Pediatric Central Nervous System Cancers, Version 2.2025

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Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Central Nervous System Cancers provide multidisciplinary diagnostic workup, staging, and treatment recommendations for diffuse high-grade gliomas and medulloblastomas in children and adolescents. This article summarizes the studies and panel discussion that serve as the rationale for comprehensive care recommendations included in the NCCN Guidelines for Pediatric Central Nervous System Cancers.

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Overview

Pediatric central nervous system (CNS) cancers are fundamentally different than adult CNS cancers in regard to tumor type, histology, tumor location, molecular characteristics, and treatment options. Although pediatric tumors are rare, accounting for only 1% of all cancer diagnoses (adult and pediatric), 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.[1] They account for 26% of all pediatric tumors and are the leading cause of cancer-related death in children.[2] More than 4,000 brain and spinal cord tumors are diagnosed each year in children and teens, and the incidence rate has remained steady in recent years.[1] According to the Central Brain Tumor Registry of the United States Statistical Report, the incidence rate of primary CNS tumors in children <20 years was 6.23 per 100,000 population between 2014 and 2018.[3] The most common malignant pediatric CNS tumors are gliomas and embryonal tumors, the latter consisting predominately of medulloblastomas.[3]

Tumor Types

The NCCN Guidelines for Pediatric Central Nervous System Cancers focus on the comprehensive care 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 updated version of the NCCN Guidelines addresses diffuse high-grade gliomas and medulloblastoma in children and adolescents.

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 and medulloblastomas should be cared for by a multidisciplinary team with experience managing

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To view disclosures of external relationships for the NCCN Guidelines panel, go to https://www.nccn.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels

The full NCCN Guidelines for Pediatric Central Nervous System Cancers are not printed in this issue of *JNCCN*. The complete and most recent version of these guidelines is available free of charge at NCCN.org.

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. 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 of the NCCN Guidelines are designed to help clinicians navigate the complex management of CNS tumors in pediatric 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 separate sections of the published fifth edition of the WHO Classification of Tumors of the Central Nervous System (WHO CNS5) and in the inaugural WHO Classification of Pediatric Tumors.[4,5] These volumes reflect 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 for 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 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), and pediatric-type diffuse high-grade gliomas (expected to have poor prognoses); circumscribed astrocytic gliomas (referring to their more concentrated growth pattern); glioneuronal and neuronal tumors; and ependymomas.[4]

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[4] and refer to children and adolescents ≤21 years of age:

- Diffuse hemispheric glioma, *H3* G34-mutant
- Diffuse pediatric-type high-grade glioma, *H3* wild-type 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 it 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 *H3* K27 trimethylation (eg, EZHIP protein overexpression).[4,5] These guidelines do not include recommendations for primary spinal cord tumors.

Introduction

Epidemiology

Pediatric diffuse high-grade glioma represents approximately 9.3% of all primary malignant and nonmalignant brain and other CNS tumors diagnosed in children and adolescents ≤19 years.[3] Although incidence rates generally decrease with age from 0 to 19 years, the rate of high-grade glioma in the brain-stem, specifically, is highest for age groups 5 to 9 years (0.56 per 100,000 population).[3] The prognosis for aggressive diffuse high-grade gliomas is generally poor, with 5-year survival rates of <20% despite the use of combined modality therapies of surgery, RT, and systemic therapy.[6] Prognosis and survival rates for diffuse high-grade gliomas depend on multiple factors, including age at presentation, tumor location, sex, extent of resection, histologic subtype, and genomic profile.[7] Althouogh diagnosis is more common in females, males typically have higher mortality rates from CNS tumors.[8]

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.[9–12] Exposure to high-dose ionizing radiation has also been linked to pediatric brain malignancies.[9,13,14] 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.[14] Estimated risk is higher for younger children, and the predicted latency between radiation exposure and brain tumor development is 7 to 9 years, with meningiomas and gliomas being the most common radiation-induced tumor types.[7–9,14]

Clinical Presentation

Presentation and symptoms depend largely on tumor location and patient age at the time of diagnosis.[15] The most common symptoms include effects of increased intracranial pressure, such as headaches that worsen 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 occur 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 (Figure 1). The goals of surgery include the safe reduction 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.[7,9,16,17] Cranial radiation may result in developmental impairments in young children; therefore, it is reasonable to defer or omit RT in children <3 years.[7] 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 Neuroimaging

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. Some imaging modalities or techniques may not be available at all institutions. Imaging is always recommended to investigate the etiology of emergent signs and symptoms. Below is a list of imaging modalities used in neuro-oncology to make treatment decisions.

