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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

The PDQ childhood brain tumor treatment summaries are organized primarily according to the World Health Organization (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.

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%.[3] Childhood and adolescent cancer survivors require close follow-up because cancer therapy side effects may persist or develop months or years after treatment. 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.

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

Gliomas arise from glial cells that are present in the brain and spinal cord. Gliomas are named according to their clinicopathologic and histologic subtype. For example, astrocytomas originate from astrocytes, oligodendrogial tumors from oligodendrocytes, and mixed gliomas from a mix of oligodendrocytes, astrocytes, and ependymal cells. Astrocytoma is the most commonly diagnosed type of glioma in children. According to the WHO classification of brain tumors, gliomas are further classified as low-grade (grades I and II) and 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 poor prognosis, unless the tumor is an anaplastic astrocytoma that can be completely resected.

Anatomy

Childhood astrocytomas can occur anywhere in the central nervous system (CNS). Refer to Table 3 for the most common CNS location for each tumor type.
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.[4]

Diagnostic Evaluation

The diagnostic evaluation for astrocytoma is often limited to a magnetic resonance imaging (MRI) of the brain or spine. Additional imaging, when clinically indicated, would consist of an MRI of the remainder of the neuraxis.

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 glial cell type of origin:

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

**WHO histologic grade**

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**

<table>
<thead>
<tr>
<th>WHO Histologic Grade</th>
<th>Grade Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Low grade</td>
</tr>
<tr>
<td>II</td>
<td>Low grade</td>
</tr>
<tr>
<td>III</td>
<td>High grade</td>
</tr>
<tr>
<td>IV</td>
<td>High grade</td>
</tr>
</tbody>
</table>

**Table 2. Histologic Grade of Childhood Astrocytomas and Other Tumors of Glial Origin**

<table>
<thead>
<tr>
<th>Type</th>
<th>WHO Histologic Grade</th>
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</thead>
<tbody>
<tr>
<td><strong>Astrocytic Tumors:</strong></td>
<td></td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>I</td>
</tr>
<tr>
<td>Pilomyxoid astrocytoma</td>
<td>II</td>
</tr>
<tr>
<td>Pleomorphic xanthoastrocytoma</td>
<td>II</td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma</td>
<td>I</td>
</tr>
<tr>
<td><strong>Diffuse astrocytoma:</strong></td>
<td></td>
</tr>
<tr>
<td>Gemistocytic astrocytoma</td>
<td>II</td>
</tr>
<tr>
<td>Protoplasmic astrocytoma</td>
<td>II</td>
</tr>
<tr>
<td>Fibrillary astrocytoma</td>
<td>II</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>III</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Oligodendrogial Tumors:</strong></td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>II</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>III</td>
</tr>
<tr>
<td><strong>Mixed Gliomas:</strong></td>
<td></td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td>II</td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma</td>
<td>III</td>
</tr>
</tbody>
</table>

*In 2007, the WHO further categorized astrocytomas, oligodendroglial tumors, and mixed gliomas according to histopathologic features and...*
biologic behavior. It was 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.[1,2,5]

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

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Common CNS Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocytic astrocytoma</td>
<td>Optic nerve, optic chiasm/hypothalamus, thalamus and basal ganglia, cerebral hemispheres, cerebellum, and brain stem; and spinal cord (rare)</td>
</tr>
<tr>
<td>Pleomorphic xanthoastrocytoma</td>
<td>Superficial location in cerebrum (temporal lobe preferentially)</td>
</tr>
<tr>
<td>Diffuse astrocytoma (including fibrillary)</td>
<td>Cerebrum (frontal and temporal lobes), brain stem, spinal cord, optic nerve, optic chiasm, optic pathway, hypothalamus, and thalamus</td>
</tr>
<tr>
<td>Anaplastic astrocytoma, glioblastoma</td>
<td>Cerebrum; occasionally cerebellum, brain stem, and spinal cord</td>
</tr>
<tr>
<td>Oligodendrogliomas</td>
<td>Cerebrum (frontal lobe preferentially followed by temporal, parietal, and occipital lobes), cerebellum, brain stem, and spinal cord</td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td>Cerebral hemispheres (frontal lobe preferentially followed by the temporal lobe)</td>
</tr>
<tr>
<td>Gliomatosis cerebri</td>
<td>Cerebrum with or without brain stem involvement, cerebellum, and spinal cord</td>
</tr>
</tbody>
</table>

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 location.[6-8]

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 high-grade gliomas (e.g., diffuse intrinsic pontine gliomas).[9,10] (Refer to the PDQ summary on Childhood Brain Stem Glioma Treatment for more information.)

