Pediatric Central Nervous System Cancers, Version 2.2023

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ABSTRACT

Central nervous system (CNS) cancers account for approximately one quarter of all pediatric tumors and are the leading cause of cancer-related death in children. More than 4,000 brain and CNS tumors are diagnosed each year in children and teens, and the incidence rate has maintained stagnant in recent years. The most common malignant pediatric CNS tumors are gliomas, embryonal tumors consisting of predominately medulloblastomas, and germ cell tumors. The inaugural version of the NCCN Guidelines for Pediatric Central Nervous System Cancers focuses on the diagnosis and management of patients with pediatric diffuse high-grade gliomas. The information contained in the NCCN Guidelines is designed to help clinicians navigate the complex management of pediatric patients with diffuse high-grade gliomas. The prognosis for these highly aggressive tumors is generally poor, with 5-year survival rates of <20% despite the use of combined modality therapies of surgery, radiation therapy and systemic therapy. Recent advances in molecular profiling has expanded the use of targeted therapies in patients whose tumors harbor certain alterations. However, enrollment in a clinical trial is the preferred treatment for eligible patients.


NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

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The complete NCCN Guidelines for Pediatric Central Nervous System Cancers are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Individual disclosures for the NCCN Pediatric Central Nervous System Cancers Panel members can be found on page 1362. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.

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Overview

Pediatric central nervous system (CNS) tumors are fundamentally different than adult CNS tumors in terms of tumor type, histology, tumor location, molecular characterization, and treatment options. Although pediatric tumors are rare, accounting for only 1% of all tumor diagnoses, they are the leading cause of disease-related death in children. CNS cancers are the second most common malignancy in children after leukemia and lymphoma combined. They account for 26% of all pediatric tumors and are the leading cause of cancer-related death in children. More than 4,000 brain and spinal cord tumors are diagnosed each year in children and teens, and the incidence rate has remained stagnant in recent years. According to the Central Brain Tumor Registry of the United States Statistical Report, the incidence rate of primary CNS tumors in children <14 years of age was 5.83 per 100,000 population between 2013 and 2017. The most common malignant pediatric CNS tumors are gliomas, embryonal tumors consisting of predominately medulloblastomas, and germ cell tumors. Information on the literature search criteria and guidelines update methodology, using the PubMed database, are available in these guidelines at NCCN.org.

Tumor Types

The NCCN Guidelines for Pediatric Central Nervous System Cancers focus on the management of pediatric patients with malignant diseases of the CNS. These guidelines will be updated annually to include new information or treatment philosophies as they become available. However, because this field continually evolves, practitioners should use all available information to determine the best clinical options for their patients. The initial version of the guidelines addresses pediatric diffuse high-grade gliomas. Additional tumor types will be addressed in subsequent versions of the NCCN Guidelines.

Principles of Management

Several important principles guide surgical management and treatment with radiation therapy (RT) and systemic therapy for children with CNS tumors, including tumor histology, patient age and performance status, location of the tumor in the brain, resectability of the tumor, and prior management. All patients with pediatric diffuse high-grade gliomas should be cared for by a multidisciplinary team with experience managing CNS tumors. The involvement of pediatric oncologists/neuro-oncologists, pediatric radiation oncologists, pathologists with expertise in neuropathology and molecular pathology, pediatric neuroradiologists, and pediatric neurosurgeons is strongly encouraged.
pediatric neurosurgeons is strongly encouraged. The pathologic diagnosis is critical and may be difficult to accurately determine without sufficient tumor tissue. Review of the tumor tissue by an experienced neuropathologist is highly recommended.

The information contained in the algorithms and principles of management sections are designed to help clinicians navigate the complex management of pediatric patients with CNS tumors. Systemic therapy options are listed in “Principles of Systemic Therapy” (page 1352); however, enrollment in a clinical trial is the preferred treatment for eligible patients.

**WHO Classification of Pediatric CNS Tumors**

Due to the unique nature of childhood tumors made clear by advancements in molecular analyses, pediatric tumors are now covered in a separate volume of the recently published fifth edition of the WHO Classification of Tumors of the Central Nervous System (WHO CNS5). The inaugural WHO Classification of Pediatric CNS Tumors featured fundamental paradigm shifts affecting pediatric CNS tumor classification, including the use of a layered, integrated diagnostic approach involving both histologic and molecular analyses; the inclusion of novel, molecularly defined tumor entities; the adaptation of tumor grading as a measure of differential aggressiveness within a tumor type rather than between tumor types; and the widespread introduction of novel molecular diagnostic tools for tumor classification.

**Pediatric Diffuse High-Grade Gliomas**

In WHO CNS5, gliomas are divided into 4 distinct categories: adult-type diffuse gliomas (the majority of primary brain tumors in adults), pediatric-type diffuse low-grade gliomas (expected to have good prognoses), pediatric-type diffuse high-grade gliomas (expected to have poor prognosis), and circumscribed astrocytic gliomas (referring to their more concentrated growth pattern).

The NCCN Guidelines for Pediatric CNS Cancers currently include recommendations for the management of the 4 types of pediatric-type diffuse high-grade gliomas recognized in WHO CNS5:

- diffuse hemispheric glioma, H3 G34-mutant
- diffuse pediatric-type high-grade glioma, H3–wild-types and IDH–wild-type
- infant-type hemispheric glioma
- diffuse midline glioma (DMG), H3 K27-altered

The first 3 are newly recognized tumor entities. Diffuse hemispheric glioma, H3 G34-mutant is a malignant,
infiltrative glioma of the cerebral hemispheres with a missense mutation in the H3F3A gene that results in a G34R/V substitution of histone H3. Diffuse pediatric-type high-grade glioma, H3–wild-type and IDH–wild-type represents a mixture of distinct molecular subtypes specified as being wild-type for both H3 and IDH gene families. Infant-type hemispheric glioma is a novel tumor type typically occurring in newborns and very young children and is associated with fusion genes involving ALK, ROS1, NTRK1/2/3, or MET. Although this is not a new entity, the nomenclature was changed from DMG, H3 K27-mutant to DMG, H3 K27-altered to include subtypes with a different mechanism for the loss of H3K27 trimethylation (eg, EZHIP protein overexpression).5,6