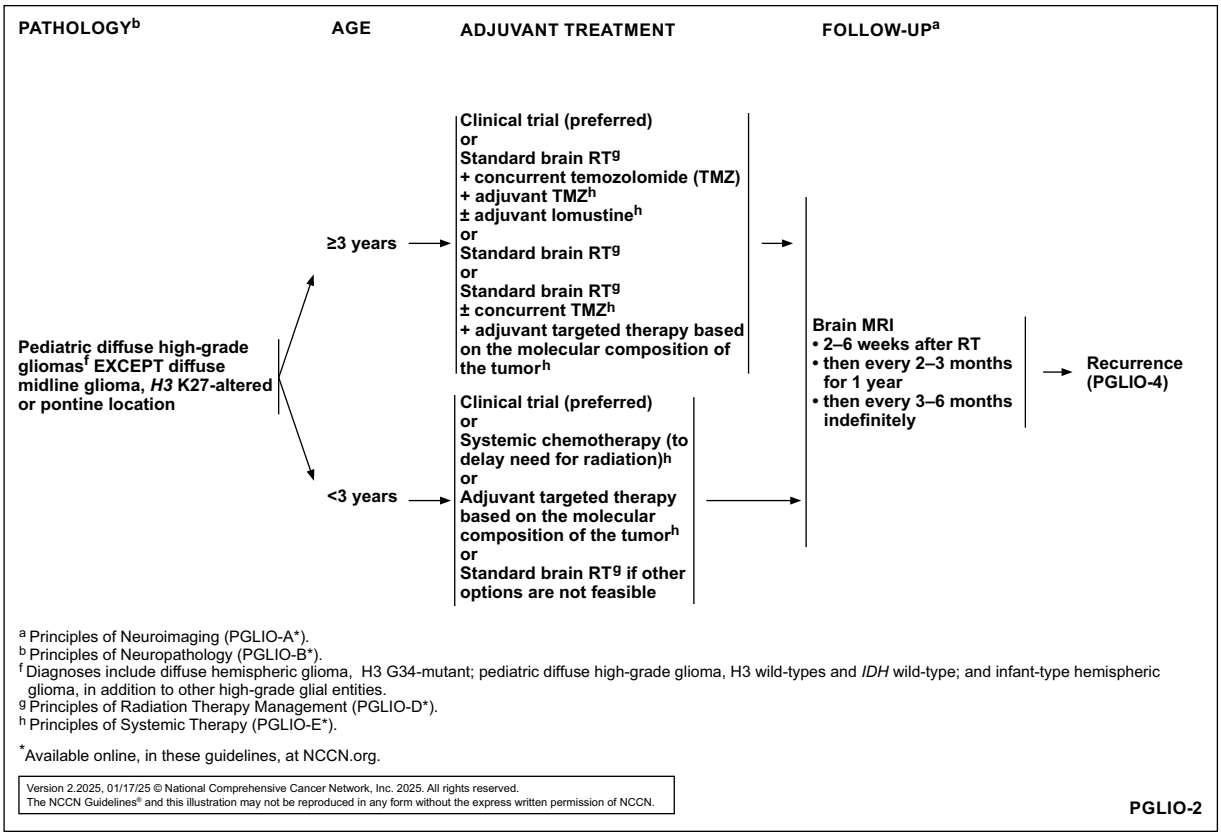

Figure 1. PGLIO-2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Central Nervous System Cancers, Version 2.2025.

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.[18] 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 there is no exposure of the patient 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.[7] They may demonstrate mass effect on surrounding structures, hemorrhage, increased perfusion, vasogenic edema, and a variable degree of contrast enhancement.[18] Higher grade components commonly enhance and demonstrate restricted diffusion, which is a key feature that reflects the high-grade nature of the tumor.[7] Rarely, high-grade pediatric gliomas may be well-circumscribed without the previously mentioned imaging features; hence, tissue biopsy is always recommended when possible. 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 unsafe nature of some implants 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-attenuated 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.[18] 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 3-dimensional sequence); T2-weighted, T2–fluid-attenuated inversion recovery, and diffusion-weighted imaging (DWI); and gradient echo or susceptibility-weighted (blood-sensitive) imaging. T2 hypointensity or reduced diffusion may indicate high cellularity.[19] 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.[19–22]

Basic MRI imaging 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 DWI 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 since many children require sedation to tolerate the examination. Baseline imaging of the brain and spine, especially by MRI, is recommended before treatment of high-grade gliomas.

More frequent imaging may be necessary in the event of clinical deterioration or evolving imaging findings concerning 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 to 3 weeks to avoid confusion with blood byproducts.

MR Perfusion

MR perfusion refers to a group of techniques that 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 pseudoprogression, distinguishing radiation necrosis from recurrent neoplasm, and choosing biopsy site.[23–25] 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.[18,26]

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.[18] Other limitations include calcification and hemorrhage-induced susceptibility within the tumor and contrast leakage due to breakdown of the blood-brain barrier.[18] DCE can be used as an alternative or complementary technique to DSC, although few studies have assessed its use in children.[27,28] 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[29]; however, DSC typically offers better blood volume estimation than DCE.[30]

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.[31–33] 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.[18,34] 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.[35]

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 pseudoprogression, distinguishing radiation necrosis from recurrent neoplasm, and choosing biopsy site.[18,25,36] 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 byproducts, and bone/soft tissue/air interfaces; long and complex acquisitions; expertise in technique/postprocessing; nonstandard acquisitions; nonstandard postprocessing; and postprocessing time.

A systematic review and meta-analysis comprising 455 patients across 18 studies showed that MR spectroscopy alone only has moderate diagnostic ability to differentiate glioma recurrence from radiation necrosis, and should therefore be combined with other techniques for this purpose.[36] 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.[25]

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; limited evaluation of metastatic disease; and metal-caused streak 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.[18]

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 is recommended when MRI is not available or in patients in whom an MRI is contraindicated because of unsafe implants or foreign bodies. However, CT is not recommended for staging and response evaluation for high-grade glioma unless in the very rare cases where MRI is not feasible.

Brain PET Studies

Brain PET studies assess brain tissue metabolism using a radiopharmaceutical, usually the glucose metabolism tracer fluorodeoxyglucose (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 most as a complementary test to provide information about whether abnormal areas seen on other imaging tests are likely to be tumors.[37] PET is more likely to be helpful for identifying high-grade tumors than low-grade tumors.[37] 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 neoplasms by coregistering the data with intraoperative guidance software. This technique is 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 with tractography may also be used to localize major white matter tracts underlying the eloquent cortex that could also compromise vital functions if injured during surgery.