High-grade astrocytomas are often locally invasive and extensive and tend to occur above the tentorium in the cerebrum.[11,12] 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 a diffuse glioma that involves widespread involvement of the cerebral hemispheres in which it may be confined, but it often extends caudally to affect the brain stem, cerebellum, and/or spinal cord.[1] It rarely arises in the cerebellum and spreads rostrally.[13] The neoplastic cells are most commonly astrocytes, but in some cases, they are oligodendrogliia. They may respond to treatment initially, but overall have a poor prognosis.[14]

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; approximately 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 fibrillary (grade II) astrocytomas.
In general, treatment is not required for incidental tumors found with surveillance scans. Symptomatic lesions or those that have radiographically progressed may require treatment.[18]

**Genomic Alterations**

**Low-grade gliomas**

Genomic alterations involving *BRAF* activation are very common in sporadic cases of pilocytic astrocytoma, resulting in activation of the ERK/MAPK pathway.

*BRAF* activation in pilocytic astrocytoma occurs most commonly through a *BRAF-KIAA1549* gene fusion, producing a fusion protein that lacks the *BRAF* regulatory domain.[19-23] This fusion is seen in most infratentorial and midline pilocytic astrocytomas, but is present at lower frequency in supratentorial (hemispheric) tumors.[19,20,24-28]

Presence of the *BRAF-KIAA1549* fusion predicted for better clinical outcome (progression-free survival [PFS] and overall survival) in one report that described children with incompletely resected low-grade gliomas.[28] However, other factors such as p16 deletion and tumor location may modify the impact of *BRAF* mutation on outcome.[29]

*BRAF* activation through the *BRAF-KIAA1549* fusion has also been described in other pediatric low-grade gliomas (e.g., pilomyxoid astrocytoma).[27,28]

Other genomic alterations in pilocytic astrocytomas that can also activate the ERK/MAPK pathway (e.g., alternative *BRAF* gene fusions, *RAF1* rearrangements, *RAS* mutations, and *BRAF V600E* point mutations) are less commonly observed.[20,22,23,31] *BRAF V600E* point mutations are observed in nonpilocytic pediatric low-grade gliomas as well, including approximately two-thirds of pleomorphic xanthoastrocytoma cases and in ganglioglioma and desmoplastic infantile ganglioglioma.[32-34] One retrospective study of 53 children with gangliogliomas demonstrated *BRAF V600E* staining in approximately 40% of tumors. Five-year recurrence-free survival was worse in the V600E-mutated tumors (about 60%) than in the tumors that did not stain for V600E (about 80%).[35] 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 (10 of 167 cases).[30]

As expected, given the role of neurofibromatosis type 1 (NF1) deficiency in activating the ERK/MAPK pathway, activating *BRAF* genomic alterations are uncommon in pilocytic astrocytoma associated with NF1.[26]

Activating mutations in *FGFR1* and *PTPN11*, as well as *NTRK2* fusion genes, have also been identified in noncerebellar pilocytic astrocytomas.[36] In pediatric grade II diffuse astrocytomas, the most common alterations reported are rearrangements in the MYB family of transcription factors in up to 53% of tumors.[37,38]

Most children with tuberous sclerosis have a mutation in one of two tuberous sclerosis genes (*TSC1*/hamartin or *TSC2*/tuberin). Either of these mutations results in an overexpression of the mammalian target of rapamycin (mTOR) complex 1. These children are at risk of developing subependymal giant cell astrocytomas, in addition to cortical tubers and subependymal nodules.

