farber Cancer Institute/Boston Children's Hospital)
- Roger J. Packer, MD (Children's National Health System)
- D. Williams Parsons, MD, PhD
- Malcolm A. Smith, MD, PhD (National Cancer Institute)

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Based on the strength of the available evidence, treatment options may be described as either “standard” or “under clinical evaluation.” These classifications should not be used as a basis for insurance reimbursement determinations. More information on insurance coverage is available on Cancer.gov on the Managing Cancer Care page.

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