Principles of Neuropathology

There are fundamental molecular differences between pediatric and adult CNS tumors, most recently recognized in WHO CNS5.[4,5,18] In contrast to tumors in adults, tumors in children typically carry a much lower burden 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.[4,5] The NCCN Guidelines describe guiding principles for the diagnosis of pediatric CNS tumors according to the parameters of WHO CNS5.[4,5] A general workflow for processing of tissue and tumor characterization using histologic, immunohistochemical (IHC), and molecular data are covered in these NCCN Guidelines. However, this is not meant to serve as an exhaustive list 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.[4] 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. Molecular alterations demonstrated by IHC may require confirmation by other techniques.

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, which underscores the importance of molecular testing in pediatric tumor diagnostics. Molecular testing is required in many cases to distinguish high-grade tumors from lower grade counterparts, and uncovering alterations that have been demonstrated to be prognostically relevant.[38–43] In addition, clinical trial stratification is becoming increasingly dependent on molecular characterization.

Considering the sheer number of genes of interest, in conjunction with the many types of recurrent alterations (including point mutations, insertion/deletions, copy number variations, and fusions), broad molecular testing is required for comprehensive classification of pediatric diffuse high-grade gliomas. Therefore, the panel recommends including tests to detect copy number changes and gene fusions via next-generation sequencing (including *ROS1, MET, NTRK1/2/3, ALK,* and *FGFR1/2/3*), RNA sequencing, or high-resolution copy number array. DNA methylation-based analysis may offer objective, more precise tumor classification; however, it should not be used as a first-line molecular test. In the pediatric population, dedicated germline testing should be strongly considered in the appropriate clinical context, recognizing that not all sequencing assays readily distinguish between germline and somatic variants.[44,45]

Limited Tissue Sample/Specimen

In cases in which limited tissue is available for processing, care should be taken to prioritize obtaining the following tests:

hematoxylin and eosin histology, limited IHC panel, next-generation sequencing, 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 next-generation sequencing 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 obtaining adequate tissue for pathologic diagnosis and molecular characterization. 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.[46] Surgical resection is not feasible for patients with DMG of the pons or most other brainstem tumors.

Preoperative Assessment

All patients being considered for surgery should undergo a preoperative assessment including laboratory work, imaging, and multidisciplinary consultation. 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. However, medications that may alter the patient's neurologic examination or increase surgical risks 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 have demonstrated an association between greater extent of resection and improved overall survival (OS) and progression-free survival (PFS) in patients with pediatric diffuse high-grade gliomas.[47–54] In the HIT-GBM study of 85 pediatric patients with malignant nonpontine gliomas, gross total resection (GTR) was the strongest predictor of OS and event-free survival (EFS).[53] In the HIT-GBM-C study, 5-year OS was significantly improved in patients with tumors that were completely resected prior to combination chemoradiotherapy (63%; n=21) when compared with historical controls (17%; P=.003).[52] The panel recommends maximal safe resection with the goal of image-verified complete resection whenever possible. In cases in which complete resection is not feasible, subtotal resection (STR) for tissue diagnosis and debulking should be considered, especially if the patient exhibits symptoms due to mass effect. In cases in which clinical benefit from cytoreduction is not feasible, biopsy is recommended.

Nearly all diffuse high-grade gliomas recur. Reresection at the time of recurrence may improve outcomes, although evidence varies widely.[49,55] 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 reresection outcomes.[55]

Postoperative Management

After surgical resection, patients should be monitored for signs and symptoms of increased intracranial pressure. Prophylaxis for seizures, infections, and venous thromboembolism can be considered.[56]

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.[57,58] Except in those with pontine DMGs, it is reasonable to defer or omit RT in patients <3 years out of concern for long-term complications with brain development.[7,9,16,17] However, standard brain RT can be considered for patients <3 years if no other options are feasible or the tumor did not respond to chemotherapy and/or additional systemic therapies. 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.

Following surgery, patients ≥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.[57,58] Initiation of RT is recommended whenever the patient has recovered from surgery and should begin within 8 weeks of resection. Intensity-modulated RT is used in most instances to allow reduction of risk or magnitude of side effects from treatment. Standard normal tissue constraints should be used, and although the prognosis of these patients is often poor, the "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. 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.[59–63]

The majority of studies on reirradiation are from adult high-grade glioma studies of recurrent glioblastoma multiforme and have suggested improvements in PFS, but limited OS gains.[55,64–67] Multiple dosing schedules have been reported for reirradiation, including stereotactic radiosurgery.[55,65–68] One of the few pediatric studies conducted was a retrospective cohort study of 40 children with recurrent supratentorial high-grade glioma who had received at least one course of RT.[69] Of the 40 children, 14 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.[17] Dose-escalated RT and concurrent or adjuvant systemic therapy have produced disappointing results in patients with pontine DMG, and therefore RT dose escalation beyond the standard RT doses is not recommended.[17,70–74] The panel recommends using intensity-modulated RT, but 3D conformal RT is also an acceptable

option.[16] Hypofractionated RT has been evaluated as an alternative 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.[75–77] Although data have shown hypofractionated RT to be statistically noninferior to conventional RT,[78,79] 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 following 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.[80–82]