**High-grade gliomas**

Pediatric high-grade gliomas, especially glioblastoma multiforme, are biologically distinct from those arising in adults.[39-42] Pediatric high-grade gliomas have *PTEN* and *EGFR* genomic alterations less frequently and *PDGF/PDGFR* genomic alterations and mutations in *histone H3.3* genes more frequently than do adult tumors. Although it was believed that pediatric glioblastoma multiforme tumors were more closely related to adult *secondary* glioblastoma multiforme tumors in which there is stepwise transformation from lower-grade into higher-grade gliomas and in which most tumors have *IDH1* and *IDH2* mutations, the latter mutations are rarely observed in childhood glioblastoma multiforme tumors.[43-45]

Based on epigenetic patterns (DNA methylation), pediatric glioblastoma multiforme tumors are separated into relatively distinct subgroups with distinctive chromosome copy number gains/losses and gene mutations.[45]
Two subgroups have identifiable recurrent H3F3A mutations, suggesting disrupted epigenetic regulatory mechanisms, with one subgroup having mutations at K27 (lysine 27) and the other group having mutations at G34 (glycine 34). The subgroups are the following:

- **H3F3A mutation at K27**: The K27 cluster occurs predominately in mid-childhood (median age, approximately 10 years), is mainly midline (thalamus, brainstem, and spinal cord), and carries a very poor prognosis. These tumors also frequently have TP53 mutations. Thalamic high-grade gliomas in older adolescents and young adults also show a high rate of H3F3A K27 mutations.[46]

- **H3F3A mutation at G34**: The second H3F3A mutation tumor cluster, the G34 grouping, is found in somewhat older children and young adults (median age, 18 years), arises exclusively in the cerebral cortex, and carries a somewhat better prognosis. The G34 clusters also have TP53 mutations and widespread hypomethylation across the whole genome.

The H3F3A K27 and G34 mutations appear to be unique to high-grade gliomas and have not been observed in other pediatric brain tumors.[47] Both mutations induce distinctive DNA methylation patterns compared with the patterns observed in IDH-mutated tumors, which occur in young adults.[43-45,47,48]

Other pediatric glioblastoma multiforme subgroups include the RTK PDGFRA and mesenchymal clusters, both of which occur over a wide age range, affecting both children and adults. The RTK PDGFRA and mesenchymal subtypes are comprised predominantly of cortical tumors, with cerebellar glioblastoma multiforme tumors being rarely observed; they both carry a poor prognosis.[45]

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. Approximately 40% of patients (7 of 18) with secondary high-grade glioma had BRAF V600E mutations, with CDKN2A alterations present in 57% of cases (8 of 14).[30]

**Oligodendroglioma**

The molecular profile of pediatric patients with oligodendrogliomas rarely demonstrates deletions of 1p and 19q, as found in 40% to 80% of adult cases. When 1p19q codeletion is observed in pediatric oligodendroglioma, it is primarily in patients older than 15 years. Similarly, IDH1 mutations are uncommon in pediatric oligodendroglioma, but when present, are observed primarily in patients older than 15 years.[37,49,50] Like other diffuse pediatric low-grade gliomas, pediatric oligodendrogliomas were noted to have FGFR1 tyrosine kinase domain duplications (3 of 5 cases studied), with an MYB fusion gene observed in one of the two remaining cases.[37]

**Prognosis**

**Low-grade astrocytomas**

Low-grade astrocytomas (grade I [pilocytic] and grade II) have a relatively favorable prognosis, particularly for circumscribed, grade I lesions where complete excision may be possible.[11,12,51-55] Tumor spread, when it occurs, is usually by contiguous extension; dissemination to other CNS sites is uncommon, but does occur.[56,57] 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:[58,59]

- Young age.
- Fibrillary histology.
- Inability to obtain a complete resection.

In patients with pilocytic astrocytoma, elevated MIB-1 labeling index, a marker of cellular proliferative activity, is
associated with shortened PFS.[8] A BRAF-KIAA fusion, found in pilocytic tumors, confers a better clinical outcome.[28]

Children with isolated optic nerve tumors have a better prognosis than those with lesions that involve the chiasm or that extend along the optic pathway.[60-63]; [64][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.[60,65]

**High-grade astrocytomas**

Biologic markers, such as p53 overexpression and mutation status, may be useful predictors of outcome in patients with high-grade gliomas.[5,66,67] MIB-1 labeling index is predictive of outcome in childhood malignant brain tumors. Both histologic classification and proliferative activity evaluation have been shown to be independently associated with survival.[68]

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.[53,69,70]

**Oligodendrogliomas**

Oligodendrogliomas are rare in children and have a relatively favorable prognosis; however, children younger than 3 years who have less than a gross-total resection have a less favorable prognosis.[71]

This summary does not address the treatment of children with oligodendrogliomas.