Introduction to Pediatric Diffuse High-Grade Glioma

Epidemiology

Pediatric diffuse high-grade glioma has an incidence rate of roughly 1.8 per 100,000 population and represents approximately 15% of all intracranial neoplasms diagnosed in children and adolescents <19 years of age (see INTRO, page 1340).1,7 Although incidence rates generally decrease with age from 0–19 years, they are highest for age groups 0–4 years (6.18/100,000 population) and 15–19 years (7.09/100,000 population).3 The prognosis for these highly aggressive tumors is generally poor, with 5-year survival rates of <20% despite the use of combined modality therapies of surgery, RT, and systemic therapy.7 Prognosis and survival rates depend on multiple factors, including age at presentation, tumor location, sex, extent of resection, histologic subtype and genomic profile.8 Although diagnosis is more common in females, males typically have higher mortality rates from CNS tumors.3

Risk Factors

Although the cause of most pediatric CNS tumors is unknown, several genetic and environmental factors have been linked to an increased risk of primary brain tumor development in children. Certain inherited cancer predisposition syndromes, including neurofibromatosis type-1, Li-Fraumeni syndrome, and Turcot syndrome/Lynch syndrome/constitutional mismatch repair deficiency (cMMRD), are associated with increased susceptibility to pediatric diffuse high-grade gliomas (see INTRO, page 1340).9–11 Exposure to high-dose ionizing radiation has also been linked to pediatric brain malignancies.9,12,13 Ionizing radiation has more carcinogenic potential in children because they are more radiosensitive than adults and have more potential years of life to express the risk.13
risk is higher for younger children, and the estimated latency between radiation exposure and brain tumor development is 7–9 years, with meningiomas and gliomas being the most common radiation-induced tumor types.3,8,9,13

Clinical Presentation
Presentation and symptoms depend largely on tumor location and patient age at the time of diagnosis.14 The most common symptoms include effects of increased intracranial pressure, such as headaches that get worse over time, nausea, vomiting, and blurred vision. These may be caused by growth of the tumor, swelling in the brain, or blocked flow of cerebrospinal fluid.1 Other presenting symptoms include seizure, hemiparesis, monoparesis, cranial nerve deficits, ataxia, hemisensory loss, dysphasia, aphasia, and memory impairment. Presenting symptoms among infants include increasing head circumference and loss of developmental milestones. School-age children may experience poor school performance, fatigue, and personality changes. Symptoms may occur gradually and worsen over time or happen suddenly, such as with a seizure.1

Treatment Overview
Treatment of pediatric diffuse high-grade glioma depends on many factors such as the type of tumor, its location and size, how far it has spread, and the age and overall health of the patient.1 The main treatment paradigm includes surgery followed by systemic therapy with or without RT. The goals of surgery include the safe resection of tumor-associated mass effect and obtaining adequate tissue for histologic and molecular classification. The location and size of the tumor and the general condition of the patient are important determinants of surgical outcome.8,9,15,16 Cranial radiation may result in developmental impairments in young children; therefore, omitting RT in children <3 years of age is reasonable.8 Despite surgery and adjuvant therapy, pediatric diffuse high-grade gliomas typically have a poor prognosis. Referral for cancer predisposition evaluation and/or genetic counseling should be considered.

Principles of Brain and Spine Tumor Imaging
Conventional MRI is recommended for tumor diagnosis, surgical guidance, and therapeutic monitoring. It may be complemented by advanced neuroimaging techniques such as MR perfusion imaging, MR spectroscopy, and PET to enhance diagnostic capability, differentiate radiation necrosis from active neoplasm, and guide biopsy. Imaging is always recommended to investigate the etiology of emergent signs and symptoms. The subsequent
sections list imaging modalities used in neuro-oncology to make treatment decisions (see PEDCNS-A, page 1346).

**MRI of the Brain and/or Spine**

Conventional MRI of the entire neural axis (with and without intravenous contrast) is the imaging modality of choice for the evaluation of pediatric diffuse high-grade gliomas.\(^\text{17}\) MRI offers excellent soft tissue contrast and depiction of neoplasms through a combination of standard, universally available pulse sequences. An additional benefit of MRI is that the patient is not exposed to ionizing radiation. Pediatric diffuse high-grade gliomas typically show an infiltrative growth pattern and present as large, heterogeneous, poorly differentiated, intracranial masses with indistinct borders occupying most of one hemisphere or spread through the corpus callosum into the other hemisphere.\(^\text{8}\) They may demonstrate mass effect on surrounding structures, hemorrhage, increased perfusion, vasogenic edema, and a variable degree of contrast enhancement.\(^\text{17}\) Higher grade components commonly enhance and demonstrate restricted diffusion, which is a key feature that reflects the high-grade nature of the tumor.\(^\text{8}\) Limitations of MRI include the relatively long examination time; requirement of deep sedation/anesthesia for younger children; metal from surgery and implants causing artifacts; and the fact that some implants are unsafe in the MRI environment.

Compared with gray matter, pediatric diffuse high-grade gliomas may demonstrate iso- to hypointense T1 signal and hyperintense T2 signal with surrounding edema, which is apparent on fluid attenuation inversion recovery images. Different signal characteristics can be seen in the case of tumor hemorrhage, such as T1 hyperintense, T2 hypointense, and low signal on susceptibility-weighted imaging.\(^\text{17}\) Therefore, basic MRI sequences of the brain should include T1-weighted images before contrast, T1-weighted images in 2 planes after contrast (one of which would ideally be acquired as a 3D sequence), T2-weighted, T2-fluid attenuation inversion, and diffusion-weighted imaging, and gradient echo or susceptibility-weighted (blood-sensitive) imaging. These images should be used for preliminary diagnostic evaluation and immediate postoperative follow-up (ideally within 24–48 hours after surgery, if clinically feasible) to evaluate disease burden (measurable and nonmeasurable disease) on initial examination and extent of resection on immediate postoperative scan.\(^\text{18–21}\)

Basic MRI of the spine should include postcontrast sagittal and axial T1-weighted images of the entire neural axis; additional sequences such as heavily T2-weighted images.
and/or diffusion-weighted imaging may be considered. These images should be used to evaluate for leptomeningeal metastasis. Preoperative spine imaging should be performed at the time of brain imaging because many children require sedation to tolerate the examination.

Follow-up studies of the brain and spine should be performed at intervals defined by the treatment algorithms (see “NCCN Recommendations,” page 1356). More frequent imaging may be necessary in the event of clinical deterioration or evolving imaging findings concerning for recurrent or residual disease. Longitudinal follow-up studies may be complemented by MR perfusion or MR spectroscopy to assess response to therapy or to evaluate for progression, pseudoprogression, or radiation necrosis. Postoperative spine MRI evaluating for leptomeningeal spread of neoplasm should be delayed 2–3 weeks to avoid confusion with blood byproducts.