Principles of Systemic Therapy

Combined Modality Therapy

The panel's preference for the use of RT with concurrent temozolomide (TMZ) followed by adjuvant TMZ and lomustine for patients ≥3 years is supported by the results of the phase II COG ACNS0423 trial. This trial 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.[57] 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).[57,58] The addition of lomustine also resulted in significantly better EFS and OS in participants without GTR (P=.019 and P=.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.[58]

Chemotherapy

It is reasonable to avoid RT in patients <3 years 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.[83,84] A Pediatric Oncology Group study showed that high-grade gliomas in children <3 years are sensitive to chemotherapy.[83] In this study, 18 children <3 years with malignant gliomas were treated with postoperative cyclophosphamide and vincristine for 2 cycles. Of the 10 patients evaluated for neuroradiologic response, the partial response rate was 60% and the 5-year PFS rate was 43%. In the Head Start II and III trials, 32 children <6 years with newly diagnosed high-grade gliomas were treated with 4 cycles of induction chemotherapy with vincristine, carboplatin, and TMZ followed by myeloablative chemotherapy and autologous hematopoietic cell transplantation.[84] The 5-year EFS and OS rates were 25% and 36%, respectively. Children <3 years 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

Advances in molecular technology have enabled the development of molecular agents capable of targeting the biologic drivers of pediatric diffuse high-grade gliomas.[85] 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 in subsequent sections.

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.[86–88] Many tumors that initially respond to *BRAF* inhibition eventually develop resistance due to reactivation of the MAPK pathway.[89,90] Combined therapy targeting *BRAF* and downstream MEK has shown success in several clinical trials in adults with cancer.[89–91] However, data on this regimen in the pediatric population are limited to case series and reports.[92,93] 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.[92] One patient who received the combination as maintenance therapy following 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 combined 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.[85,94,95] In the phase I trial of the Pediatric Neuro-Oncology Consortium study, 19 pediatric patients with recurrent or progressive *BRAF* V600E–mutated high-grade gliomas were treated with vemurafenib for a median of 23 cycles.[85] 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. The phase II part of the trial is currently ongoing (ClinicalTrials.gov identifier: NCT01748149).

Tropomyosin Receptor Kinase Fusion-Positive Tumor

Gene fusions involving *NTRK1*, *NTRK2*, or *NTRK3* encode for tropomyosin receptor kinase (TRK) fusion proteins (ie, TRKA, TRKB, TRKC) that have increased kinase function and are implicated in the oncogenesis of many solid tumors.[96,97] The small-molecule TRK inhibitors larotrectinib and entrectinib have demonstrated activity in several trials of adults and children with various cancers.[98–101] 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.[100] In patients with TRK fusion-positive tumors, the objective response rate (ORR) was 93% compared with 0% in patients without TRK fusion. In addition to a high ORR, larotrectinib was also well tolerated, with most patients experiencing only grade 1 adverse events and dose-limiting toxicity in one patient. The phase II part of this trial is currently ongoing (ClinicalTrials.gov identifier: NCT02637687).

The phase I/II STARTRK-NG trial assessed the activity of entrectinib in 43 pediatric patients (aged <22 years) with solid tumors including primary CNS tumors, regardless of TRK fusion status.[99] 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).

Based on the TRIDENT trial, the FDA issued accelerated approval for repotrectinib, another *NTRK*-based regimen, for adult and pediatric patients ≥12 years with solid tumors that have an *NTRK* gene fusion, are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and that have progressed following treatment or have no satisfactory alternative therapy.[102,103] An ongoing phase I/II CARE study is recruiting children and young adults with advanced or metastatic solid tumors to evaluate repotrectinib in combination with chemotherapy (ClinicalTrials.gov identifier: NCT05004116). The panel recommends repotrectinib as an option in both adjuvant and recurrent or progressive disease for diffuse high-grade gliomas.

ALK Rearrangement-Positive Tumor

The panel included options for ALK rearrangement-positive, high-grade gliomas based on studies/case report for this hard-to-treat young population group. Alectinib and lorlatinib were tolerated in these small subgroups and showed clinically beneficial outcomes.[104,105] Both alectinib and lorlatinib are included as options in both adjuvant and recurrent or progressive disease for diffuse high-grade gliomas.

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.[106] The resultant hypermutant tumors may be amenable to immune checkpoint inhibition; however, evidence of their efficacy is currently limited to case reports and single-institution experiences.[106–108] In one such case report, 2 siblings with recurrent hypermutant pediatric diffuse high-grade gliomas were treated with the antiprogrammed cell death protein 1 inhibitor nivolumab, which resulted in significant clinical and radiologic responses in both children following several months of treatment.[106] A retrospective chart review of 11 pediatric patients with recurrent or refractory CNS tumors treated with ipilimumab/nivolumab, nivolumab, or pembrolizumab showed that immune checkpoint inhibitors are reasonably well tolerated in pediatric patients and warrant further study in clinical trials.[108]

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.[106] Patients with recurrent or progressive disease have a median OS of <6 months, and no effective therapies currently exist.[106] The use of systemic therapy for the management of recurrent or progressive disease depends on the extent of disease and the patient's condition (Figure 2). Targeted therapy based on the molecular composition of the tumor is