**References**


**Stage Information for Childhood Astrocytomas**

There is no generally recognized staging system for childhood astrocytomas. For the purposes of this summary, childhood astrocytomas will be described as follows:

- **Low-grade astrocytoma**—grades I and II (e.g., pilocytic astrocytomas and diffuse fibrillary astrocytomas).
  - Newly diagnosed.
  - Recurrent.

- **High-grade astrocytoma**—grades III and IV (anaplastic astrocytomas and glioblastoma).
  - Newly diagnosed.
  - Recurrent.

**Treatment Option Overview for Childhood Astrocytomas**

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.

To determine and implement optimum treatment, planning by a multidisciplinary team of cancer specialists who have experience treating childhood brain tumors is required. Radiation therapy 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.
Debilitating effects on growth and neurologic development have frequently been observed following radiation therapy, especially in younger children.[1-3] Also, there are other less-common complications of radiation therapy, including cerebrovascular accidents.[4] For this reason, the role of chemotherapy in allowing a delay in the administration of radiation therapy is under study, and preliminary results suggest that chemotherapy can be used to delay, and sometimes obviate, the need for radiation therapy in children with benign and malignant lesions.[5] Long-term management of these patients is complex and requires a multidisciplinary approach.

Table 4. Standard Treatment Options for Childhood Astrocytomas

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Standard Treatment Options</th>
</tr>
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<tbody>
<tr>
<td><strong>Childhood low-grade astrocytomas:</strong></td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed childhood low-grade</td>
<td>Surgery</td>
</tr>
<tr>
<td>astrocytomas</td>
<td>Adjuvant therapy (for tumors that are incompletely resected):</td>
</tr>
<tr>
<td></td>
<td>— Observation</td>
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<td></td>
<td>— Radiation therapy</td>
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<td></td>
<td>— Second surgery</td>
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<tr>
<td></td>
<td>— Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>— Targeted therapy (for subependymal giant cell astrocytomas)</td>
</tr>
<tr>
<td>Recurrent childhood low-grade astrocytomas</td>
<td>Second surgery</td>
</tr>
<tr>
<td></td>
<td>Radiation therapy</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
</tr>
<tr>
<td><strong>Childhood high-grade astrocytomas:</strong></td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed childhood high-grade</td>
<td>Surgery</td>
</tr>
<tr>
<td>astrocytomas</td>
<td>Adjuvant therapy:</td>
</tr>
<tr>
<td></td>
<td>— Radiation therapy</td>
</tr>
<tr>
<td></td>
<td>— Chemotherapy</td>
</tr>
<tr>
<td>Recurrent childhood high-grade astrocytomas</td>
<td>Surgery (not considered standard treatment)</td>
</tr>
<tr>
<td></td>
<td>Entry into an early-phase clinical trial (not considered standard treatment)</td>
</tr>
<tr>
<td></td>
<td>High-dose chemotherapy with stem cell transplant (not considered standard treatment)</td>
</tr>
<tr>
<td></td>
<td>Targeted therapy with a BRAF inhibitor, for patients with a BRAF V600E mutation (not considered standard treatment)</td>
</tr>
</tbody>
</table>

References


**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.

In infants and young children, low-grade astrocytomas presenting in the hypothalamus make surgery difficult; consequently, biopsies are not always done. This is especially true in patients with neurofibromatosis type 1 (NF1).[1] When associated with NF1, tumors may be of multifocal origin.

For children with low-grade optic pathway astrocytomas, treatment options should be considered not only to improve survival but also to stabilize visual function.[2,3]

**Treatment of Newly Diagnosed Childhood Low-Grade Astrocytomas**

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

1. Observation.
2. Surgery.
3. Adjuvant therapy.
   - Observation.
   - Radiation therapy.
   - Second surgery.
   - Chemotherapy.
   - Targeted therapy (for subependymal giant cell astrocytomas).