**MR Perfusion**

MR perfusion refers to a group of techniques which measure cerebral blood volume and/or cerebral blood flow (CBF) in neoplasms. These techniques may be useful for grading, response assessment, identifying malignant degeneration and pseudo-progression, distinguishing radiation necrosis from recurrent neoplasm, and choosing biopsy site. Limitations of MR perfusion include the degradation of reliability by adjacent metal, blood byproducts, air, and bone/soft tissue interface; and other general limitations of MRI as listed previously. Generally, most high-grade gliomas show higher perfusion (increased cerebral blood volume and/or CBF) than low-grade gliomas.

Various MR perfusion techniques include dynamic susceptibility contrast-enhanced (DSC), dynamic contrast-enhanced (DCE), and arterial spin labeling (ASL) perfusion. The choice among these will depend on user availability and preference. DSC perfusion is the most commonly used technique. Due to the need for power injectors and large-bore intravenous access, DSC is challenging to perform on infants but is feasible in young children. Other limitations include calcification and hemorrhage-induced susceptibility within the tumor and contrast leakage due to breakdown of the blood-brain barrier. DCE can be used as an alternative or complementary technique to DSC, although few studies have assessed its use in children. The advantages of DCE over DSC are fewer artifacts, multiparametric characterization of tumor microvasculature, and the quantification of leakage to assess blood-brain barrier integrity; however,
DSC typically offers better blood volume estimation than DCE.29

ASL perfusion, which uses magnetically labeled water as contrast, has been shown to be effective in grading and choosing biopsy site in children with brain tumors.30–32 ASL lacks contrast injection and high-flow injections making it advantageous for pediatric use. Other advantages include easier potential for CBF quantification, better image quality in younger children due to their immature sinus cavities, and the ability to repeat the test if the patient moves.17,33 Limitations of ASL perfusion include a low signal-to-noise ratio, the need for greater magnetic field strength and the fact that assessment is limited to CBF.34

MR Spectroscopy

MR spectroscopy is used to assess the metabolites of tissues including neoplasms and may be useful for grading, response assessment, identifying malignant degeneration and pseudo-progression, distinguishing radiation necrosis from recurrent neoplasm, and choosing biopsy site.17,24,35 The choice between single voxel and multivoxel spectroscopy will depend on user preference and availability. The limitations of MR spectroscopy include the degradation of reliability by adjacent metal, blood by-products, and bone/soft tissue/air interfaces; long and complex acquisitions; nonstandard acquisitions; nonstandard postprocessing; and postprocessing time.

A systematic review and meta-analysis comprising 455 patients across 18 studies showed that MR spectroscopy alone has only moderate diagnostic ability to differentiate glioma recurrence from radiation necrosis, and should therefore be combined with other techniques for this purpose.35 Conversely, another systematic review and meta-analysis comparing the diagnostic accuracy of advanced MRI techniques to conventional MRI found that MR spectroscopy had the highest diagnostic accuracy for treatment response evaluation in patients with high-grade glioma, supporting its use for this purpose.24

CT of the Brain

MRI scans are used more often than CT scans for brain and spine imaging because they are more detailed and do not use radiation. However, there are some circumstances in which CT scan provides advantages over MRI. CT offers higher sensitivity to dystrophic calcification in neoplasms. It also provides greater detail of bone structures and therefore might show the effects of tumors on the skull.1 CT also has a shorter acquisition time, and sedation is generally not needed. Limitations of CT include limited
soft tissue contrast; patient exposure to ionizing radiation; and metal-caused artifacts.

On CT, pediatric diffuse high-grade gliomas typically present as heterogeneous lesions with mass effect, poorly defined margins, and variable areas of hyperattenuation, which may reflect hemorrhage, necrosis, or surrounding edema. Contrast-enhanced CT features are variable.17 CT of the brain (without contrast or with and without contrast) is ideal for rapid assessment in the acute or immediate postoperative setting and for the evaluation of acute intracranial hemorrhage, ventriculomegaly, and shunt related issues. CT should also be used in patients in whom an MRI is contraindicated because of unsafe implants or foreign bodies.

**Brain PET Studies**

Brain PET studies assess brain tissue metabolism using a radiopharmaceutical, usually the glucose metabolism tracer FDG. PET is typically combined with anatomic imaging and may be useful in differentiating between neoplasm and radiation necrosis, tumor grading, or identifying more aggressive focus for biopsy. Since PET scan images are not as detailed as CT or MRI, it is used mostly as a complementary test to provide information about whether abnormal areas seen on other imaging tests are likely to be tumors.36 PET is more likely to be helpful for identifying high-grade tumors than low-grade tumors.36 Additional limitations of PET include availability of radioisotopes and radiation exposure to the patient.

**Supplemental Imaging for Preoperative Planning**

Isotropic volumetric MRI may be used for preoperative planning to accurately localize the neoplasms by coregistering the data with intraoperative guidance software; often complemented with isotropic CT studies to improve localization. Functional MRI studies can be used to depict spatial relationships between eloquent cortex (eg, regions of the brain primarily responsible for speech, vision, and motor and sensory function) and the neoplasms to serve as a road map and promote safe resections. Diffusion tensor imaging may also be used to localize major white matter tracts underlying the eloquent cortex that could also compromise vital functions if injured during surgery.36 Some imaging modalities or techniques may not be available at all institutions.
of genetic aberrations (except for hypermutant tumors) and are often driven by a single genetic driver event, such as a point mutation or translocation leading to an oncogenic fusion.5,6 The NCCN Guidelines describe guiding principles for the diagnosis of pediatric CNS tumors according to the parameters of WHO CNS5.5,6 A general workflow for processing of tissue and tumor characterization using histologic, immunohistochemical (IHC), and molecular data are presented in the “Principles of Pathology” section of the algorithm (see PEDCNS-B, page 1349). However, this is not meant to serve as an exhaustive algorithm for diagnosis and classification of the multitude of subtypes of pediatric diffuse high-grade gliomas that have presently been described.