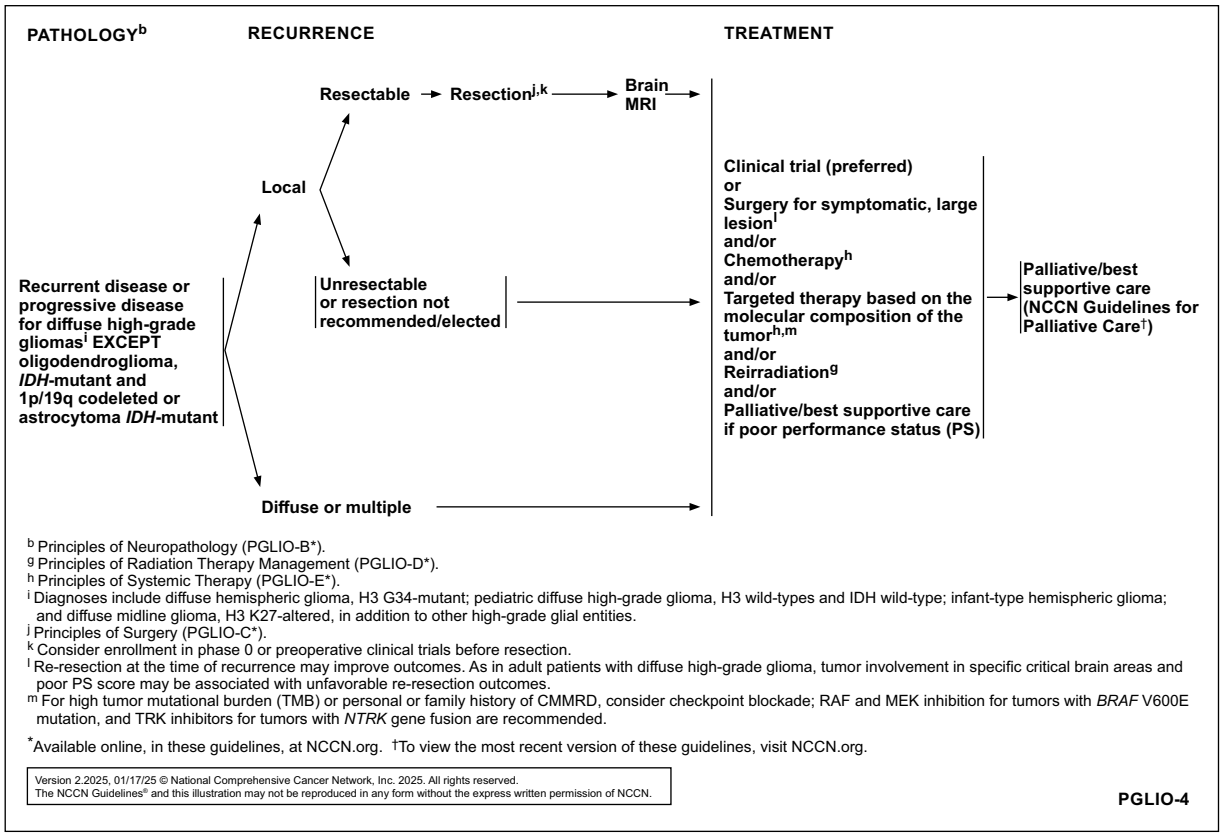

Figure 2. PGLIO-4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Central Nervous System Cancers, Version 2.2025.

recommended for patients with good performance status. 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, TRK inhibitors for tumors with *NTRK* gene fusion, and ALK inhibitors for *ALK* rearrangement-positive tumors.

Patients with poor performance status may receive palliative chemotherapy with oral etoposide,[109] bevacizumab (or an FDA-approved biosimilar),[110] or single-agent nitrosoureas (lomustine or carmustine).[57] 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.[109] Three of the 4 patients with medulloblastoma exhibited a partial response and 2 of the 5 patients with ependymoma had a response (1 a complete response and 1 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 (1 with grade 4 thrombocytopenia and 1 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.[110] Median EFS did not differ significantly between the treatment groups and the addition of bevacizumab did not reduce the risk of death. Adding bevacizumab to RT plus TMZ did not improve EFS in pediatric patients with newly diagnosed high-grade gliomas. Therefore, 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.

Brief Summary of NCCN Recommendations for Diffuse High-Grade Gliomas

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. 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. 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.[19–22] 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 NCCN Guidelines. 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. Outside of a clinical trial, patients ≥3 years with pediatric diffuse high-grade gliomas, except DMG, *H3* K27-altered or other tumor with a pontine tumor location, can receive standard brain RT with concurrent and adjuvant TMZ without lomustine or with lomustine (preferred).[57,58] 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 can receive systemic chemotherapy with either cyclophosphamide, vincristine, cisplatin, and etoposide[83] or vincristine, carboplatin, and TMZ[84] 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. 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 should be followed closely with brain MRI scans starting at 2 to 6 weeks postirradiation, then every 2 to 3 months for 1 year, then every 3 to 6 months indefinitely after the completion of treatment of newly diagnosed disease. Pseudo-progression may occur within 6 to 9 months after RT and can be seen on MRI; therefore, pseudo-progression should be considered if MRI changes are noted in this 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. 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 reresection outcomes. In cases of poor performance status or where aggressive therapy is unlikely to provide meaningful survival benefit, palliative and best supportive care including family-centered care with attention on quality of life is recommended.