**Observation**

Observation is an option for patients with NF1 or nonprogressive masses.[4-7] Spontaneous regressions of optic pathway gliomas have been reported in children with and without NF1.[8-10]

**Surgery**

Surgical resection is the primary treatment for childhood low-grade astrocytoma [1,4,5,11] and surgical feasibility is determined by tumor location.

- **Cerebellum:** Complete or near-complete removal can be obtained in 90% to 95% of patients with pilocytic tumors that occur in the cerebellum.[11]

- **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.

- **Midline structures (hypothalamus, thalamus, brain stem, and spinal cord):** Low-grade astrocytomas that occur in midline structures can be aggressively resected, with resultant long-term disease control;[8,9,12]; [13][Level of evidence: 3iiiA] however, such resection may result in significant neurologic sequelae, especially in children younger than 2 years at diagnosis.[8]; [14][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.[15][Level of evidence: 3iiiDiii]

- **Cerebrum:** Circumscribed, grade I hemispheric tumors are often amenable to complete surgical resection.[16]

- **Diffuse:** Diffuse astrocytomas may be less amenable to total resection, and this may contribute to the poorer outcome.
In some low-grade astrocytomas, surgical resection can be performed more safely.[17] 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.[18]; [19][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.[11] Overall outcome for the entire group was 78% progression-free survival (PFS) at 8 years and 96% overall survival (OS) at 8 years. The following factors were related to prognosis:[11]

- **Tumor location:** Cerebellar and cerebral tumors showed higher PFS at 8 years compared with patients with midline and chiasmatic tumors (84% ± 1.9% versus 51% ± 5.9%).
- **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 exceeding 90% and OS 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 exceeded 90%.[11]

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.[1, 6, 11]

- **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.[20]

The long-term functional outcome of cerebellar pilocytic astrocytomas is relatively favorable. Full-scale mean 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.[21, 22][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.**
- **Radiation therapy.**
- **Second surgery.**
- **Chemotherapy.**
- **Targeted therapy (for subependymal giant cell astrocytomas).**

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

**Observation**

In selected 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.[11]

**Radiation therapy**

Radiation therapy is usually reserved until progressive disease is documented [16, 23] and may be further delayed through the use of chemotherapy, a strategy that is commonly employed in young children.[24, 25] For children with
low-grade gliomas for whom radiation therapy is indicated, approaches that contour the radiation 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.[26,27];[28][Level of evidence: 3iDiii] Care must be taken in separating 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.[29-32];[33][Level of evidence: 2A];[34][Level of evidence: 2C];[35][Level of evidence: 3iiiDi];[36][Level of evidence: 3iiiDii];[15,37][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, and possibly an increased risk of secondary tumors.[8,38-40];[34][Level of evidence: 2C]

Radiation therapy and alkylating agents are used as a last resort for patients with NF1, given the theoretically heightened risk of inducing neurologic toxic effects and second malignancy in this population.[41] Children with NF1 may be at higher risk for radiation-associated secondary tumors and morbidity due to vascular changes.

**Second surgery**

An alternative to immediate radiation therapy is subtotal surgical resection, but it is unclear how many patients will have stable disease and for how long.[8]

**Chemotherapy**

Given the 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. [24,25,42,43] Chemotherapy is also an option that may delay or avoid radiation therapy in adolescents with optic nerve pathway gliomas.[44][Level of evidence: 3iiiD] 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.[45]

The most widely used regimens to treat tumor progression or symptomatic nonresectable, low-grade gliomas are the following:

- Carboplatin with or without vincristine.[24,25,46]
- Combination of thioguanine, procarbazine, lomustine, and vincristine (TPCV).[43];[47][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 using one of two regimens: carboplatin and vincristine (CV) or TPCV. The 5-year event-free survival rate was 39% ± 4% for the CV regimen and 52% ± 5% for the TPCV regimen.[47]

Other chemotherapy approaches have been employed to treat children with progressive low-grade astrocytomas, including multiagent, platinum-based regimens [25,42,48];[49][Level of evidence: 2Dii] and temozolomide.[50,51] Reported 5-year PFS rates have ranged from approximately 35% to 60% for children receiving platinum-based chemotherapy for optic pathway gliomas,[25,42] but most patients ultimately require further treatment. This is particularly true for children who initially present with hypothalamic/chiasmatic gliomas that have neuraxis dissemination.[52][Level of evidence: 3iiiDii]