**Standard Histopathologic Examination and Classification**

Integrated histopathologic and molecular characterization of gliomas per WHO CNS5 should be standard practice.5 Molecular and genetic characterization complements standard histopathologic analysis, providing additional diagnostic and prognostic information that improves diagnostic accuracy and aids in treatment and clinical trial selection. Therefore, histologic and IHC examination should be performed on all tumors. Care should be taken to conserve tissue, and IHC studies for molecular markers may be skipped in lieu of submitting tissue directly for molecular studies in cases where the specimen is scant. Commonly used IHC markers for molecular alterations, and broad indications for using them, are listed in the algorithm (see PEDCNS-B 1 of 4, page 1349). However, as stated previously, this is not intended to be an exhaustive list. Molecular alterations demonstrated by IHC may require confirmation by molecular methods (see “Molecular Characterization,” next section).

**Molecular Characterization**

Pediatric diffuse high-grade gliomas comprise a biologically diverse group of tumors. There is a high degree of histologic overlap and nonspecificity of histologic features among the numerous recognized pathologic entities of pediatric tumors, and underlying molecular alterations in pediatric gliomas are distinct from those seen in adults. This uncertainty that can be posed by overlapping tumor features underscores the immense importance of molecular testing in pediatric tumor diagnostics. Molecular testing in many cases is critical to diagnosis, distinguishing high-grade tumors from lower grade counterparts, and uncovering alterations that have been demonstrated to be prognostically relevant.37–42 In addition, clinical trial stratification is becoming increasingly dependent on molecular characterization. See Table 1 on PEDCNS-B 3 of 4.
PRINCIPLES OF BRAIN TUMOR PATHOLOGY

The standard practice for tumor classification should involve integration of histologic and molecular features, as per the World Health Organization (WHO) 2021 Classification of Tumors of the Central Nervous System. A general workflow for processing of tissue and tumor characterization using histologic, immunohistochemical (IHC), and molecular data is presented. However, this is not meant to serve as an exhaustive algorithm for diagnosis and classification of the multitude of subtypes of pediatric diffuse high-grade gliomas that have presently been described.

Standard Histopathologic Examination and Classification

Histologic and IHC examination of the tumor should be performed. Care should be taken to conserve tissue, and IHC studies for molecular markers may be skipped in lieu of submitting tissue directly for molecular studies in cases where the specimen is scant. Commonly used IHC markers for molecular alterations, and broad indications for using them, are presented below. Molecular alterations demonstrated by IHC may require confirmation by molecular methods (see Molecular Characterization [PEDCNS-B 2 of 4]).

Commonly Used IHC Markers for High-Grade Glial Tumors
- **BRAF** V600E (particularly if epithelioid or piloid histology): potentially therapeutically actionable
- **H3 K27me3** (particularly for midline, diffuse glial tumors): Loss (negativity) is diagnostic of diffuse midline glioma, H3 K27-altered, WHO grade 4, with fulfillment of appropriate histologic parameters, particularly with a supportive molecular profile. Should be used in conjunction with H3 K27M, in which positivity is also diagnostic of this entity in the appropriate context
- **INI1** (SMARCB1) rhabdoid morphology
- **IDH1** R132H (particularly for AYA patients): Positivity is diagnostic of an IDH-mutant diffuse glioma including oligodendroglioma; IDH-mutant and 1p/19q codeleted, and astrocytoma, IDH-mutant. These tumors are considered to be adult-type diffuse gliomas and are beyond the scope of these guidelines. Please refer to the adult NCCN Guidelines for Central Nervous System Cancers.

Limited Tissue Sample/Specimen

- When tissue is limited, recommend obtaining the following if possible:
  - Hematoxylin and eosin (H&E) histology
  - Limited IHC panel
  - Next-generation sequencing (NGS)
  - Methylation profiling
- Limited IHC panels should only employ stains that would provide essential diagnostic information; in cases of particularly limited tissue, stains for mutations (such as **IDH1** R132H or **BRAF** V600E) already covered by NGS can also be omitted if redundant.

Limited Tissue Sample/Specimen

In cases where tissue available for processing is limited, care should be taken to prioritize obtaining the following tests: hematoxylin and eosin histology, limited IHC panel, NGS and methylation profiling. The limited IHC panels should only use stains that would provide essential diagnostic information. In cases of particularly limited tissue, stains for mutations (such as **IDH1** R132H or **BRAF** V600E) already covered by NGS can be omitted if redundant.

Principles of Surgery

Surgical resection plays an important role in the primary treatment of nonpontine pediatric diffuse high-grade gliomas. The goals of surgery are maximal safe tumor resection, alleviation of symptoms related to increased intracranial pressure or tumor mass effect, increased survival, decreased need for corticosteroids, and obtainment of adequate tissue for a pathologic diagnosis and molecular genetic characterization (see PEDCNS-C, page 1353). The histology and location of the tumor, as well as the extent of possible resection, are significant prognostic factors that influence the decision for surgical management. Surgical resection is not feasible for patients with DMG of the pons (previously called diffuse intrinsic pontine glioma) or most other brainstem tumors.

Preoperative Assessment

All patients being considered for surgery should undergo a preoperative assessment including laboratory work,
imaging, and multidisciplinary consult. Advanced imaging can be considered in cases where patients may benefit from it. Emergent situations should be treated before further investigative studies or interventions. Consider medical management to treat focal neurologic deficits, seizure, and pain (ie, dexamethasone, antiepileptics, acetaminophen). However, medications that may alter the patient’s neurologic examination or increase surgical risks (eg, narcotics) should be avoided. Outside of emergent clinical presentations, multidisciplinary case discussion should be used for treatment planning and optimization of patient care, including radiation oncology, neurosurgery, radiology, and oncology/neuro-oncology. Physical therapy/occupational therapy and sleep and swallow assessments can be considered to assist with comorbidity management and referral to a child life social worker can be considered for family/patient support.

**Surgical Procedure**

Study-level and individual patient data meta-analyses, as well as a small number of prospective and retrospective studies have demonstrated an association between greater extent of resection and improved overall survival (OS) and progression-free survival in patients with pediatric diffuse high-grade gliomas. In the HIT-GBM study of 85 pediatric patients with malignant nonpontine gliomas, gross total resection was the strongest predictor of OS and event-free survival (EFS). In the HIT-GBM-C study, 5-year OS was significantly improved in patients with tumors that were completely resected before combination chemoradiotherapy (63%; n = 21) when compared with historical controls (17%; P = .003). Nearly all diffuse high-grade gliomas recur. Resection at recurrence may improve outcomes, although evidence varies widely. As in adult patients with diffuse high-grade gliomas, tumor involvement in specific critical brain areas and poor performance status may be associated with unfavorable resection outcomes.