Preferred systemic therapy options for recurrent disease include but are not limited to dabrafenib/trametinib[92] or vemurafenib[85] for *BRAF* V600E-mutated tumors, larotrectinib[100] or

entrectinib[99] for *TRK* fusion-positive tumors, nivolumab[106,107] or pembrolizumab[108] for hypermutant tumors, and lorlatinib or alectinib for *ALK* rearrangement-positive 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,[109] bevacizumab (or an FDA-approved biosimilar),[110] or nitrosoureas (lomustine or carmustine).[57]

Pediatric Medulloblastoma

Introduction

Epidemiology

Medulloblastoma is one of the most common types of brain tumors in children, accounting for about 10%–20% of all brain tumors (0.47 per 100,000 for children 0–14 years).[111] The prognosis for medulloblastoma, predominantly found in the cerebellum, is worse for patients <3 years or those with metastatic disease, suboptimal resection, and certain molecular subtypes. However, with advances in multimodality therapies, approximately 75% of children with medulloblastoma will have prolonged survival.[112] Pediatric medulloblastoma consists of at least 4 distinct molecular subtypes, which includes wingless (WNT), sonic hedgehog (SHH), group 3, and group 4.[113] Group 3 and 4 have been combined and are collectively referred to as "non-WNT/non-SHH" medulloblastoma. Incidence of the different molecular subtypes of medulloblastoma can vary with age and sex and are detailed in this section.[113,114] Current therapeutic regimens are highly effective for certain molecular groups of medulloblastoma, leading to a high rate of cure in these subgroups. WNT-activated tumors represent 10% of medulloblastoma and are most common in children aged 7 to 14 years with a good prognosis (long-term survival rates >90%). The SHH-activated, *TP53*-wild-type or -mutant tumors represent 10%–20% of medulloblastomas, and *TP53* mutations and/or *MYCN* amplification in this subtype is associated with poor prognosis. The WHO classifies SHH-activated/*TP53*-wild-type and SHH-activated/*TP53*-mutant tumors as separate subtypes. *TP53* mutation and *MYCN* amplification are associated with each other and with a very poor outcome, worse than that of *TP53* mutation alone.[115] Finally, group 3 and 4 tumors represent about 25%–35% of medulloblastomas, respectively. Even though they are combined, group 3 tumors have a less favorable prognosis (5-year survival rates between 20%–30%) compared with group 4 tumors (OS rates between 75%–90%).

Risk Factors/Genetic Predisposition

The risk factors for pediatric medulloblastoma are not well-known. However, certain genetic conditions and germline mutations are associated with a higher risk of developing medulloblastoma at a young age. These include Li-Fraumeni syndrome that occurs due to germline *TP53* mutations and/or family history of certain cancers; Turcot syndrome/Lynch syndrome/CMMRD that presents with mutations in *hMSH2, hMSH6, hMLH1*, and *hPMS2*; and Gorlin syndrome (nevoid basal cell carcinoma syndrome).[116] Germline mutations in *APC*, *BRCA2*, *PALB2*, *GPR161*, *ELP1*, *CREBBP*, and *EP300* can also predispose children to develop pediatric medulloblastoma.[117] The WNT and SHH subgroups have the highest occurrence of these mutations and syndromes, with a much lower frequency of genetic alterations in group 3 and 4 tumors. Individuals who should be referred to evaluation of cancer predisposition include those whose tumors harbor genetic alterations or with a clinical history suggestive of predisposition to inherited cancer. The panel notes that genetics associated risk factors may be updated in the future with emerging data and new discoveries in this field.

Clinical Presentation

The symptoms, which can develop in weeks or gradually over months, can be intermittent and subtle at first. The most common symptoms include consequences of increased intracranial pressure, such as headache, nausea, and vomiting. Prolonged elevated intracranial pressure can lead to papilledema and changes in vision.[15] Other presenting symptoms include ataxia, cranial nerve deficits, loss of developmental milestones, and back pain.

Treatment Overview

Treatment of medulloblastoma includes surgery, RT, and chemotherapy. The goals of surgery include maximal safe resection, to reduce tumor-associated mass effect, to provide relief from hydrocephalus, and to obtain adequate tissue for histologic and molecular classification. The panel encourages enrollment in molecular classification-based clinical trials, if available. Postoperative staging should include molecular findings along with clinical factors to ascertain risk for recurrence that informs adjuvant therapy options. Given the younger age of diagnosis, the panel recommends referring patients to infertility risk/fertility preservation counselling, especially for those who are or will be treated with chemotherapy. The panel also suggests referring to the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology (available at NCCN.org). The panel notes that treatment of children <3 years is not covered in this guideline.

Principles of Neuroimaging

The current guideline recommendations incorporate imaging followed by molecular subtyping to determine risk for recurrence and adjuvant/maintenance therapy. The panel includes imaging modalities, among other tests, as follow-up/surveillance tools after adjuvant therapy to monitor response and disease status. The recommendations for imaging medulloblastomas mostly follow that of diffuse high-grade gliomas. However, keeping in mind the challenges associated with certain molecular subtypes, there are certain key differences regarding tumor appearance on imaging and/or acquisition of high-quality images that are listed below:

- Pediatric medulloblastoma usually appears as a large, heterogeneous, posterior fossa mass that occupies either the fourth ventricle or cerebellar hemisphere. The mass characteristically demonstrates reduced diffusion due to high cellularity, with most cases exhibiting heterogeneous cyst formation or necrosis, with varying degrees of enhancement.
- Medulloblastoma associated with leptomeningeal dissemination in the spine is more evident on an MRI.[118] The panel recommends obtaining sagittal T2-weighted images, and postcontrast sagittal and axial T1-weighted images of the entire spine. Additional sequences such as high-resolution heavily T2-weighted images, 3D bSSFP sequence (CISS/FIESTA-C), and/or DWI may be helpful and, when feasible, should also be obtained.[119] Furthermore, the apparent diffusion coefficient value calculation using DWI, among other imaging features, may aid in predicting

molecular subtypes and optimizing planning related to surgery.[120,121]