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.[25,42,48] Whether vision is improved with chemotherapy is unclear.[53,54][Level of evidence: 3iiiC]

**Targeted therapy**

For children with symptomatic subependymal giant cell astrocytomas (SEGAs), agents that inhibit mTOR (e.g.,
everolimus and sirolimus) have been shown in small series to cause significant reductions in the size of these tumors, often eliminating the need for surgery.[55]; [56][Level of evidence: 2C]; [57][Level of evidence: 3iiDiv]; [58][Level of evidence: 3iiiC] A multicenter, phase III, placebo-controlled trial of 117 patients confirmed these earlier findings; 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.[59][Level of evidence: 1iDiv] Whether reduction in size of the mass is durable, obviating the need for future surgery, is unknown.

**Treatment options under clinical evaluation**

The following is an example of a national and/or institutional clinical trial that is currently being conducted. Information about ongoing clinical trials is available from the NCI website.

- **PBTC-029 (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**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with childhood low-grade untreated astrocytoma or other tumor of glial origin. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

**Treatment of Recurrent Childhood Low-Grade Astrocytomas**

Childhood low-grade astrocytomas may recur many years after initial treatment. An individual plan needs to be tailored based on 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.[60,61] Most children whose low-grade fibrillary astrocytomas recur will harbor low-grade lesions; however, transformation into a higher grade tumor is possible.[62] Surveillance imaging will frequently identify asymptomatic recurrences.[63]

At the time of recurrence, a complete evaluation to determine the extent of the relapse is indicated. 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. 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.

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

1. Second surgery.
2. Radiation therapy.
3. Chemotherapy.

Second surgery

Patients with low-grade astrocytomas who relapse after being treated with surgery alone should be considered for another surgical resection.[64]

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 Newly Diagnosed 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.[65][Level of evidence: 3iA]; [66][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. [30,34]

Chemotherapy

If there is recurrence at an unresectable site that has been previously irradiated, chemotherapy should be considered.[67]

In patients previously treated with surgery and radiation therapy, chemotherapy should be considered. Chemotherapy may result in relatively long-term disease control.[25,68] Vinblastine alone, temozolomide alone, or temozolomide in combination with carboplatin and vincristine may be useful at the time of recurrence for children with low-grade gliomas.[25,50,68]

Antitumor activity has also been observed for bevacizumab given in combination with irinotecan, which, in some cases, also results in clinical or visual improvement.[69] In a phase II study of bevacizumab plus irinotecan for children with recurrent low-grade gliomas, sustained partial response was observed in only two patients (5.7%), but the 6-month PFS was 85.4% (standard error [SE] ± 5.96%) and the 2-year PFS was 47.8% (SE ± 9.27%).[70] A pilot study of 14 patients with recurrent low-grade gliomas also evaluated bevacizumab plus irinotecan and observed 12 patients (86%) with objective responses.[71][Level of evidence: 3iiDi]; [72][Level of evidence: 3iiiDiv] No patients progressed on therapy (median treatment duration, 12 months), but 13 of 14 progressed after stopping bevacizumab at a median of 5 months. Bevacizumab has also been employed for children with low-grade gliomas and symptomatic radiation-induced tumor enlargement; it produced radiographic improvement (five of five patients) and allowed weaning off steroids (four of four patients).[73]

Treatment options under clinical evaluation

The following is an example of a national and/or institutional clinical trial that is currently being conducted. Information about ongoing clinical trials is available from the NCI website.

- ACNS1022 (NCT01553149) (Low-Dose or High-Dose Lenalidomide in Treating Younger Patients With Recurrent, Refractory, or Progressive Pilocytic Astrocytoma or Optic Pathway Glioma): This is a randomized phase II clinical trial comparing low-dose to high-dose lenalidomide to see how well each works in treating children with recurrent, refractory, or progressive juvenile pilocytic astrocytomas or optic nerve pathway gliomas. This clinical trial is based on results of a phase I study that observed tumor responses and long-term stable clinical disease for lenalidomide across a range of dose levels for children with recurrent low-grade gliomas.[74]

Current Clinical Trials

Check the list of NCI-supported cancer clinical trials that are now accepting patients with recurrent childhood astrocytoma or other tumor of glial origin. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.
General information about clinical trials is also available from the NCI website.