**Postoperative Management**

After surgical resection, patients should be monitored for signs and symptoms of increased intracranial pressure, fluctuations in blood pressure, and sodium and serum osmolarity. Prophylaxis for seizures, infections and deep vein thrombosis can be considered.

**Principles of RT Management**

RT plays an essential role in the adjuvant treatment of patients with pediatric diffuse high-grade gliomas who are 3 years of age and older. Out of concern for long
term complications with brain development, it is reasonable to omit RT in patients <3 years of age.\textsuperscript{8,9,15,16} Child life specialists, audio and video distraction techniques, and other pediatric-friendly interventions are recommended to improve pediatric tolerance of RT without anesthesia. The dose of RT administered varies depending on the setting and pathology (see PEDCNS-D, page 1354).

After surgery, patients aged ≥3 years with pediatric diffuse high-grade gliomas (except for those with pontine DMG) are treated with RT combined with concurrent and/or adjuvant systemic therapy.\textsuperscript{56,57} Initiation of RT is recommended whenever the patient has recovered from surgery and should begin within 4 to 8 weeks of resection. Intensity-modulated RT (IMRT) is used in most instances to allow reduction of risk or magnitude of side effects from treatment. Accepted normal tissue constraints should be used, and although the prognosis of these patients is often poor, as low as reasonably achievable principle still applies to the lenses, retina, pituitary gland/hypothalamus, cochlea, lacrimal glands, hippocampi, temporal lobes, spinal cord, and uninvolved brain. Normal tissue constraints can be found in PEDCNS-D (page 1354). Proton therapy, which offers maximal sparing of normal tissue, may be considered for patients with better prognoses (eg, IDH1-mutated tumors, 1p/19q-codeleted, younger age), since most of the data are derived from studies involving pediatric patients with low-grade glioma.\textsuperscript{58–62}

Most studies on reirradiation are from adult high-grade glioma studies of recurrent glioblastoma multiforme (GBM) and have suggested improvements in progression-free survival, but limited OS gains.\textsuperscript{54–66} Multiple dosing schedules have been reported for reirradiation, including stereotactic radiosurgery.\textsuperscript{54–67} One of the few pediatric studies conducted was a retrospective cohort study of 40 children with recurrent supratentorial high-grade glioma who had received ≥1 course of RT.\textsuperscript{68} Of the 40, 14 children received reirradiation and had improved median survival from the time of first disease progression when compared with the 26 patients who were not offered reirradiation (9.4 vs 3.8 months; \(P=.005\)), suggesting that reirradiation can be effective for short-term disease control.

Patients with pontine DMG should begin RT as soon as possible after diagnosis, regardless of age, given the highly effective nature of this modality for symptom control.\textsuperscript{16} Dose-escalated RT and concurrent or adjuvant systemic therapy have produced disappointing results in patients with pontine DMG, and are therefore not recommended.\textsuperscript{16,69–73} The NCCN Panel recommends using IMRT, but 3D conformal RT is an also acceptable option.\textsuperscript{15} Hypofractionated RT has been evaluated as an alternative

### Table 1^\textsuperscript{6,7}

<table>
<thead>
<tr>
<th>Molecular Alterations of Significance in Pediatric Gliomas</th>
<th>Molecular Alterations Consistent with “High Grade” in Pediatric Diffuse Gliomas</th>
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<tbody>
<tr>
<td>• IDH1/2 mutations with or without 1p/19q co-deletion (adult type gliomas)</td>
<td>• Homozygous deletion of CDKN2A/2B</td>
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<td>• H3 K27M3a loss (epigenetic loss of trimethylation at this site)</td>
<td>• TP53 mutation</td>
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<td>• H3-3A K27M mutation (historic synonyms H3.3 K27M, H3F3A p.K28M)</td>
<td>• Amplification of PDGFRA, EGFR, MET, or MYCN</td>
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<tr>
<td>• H3C2 p.K28M mutation (historic synonyms H3.1 K27M and HIST1H3B K27M)</td>
<td>• Complex karyotype</td>
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<tr>
<td>• H3C3 p.K28M mutation (historic synonym HIST1H3C K27M)</td>
<td>• H3 K27M3a loss by IHC/H3 K27M mutation by sequencing—informs a grade IV neoplasm in appropriate context</td>
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<td>• H3 G34 mutation</td>
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<td>• MYB fusion</td>
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<td>• MYB1 fusion</td>
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<tr>
<td>• BRAFV600E mutation</td>
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<tr>
<td>• BRAF fusion</td>
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<td>• BCOR internal tandem duplication</td>
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<tr>
<td>• EGFR mutations</td>
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<tr>
<td>• FGFR1 TKD-duplicated</td>
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<td>• FGFR1 mutation</td>
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<tr>
<td>• FGFR2 fusion</td>
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<td>• FGFR2 fusion</td>
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<td>• NTRK1/2/3 fusion</td>
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<td>• ALK fusion</td>
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<td>• ROS1 fusion</td>
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<td>• MET fusion</td>
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<tr>
<td>• Other MAPK pathway alterations</td>
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to standard fractionation in the first-line and reirradiation settings, although data are limited and studies are ongoing to assess the benefits and safety of this approach.74–76 Although recent data have shown hypofractionated RT to be statistically noninferior to conventional RT,77,78 larger, multi-institutional trials are needed to elucidate the optimal technique, dose, and fractionation for RT in the treatment of pediatric patients with pontine DMG. Patients with pontine DMG whose tumors progress or recur after initial RT have poor prognosis and limited treatment options. Palliative reirradiation has been shown to alleviate symptoms in these patients and improve quality of life.79–81

Principles of Systemic Therapy

Combined Modality Therapy

The panel’s preference for the use of RT with concurrent and adjuvant temozolomide (TMZ) and lomustine for patients 3 years of age or older is supported by the results of the phase II COG ACNS0423 trial, which reported the results of 108 pediatric patients with high-grade gliomas who received RT with concurrent and adjuvant TMZ plus lomustine for 6 cycles after maximal surgical resection (see PEDCNS-E, page 1357).36,56 The 3-year EFS and OS were significantly improved compared with the participants of the ACNS0126 study who received adjuvant TMZ alone without lomustine (0.22 vs 0.11; \(P = .019\)) and 0.28 vs 0.19; \(P = .019\), respectively).36,57 The addition of lomustine also resulted in significantly better EFS and OS in participants without gross-total resection (\(P = .019\) and .00085, respectively). Although the addition of lomustine resulted in modest outcome benefits compared with TMZ alone, survival rates remained low. Therefore, use of this regimen without lomustine is also an option for adjuvant therapy.57