- FDG-PET/CT can be a useful imaging tool in evaluating pediatric medulloblastoma. A case study involving serial MRIs in a 20-year-old patient after radiation and adjuvant chemotherapy showed no disease progression even though the patient had declining functional abilities.[122] A follow-up FDG-PET/CT evaluation showed increased uptake along the length of the thecal sac suggesting metastatic disease, which was confirmed by spine MRI with gadolinium contrast. In another study of patients with medulloblastoma (N=22), increased FDG uptake correlated negatively with survival.[123] These studies suggest the potential utility of FDG-PET/CT in evaluating metastatic disease and prognosis.
- Deep learning and artificial intelligence (AI) techniques using imaging scans to predict the molecular subtypes are currently being investigated. Although acknowledging that such studies are in very early stages of development, the panel notes that there is a possibility of improving medulloblastoma classification by merging data from textured images and the original histopathologic images. A retrospective study across 12 international pediatric sites (N=263) applied machine learning to MRI scans and constructed algorithms to predict the 4 major molecular subtypes with some success.[124] Another study found an increased frequency of equivocal findings on MRI in the SHH subtype compared with any other molecular subgroup.[125] Based on these and other ongoing studies, the panel notes that evaluations combining radiology and genomics could become more clinically relevant in the future.

Principles of Neuropathology

All types of medulloblastomas are embryonal tumors composed of small, poorly differentiated cells with high nuclear:-cytoplasmic ratio, increased mitotic activity, and prominent apoptosis. All medulloblastomas are CNS WHO grade 4 and categorized by molecular group based on the 2021 CNS WHO Classification (fifth edition).[4] Morphologic patterns remain a critical clinicopathologic tool that can correlate well with molecular subtypes and in some cases even predict molecular findings. However, some observed morphologic patterns (for example: large cell/anaplastic histology) are subjective and depend on the pathologist's expertise; therefore, molecular characterization is now the gold standard for medulloblastoma classification. IHC analysis can provide rapid screening for specific genetic alterations (eg, β-catenin, p53, *INI1*/*SMARCB1*). Altogether, the panel deems integration of morphologic, IHC, and molecular data as necessary for diagnosing and treating pediatric medulloblastomas. In addition, the panel recommends germline testing and genetic counseling in all diagnosed cases of medulloblastoma.

Molecular Characterization

The well-established molecular subtypes of medulloblastoma include WNT-activated, SHH-activated/*TP53* wild-type, SHH-activated/*TP53*-mutant, and combined groups 3 and 4, and are characterized by specific genetic alterations.[113,117,126–128] WNT-activated tumors are distinguished by *CTNNB1* mutation in 90% of cases and usually result in a positive nuclear β-catenin IHC and chromosome 6 loss, whereas germline mutations like *CMMRD* and *APC* are rare in this subtype. IHC for β-catenin may particularly be helpful to demonstrate WNT pathway activation in patients within the low-risk group within WNT-activated medulloblastoma. In SHH-activated/*TP53* wild-type tumors, frequent mutations, including those in *PTCH1* (Gorlin syndrome), *SUFU*, *SMO*, *MLL1*, *MYCN*, *LDB1*, and *GLI1*, occur. In contrast, DNA methylation changes appear more commonly in SHH-activated/*TP53*-mutant tumors. Group 3 and 4 tumors are generally not associated with germline mutations but *MYC* amplification and isodicentric 17q alterations can be found in select cases. The panel notes that although DNA methylation profiling is robust for medulloblastoma subtyping, the data are yet to fully mature and therefore are not currently included in these guidelines. The panel recommends that when DNA methylation analysis is performed, these findings should be integrated with genetic profiling that includes germline testing.

After in-depth discussion, the panel decided that considering molecular features in the context of clinical findings is the best approach to risk-stratify patients. Factors considered as risk for recurrence, based on current evidence and panel consensus, are described in the algorithm pages (Figure 3 and Figure 4). The panel agrees that metastatic disease, STR, or *MYC* amplification will automatically classify a patient into the high-risk group irrespective of the molecular subgroup. However, the prognosis of patients with high-risk features may vary with different molecular characteristics. Furthermore, discerning molecular features can be important for enrolling patients into appropriate clinical trials. For Version.1.2025 of these guidelines, the intermediate risk category for groups 3 and 4 tumors was removed because the panel felt that this risk category is an ongoing area of investigation and does not have enough compelling evidence to be put in current clinical practice. Classifying a patient into a certain risk category can depend on age; for example, a 4-year old's relative risk with M0, GTR, *MYC* gain, large cell/anaplastic histology may be viewed differently from a 10-year old's relative risk with the same features. These nuances should be kept in mind and clinical judgement should be used to treat these patients. Diagnosis of large cell/anaplastic histology is subjective, especially in cases of mixed histology, and varies across different institutions. Although noting that large cell/anaplastic histology usually occurs with some other clinical/histologic/molecular features, the panel determined that diagnosis of large cell/anaplastic histology alone is not considered a risk factor for recurrence. Additionally, *MYC* gain is different from *MYC* amplification, but the distinguishing features between the 2 are not clearly defined. The panel contends that more data are needed to integrate the subtle differences between gains and amplifications into risk stratification. Finally, the panel emphasized that the molecular classification and associated risk stratification, particularly for pediatric medulloblastoma, is an evolving field and will be updated based on ongoing studies and available data.