References


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Treatment of Childhood High-Grade Astrocytomas

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

Treatment of Newly Diagnosed Childhood High-Grade Astrocytomas

Outcomes in high-grade gliomas occurring in childhood are 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.[1]

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:

2. Adjuvant therapy.
   a. Radiation therapy.
   b. Chemotherapy.

Surgery

The ability to obtain a complete resection is associated with a better prognosis.[2,3] Among patients treated with surgery, radiation therapy, and nitrosourea (lomustine)-based chemotherapy, 5-year progression-free survival was 19% ± 3%; survival was 40% in those who had total resections.[4] Similarly, in a trial of multiagent chemoradiation therapy and adjuvant chemotherapy in addition to valproic acid, 5-year event-free survival (EFS) was 13%, but for children with a complete resection of their tumor, the EFS was 48%.[5][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 rates remain poor. Similarly poor survival is seen in children with spinal cord primaries and children with thalamic high-grade gliomas treated with radiation therapy.[6,7]; [8,9][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.[10]

The use of temozolomide to treat glioblastoma was initially investigated in adults. In adults, the addition of temozolomide during and after radiation therapy resulted in improved 2-year EFS as compared with treatment with radiation therapy alone. Adult patients with glioblastoma with a methylated O6-methylguanine-DNA-methyltransferase (MGMT) promoter benefitted from temozolomide, whereas those who did not have a methylated MGMT promoter did not benefit from temozolomide.[11,12] 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 [13] and again demonstrated an EFS advantage for those children without MGMT overexpression.

Younger children may benefit from chemotherapy to delay, modify, or, in selected cases, obviate the need for radiation therapy.[14-16]

Clinical trials that evaluate chemotherapy with or without radiation therapy are ongoing. Information about ongoing clinical trials is available from the NCI website.

**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 (PBTC), or other entities. Information about ongoing clinical trials is available from the NCI website.

**Current Clinical Trials**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with childhood high-grade untreated astrocytoma or other tumor of glial origin. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

**Treatment of Recurrent Childhood High-Grade Astrocytomas**

Most patients with high-grade astrocytomas or gliomas will eventually have tumor recurrence, usually 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:

2. Entry into an early-phase clinical trial.
3. High-dose chemotherapy with stem cell transplant (SCT).
4. Targeted therapy with a **BRAF** inhibitor, for patients with a **BRAF** V600E mutation.

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.

Patients for whom initial treatment fails may benefit from additional treatment, including entry into clinical trials of novel therapeutic approaches.[17] 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.[18]; [19][Level of evidence: 3iiiA]

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.[20] 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.[21]

**Treatment options under clinical evaluation**

Early-phase therapeutic trials may be available for selected patients. These trials may be available via the COG, the PBTC, or other entities. Information about ongoing clinical trials is available from the NCI website.

- **NCT01677741** (A Study to Determine Safety, Tolerability, and Pharmacokinetics of Oral Dabrafenib In Children and Adolescent Subjects): This phase I/IIa clinical trial is determining the safety, tolerability, and pharmacokinetics of the **BRAF** inhibitor dabrafenib in children and adolescents with advanced **BRAF** V600–mutation positive solid tumors and brain tumors.

**Current Clinical Trials**

Check the list of NCI-supported cancer clinical trials that are now accepting patients with recurrent childhood astrocytoma or other tumor of glial origin. The list of clinical trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the NCI website.

**References**

Changes to this Summary (03/17/2016)

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.

Editorial changes were made to this summary.

This summary is written and maintained by the PDQ Pediatric Treatment Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ® - NCI's Comprehensive Cancer Database pages.

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.

Reviewers and Updates
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).

Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
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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 (Dana-Farber Cancer Institute/Boston Children's Hospital)
- Roger J. Packer, MD (Children's National Medical Center)
- Malcolm A. Smith, MD, PhD (National Cancer Institute)

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