Chemotherapy

Avoiding RT in patients <3 years of age is reasonable due to the risk of brain injury; therefore, chemotherapy alone is recommended for these patients. The chemotherapy regimens recommended by the panel in this setting are cyclophosphamide, vincristine, cisplatin, and etoposide and vincristine, carboplatin, and TMZ (see PEDCNS-E, page 1357).32,81 A Pediatric Oncology Group study showed that high-grade gliomas in children <3 years of age are sensitive to chemotherapy.82 In this study, 18 children <3 years of age with malignant gliomas were treated with postoperative chemotherapy with cyclophosphamide and vincristine for 2 cycles. Of the 10 patients evaluated for neuroradiologic response, the partial response rate was 60% and the 5-year progression-free survival rate was 43%.
and III trials, 32 children <6 years of age with newly-diagnosed high-grade gliomas were treated with 4 cycles of induction chemotherapy with vincristine, carboplatin, and TMZ followed by myeloablative chemotherapy and stem cell rescue. The 5-year EFS and OS rates were 25% and 36%, respectively. Children <3 years of age had improved 5-year EFS and OS (44% and 63%, respectively) compared with older children (31% and 38% for children aged 36–71 months and 0% and 13% for children ≥72 months).

**Targeted Therapy**

Recent advances in molecular technology have enabled the development of molecular agents capable of targeting the biologic drivers of pediatric diffuse high-grade gliomas. These targeted therapies provide a means for treating pediatric patients without the involvement of cytotoxic chemotherapy and radiation. Evidence for the use of several targeted therapies in the treatment of patients with pediatric diffuse high-grade gliomas with various molecular signatures is discussed in further detail subsequently.

**BRAF V600E Mutated Tumor**

The BRAF V600E point mutation, which results in constitutive activation of the MEK/ERK pathway, is detected in approximately 10%–15% of pediatric high-grade gliomas. Many tumors that initially respond to BRAF inhibition eventually develop resistance due to reactivation of the MAPK pathway. Combined therapy targeting BRAF and downstream MEK has shown success in several clinical trials in adults with cancer. However, data on this regimen in the pediatric population are limited to small case series and reports. In one such case series, 3 pediatric patients with BRAF V600E–mutated high-grade gliomas exhibited clinical responses to combined BRAF/MEK blockade using dabrafenib and trametinib. One patient who received the combination as maintenance therapy after resection and RT remained disease-free for 20 months, at which time disease progression was noted. The other 2 patients who were treated with the combination regimen at the time of disease progression or at initial diagnosis, experienced a reduction in tumor size and stabilized disease for 32 and 23 months, respectively. None of the patients exhibited significant toxicities.

BRAF blockade with vemurafenib has also shown early success in treating patients with pediatric diffuse high-grade gliomas. In the phase I trial of the Pacific Pediatric Neuro-Oncology Consortium study (PNOC-002), 19 pediatric patients with recurrent or progressive BRAF V600E–mutated high-grade gliomas were treated with vemurafenib for a median of 23 cycles. One patient had a complete response, 5 patients had partial responses and 13 patients experienced stabilized disease. Grade ≥3
adverse events included secondary keratoacanthoma, rash, and fever. Due to promising antitumor activity and manageable toxicities, the phase II part of the trial is currently ongoing (ClinicalTrials.gov identifier: NCT01748149).

TRK-Fusion–Positive Tumor

Gene fusions involving NTRK1, NTRK2, or NTRK3 encode for TRK fusion proteins (TRKA, TRKB, TRKC) which have increased kinase function and are implicated in the oncogenesis of many solid tumors.95,96 The small-molecule TRK inhibitors larotrectinib and entrectinib have demonstrated activity in several trials of adults and children with various cancers.97–100 In the multicenter phase I SCOUT trial, 24 pediatric and adolescent patients (aged 1 month to 21 years; median age, 4.5 years) with advanced solid or primary CNS tumors were treated with larotrectinib, regardless of TRK fusion status.98 In patients with TRK-fusion–positive tumors, the ORR was 58% and the median duration of treatment was 11 months. The median duration of response was not reached. Treatment with entrectinib resulted in antitumor activity in patients with TRK-fusion–positive tumors; however, it also led to dose-limiting toxicities in 4 patients (9%). The most common treatment-related adverse events were weight gain (49%) and bone fractures (21%). The phase II part of this trial is currently ongoing (ClinicalTrials.gov identifier: NCT02650401).

Hypermutant Tumor

The inherited cancer predisposition syndrome cMMRD often leads to the development of pediatric diffuse high-grade gliomas characterized by a higher mutational burden than typically seen in sporadically occurring brain tumors or other solid tumors.101 The resultant hypermutant tumors may be amenable to immune checkpoint inhibition; however, evidence of their efficacy is currently limited to small case reports and single-institution experiences.101–103 In one such case report, 2 siblings with recurrent hypermutant pediatric diffuse high-grade gliomas were treated with the antiprogrammed death-1 inhibitor nivolumab, which resulted in significant clinical and radiologic responses in both children after several months
of treatment. A retrospective chart review of 11 pediatric patients with recurrent or refractory CNS tumors treated with ipilimumab, nivolumab, and/or pembrolizumab at Dana-Farber/Boston Children’s Hospital showed that immune checkpoint inhibitors are reasonably well tolerated in pediatric patients and warrant further study in clinical trials.

Palliative Systemic Therapy for Recurrent or Progressive Disease

Despite aggressive primary management, most patients with pediatric diffuse high-grade gliomas will experience recurrence or disease progression. Patients with recurrent or progressive disease have a median OS of <6 months, and no effective therapies currently exist. The use of systemic therapy for the management of recurrent or progressive disease depends on the extent of disease and the patient’s condition. Targeted therapy based on the molecular composition of the tumor is recommended for patients with good performance status (see PEDCNS-E, page 1357). This includes but is not limited to the following: checkpoint blockade for high tumor mutational burden or personal or family history of cMMRD; RAF and MEK inhibition for tumors with BRAF V600E mutation, and TRK inhibitors for tumors with NTRK gene fusion.

Patients with poor performance status may receive palliative chemotherapy with oral etoposide, bevacizumab (or an FDA-approved biosimilar), or single-agent nitrosoureas (lomustine or carmustine). In a phase II trial, 28 children with recurrent brain and solid tumors received daily oral etoposide for 21 consecutive days with courses repeating every 28 days pending bone marrow recovery. Three of the 4 patients with medulloblastoma exhibited a partial response and 2 of the 5 patients with ependymoma showed response (one with a complete response and one with a partial response), demonstrating activity for etoposide in recurrent brain tumors. Toxicity was manageable, with only 1 hospitalization for neutropenic fever and 2 patients who withdrew due to treatment-related adverse events (one with grade 4 thrombocytopenia and one with grade 2 mucositis).

The multicenter phase II HERBY trial evaluated the addition of bevacizumab to RT plus TMZ for treatment of pediatric patients (n=121, aged between 3 and 18 years) with newly diagnosed nonpontine high-grade gliomas. Median EFS did not differ significantly between the treatment groups, and the addition of bevacizumab did not reduce the risk of death. Because adding BEV to RT+TMZ did not improve EFS in pediatric patients with newly diagnosed high-grade glioma, the panel has reserved use of bevacizumab (or...
an FDA-approved biosimilar) as a single agent in the palliative setting for patients with recurrent or progressive disease.

NCCN Recommendations

Radiologic Presentation and Multidisciplinary Review
When a patient presents with a clinical and radiologic picture suggestive of pediatric diffuse high-grade gliomas, input from a multidisciplinary team is needed for treatment planning (see PGLIO-1, page 1342). The involvement of pediatric oncologists/neuro-oncologists, pediatric radiation oncologists, pathologists with expertise in neuropathology and molecular pathology, pediatric neuroradiologists, and pediatric neurosurgeons with specific expertise in the management of pediatric high-grade gliomas is strongly encouraged. Neurosurgical input is needed to determine the feasibility of maximal safe resection. A pathologic diagnosis is critical and may be difficult to accurately determine without sufficient tumor tissue obtained during biopsy. Review of the tumor tissue by an experienced neuropathologist is highly recommended.

Primary Treatment and Pathologic Diagnosis
For primary treatment of pediatric diffuse high-grade gliomas, the NCCN Guidelines recommend maximal safe resection with the goal of image-verified complete resection, whenever possible (see PGLIO-1, page 1342). If the patient is symptomatic because of mass tumor effect but complete resection is not feasible, then subtotal resection is recommended for tissue diagnosis and debulking. A postoperative MRI is recommended, ideally within 24 to 48 hours after surgery, to confirm extent of resection.18–21 If a clinically beneficial cytoreduction is not feasible, then a stereotactic biopsy or open biopsy is recommended for pathologic analysis. Recommendations for molecular testing of diffuse high-grade glioma tumors are provided in the “Principles of Brain Tumor Pathology” section (see page 1351). The resulting information should be used to form a pathologic diagnosis. Detection of genetic alterations may also expand clinical trial options for the patient.

Adjuvant Therapy
The NCCN Panel recommends clinical trial enrollment whenever possible as the preferred treatment option for all pediatric patients with diffuse high-grade gliomas (see PGLIO-2, page 1343). Outside of a clinical trial, patients ≥3 years of age with pediatric diffuse high-grade gliomas, except DMG, H3 K27-altered or other tumor with a

<table>
<thead>
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<th>Organs at Risk (OAR)</th>
<th>Constraints</th>
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<tr>
<td>Cochlea</td>
<td>D50% &lt; 35 Gy</td>
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<td>Optic globes</td>
<td>D50% ≤ 10 Gy</td>
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<td></td>
<td>D10% ≤ 35 Gy</td>
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<tr>
<td>Optic nerves and chiasm</td>
<td>D50% ≤ 55 Gy</td>
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<td></td>
<td>D10% ≤ 56 Gy</td>
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<tr>
<td>Spinal cord</td>
<td>D50% ≤ 52 Gy</td>
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<td></td>
<td>D10% ≤ 57 Gy</td>
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<tr>
<td>Brainstem</td>
<td>Cannot exceed 60 Gy max</td>
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<td>For 60 Gy &lt; 0.3 cc, mean dose &lt; 56.1 Gy</td>
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<td>If protons are used for a non-brainstem primary in patient with good prognosis:</td>
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<td></td>
<td>Max brainstem dose &lt; 56.6 Gy</td>
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<td>D50% &lt; 52.4 Gy</td>
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<tr>
<td>Pituitary gland/hypothalamus</td>
<td>Mean dose &lt; 25 Gy</td>
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<tr>
<td>Hippocampi</td>
<td>Mean &lt; 30 Gy</td>
</tr>
<tr>
<td>Temporal lobes</td>
<td>No more than 1 cc exceeding 60 Gy, maximum dose of 65 Gy</td>
</tr>
<tr>
<td>Uninvolved brain (Brain – PTV)</td>
<td>No more than 1% or 1 cc of the tissue outside of either PTV receiving more than 110% of the prescribed dose.</td>
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<tr>
<td>Lenses</td>
<td>As low as possible</td>
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*The noted normal tissue constraints are per CGG.ACNS0931 and ARAR0331.

In general normal tissues should be as low as reasonably achievable even if the constraint is achieved (ALARA principle).
pontine tumor location, can receive standard brain RT with concurrent and adjuvant TMZ without lomustine or with lomustine (preferred). Standard brain RT alone and standard brain RT with concurrent TMZ and adjuvant targeted therapy based on the molecular composition of the tumor are also options in this setting. Patients <3 years of age can receive systemic chemotherapy with either cyclophosphamide, vincristine, cisplatin, and etoposide or vincristine, carboplatin, and TMZ to delay the need for RT or with adjuvant targeted therapy based on the molecular composition of the tumor.

Patients with nonpontine DMG, H3 K27-altered can receive either standard brain RT alone or standard brain RT with concurrent and adjuvant TMZ alone or with lomustine (see PLGIO-3, page 1344). Patients with pontine located tumors, including DMG, H3 K27-altered or pediatric diffuse high-grade glioma, H3–wild-type and IDH–wild-type, should receive standard brain RT alone if clinical trial enrollment is not possible.

**Follow-up and Recurrence**

Most pediatric patients with diffuse high-grade gliomas eventually develop tumor recurrence or progression. Therefore, patients with recurrent or progressive disease should be followed closely with brain MRI scans starting at 2–6 weeks postirradiation, then every 2–3 months for 1 year, then every 3–6 months indefinitely after the completion of treatment of newly diagnosed disease. Pseudoprogression may occur within 6–9 months after RT and can be seen on MRI; therefore, pseudoprogression should be considered if MRI changes are noted in this time period. Management of recurrent or progressive disease depends on the extent of disease and the patient’s condition. The efficacy of current treatment options remains poor; therefore, enrollment in a clinical trial, whenever possible, is preferred for the management of recurrent or progressive disease (see PGLIO-4, page 1345). Surgical resection of locally recurrent disease is reasonable followed by an additional brain MRI scan. However, enrollment in a phase 0 or preoperative clinical trial should be considered before resection. If recurrent or progressive local disease is not resectable or if it is diffuse with multiple lesions, then surgery can still be considered for large symptomatic lesions. Reresection at the time of recurrence may improve outcomes; however, tumor involvement in specific critical brain areas and poor performance status may be associated with unfavorable resection outcomes.

Preferred systemic therapy options for recurrent disease include but are not limited to dabrafenib/trametinib. 

### Table: Preferred Regimens vs Other Recommended Regimens

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
<th>Useful in Certain Circumstances</th>
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<tbody>
<tr>
<td><strong>Adjuvant Therapy</strong></td>
<td><strong>RT + concurrent TMZ + adjuvant TMZ</strong></td>
<td><strong>RT + concurrent TMZ</strong></td>
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<tr>
<td><strong>Age &lt;3 years:</strong></td>
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<td><strong>adjuvant targeted therapy including,</strong></td>
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<td><strong>but not limited to the following:</strong></td>
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<td><strong>– If BRAF V600E mutated:</strong></td>
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<td></td>
<td><strong>– Dabrafenib/trametinib</strong></td>
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<td><strong>– Vemurafenib</strong></td>
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<td><strong>– If TRK fusion-positive:</strong></td>
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<td></td>
<td></td>
<td><strong>– Larotrectinib</strong></td>
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<td><strong>– Entrectinib</strong></td>
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<td></td>
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<td><strong>– Hypermutant tumor:</strong></td>
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<td></td>
<td></td>
<td><strong>– Nivolumab</strong></td>
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<td><strong>– Pembrolizumab</strong></td>
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**Recurrent or Progressive Disease**

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<tr>
<th>Targeted therapy including, but not limited to the following:</th>
<th>Reirradiation if feasible</th>
<th>For palliation:</th>
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<tr>
<td><strong>If BRAF V600E mutated:</strong></td>
<td></td>
<td><strong>Oral etoposide</strong></td>
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<tr>
<td><strong>– Dabrafenib/trametinib</strong></td>
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<td><strong>Bevacizumab</strong></td>
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<td><strong>– Vemurafenib</strong></td>
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<td><strong>Nitrosoourea (lomustine or carmustine)</strong></td>
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<td><strong>If TRK fusion-positive:</strong></td>
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<tr>
<td><strong>– Larotrectinib</strong></td>
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<td><strong>– Entrectinib</strong></td>
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<tr>
<td><strong>If hypermutant tumor:</strong></td>
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<tr>
<td><strong>– Nivolumab</strong></td>
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<td><strong>– Pembrolizumab</strong></td>
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dabrafenib/trametinib

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or vemurafenib,44 for BRAF V600E-mutated tumors, larotrectinib,89 or entrectinib96 for TRK-fusion–positive tumors, and nivolumab100,101 or pembrolizumab102 for hypermutant tumors. Reirradiation, if feasible, is an alternative option. Patients with poor performance status should receive palliative/best supportive care. Recommended regimens for palliation are oral etoposide,104 bevacizumab (or an FDA-approved biosimilar),105 or nitrosoureas (lomustine or carmustine).56

Summary
Pediatric CNS cancers are the leading cause of cancer-related death in children. The initial version of the NCCN Guidelines for Pediatric CNS Cancers provides an evidence- and consensus-based treatment approach for the management of patients with pediatric diffuse high-grade gliomas, which are highly aggressive tumors with a poor prognosis. Referral for cancer predisposition evaluation and/or genetic counseling should be considered for patients with pediatric diffuse high-grade gliomas linked to certain inherited cancer predisposition syndromes. All patients should be cared for by a multidisciplinary team with experience managing pediatric CNS tumors. The NCCN panel recommends clinical trial participation as the preferred treatment option for patients with pediatric diffuse high-grade gliomas. Outside of a clinical trial, the main treatment paradigm includes surgery followed by systemic therapy with or without RT. Recent advances in molecular profiling has expanded the use of targeted therapies in patients whose tumors harbor certain alterations. However, nearly all patients will experience recurrent disease, which has limited treatment options. Subsequent versions of the guidelines will address additional tumor types.

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multicenter trial (HERBY) of bevacizumab in pediatric patients with newly
### Individual Disclosures for the Pediatric Central Nervous System Cancers

<table>
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<th>Panel Member</th>
<th>Clinical Research Support/Data Safety Monitoring Board</th>
<th>Scientific Advisory Boards, Consultant, or Expert Witness</th>
<th>Promotional Advisory Boards, Consultant, or Speakers Bureau</th>
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<td>Mohamed Abdelbaki, MD</td>
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<td>Joshua Palmer, MD</td>
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<td>Novocure</td>
<td>Varian Medical Systems, Inc.</td>
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<td>Sonia Partap, MD</td>
<td>None</td>
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<td>AlphaSights; Cancer Expert Now; GLG group; Guidepoint Global; Mass Medical International; and Ology Medical Education</td>
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<td>Ashley Plant, MD</td>
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<td>Sumit Pruthi, MD</td>
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<td>Katherine Warren, MD</td>
<td>Bristol-Myers Squibb Company; Celgene Corporation; Oncocutecics; and ymAbs</td>
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<td>Nicholas Whipple, MD, MPH</td>
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<td>Wafik Zaky, MB&amp;BCh</td>
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The NCCN Guidelines Staff have no conflicts to disclose.

*The following individuals have disclosures relating to employment/governing board, patent, equity, or royalty:

- Kathleen Dorris, MD: Amgen Inc., and Gilead Sciences, Inc.
- Anita Mahajan, MD: ASTRO, Pediatric Radiation Oncology Society, and PTCOG-NA.