Principles of Surgery

The principles of surgery for medulloblastoma are largely similar to those for high-grade gliomas. One of the primary goals during surgery is to maintain the fine balance between maximal cytoreduction and preserving quality of life of the patient. Additional considerations for surgical resection of medulloblastoma are listed below.

- Initial surgery should be performed with the goal of GTR while minimizing neurologic deficits incurred from surgery. Near total

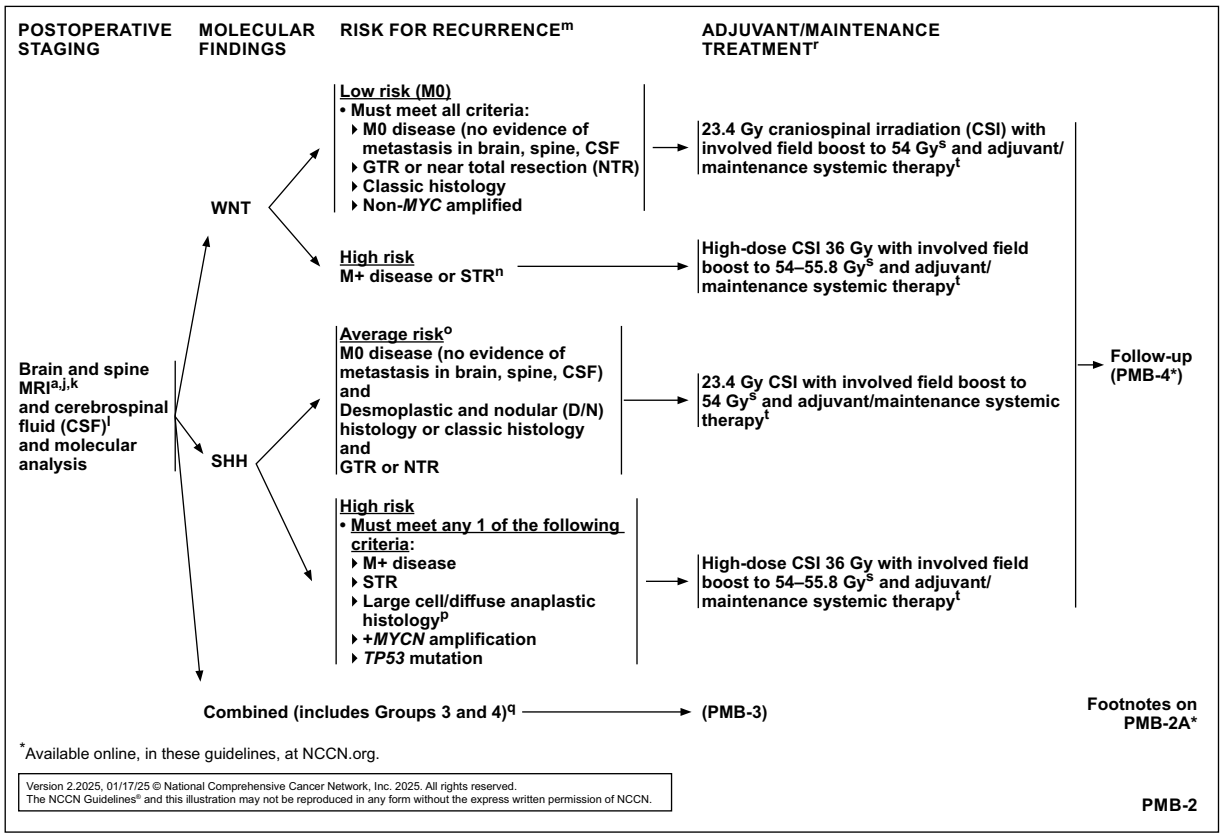

Figure 3. PMB-2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Central Nervous System Cancers, Version 2.2025.

resection (≤1.5 cm^2 residual) is acceptable in some settings. Less than near total resection is also acceptable after review postoperatively by a multidisciplinary team. A retrospective study that included 787 patients found that extent of resection in only group 4 tumors was associated with poor survival, with the authors acknowledging that the reason behind this correlation is not clear.[112] Other studies have shown that extent of residual tumor is correlated with PFS in kids with no disseminated disease.[129,130]

- Medulloblastoma usually appears as a posterior fossa mass, but the nature of the mass may vary depending on the subtype. For example, the WNT medulloblastoma subtype is known to display intratumoral hemorrhage more frequently than the other molecular subtype.[131]
- The panel recommends obtaining adequate tissue for histopathologic diagnosis and molecular genetic characterization. Molecular findings after surgery are important for further risk stratification.
- For patients with resectable residual disease, the panel contends considering if a second-look surgery is acceptable. Careful reinspection of the area of resected tumor can reveal residual disease.[132] Reresection at the time of recurrence may confer OS benefit in the setting of a single, focal posterior fossa recurrence.
- Any medulloblastoma that recurs after 3 to 5 years could be a second malignancy. Therefore, the panel emphasizes the need to rebiopsy the tumor to distinguish between medulloblastoma and diffuse high-grade gliomas. Biopsy of recurrent disease may also identify actionable molecular findings, or rarely, a secondary malignancy.
- The panel notes that cerebrospinal fluid diversion techniques including ventriculoperitoneal shunt or endoscopic third ventriculostomy are acceptable.

Principles of RT Management

Radiation is an essential component of adjuvant therapy for all risk categories of medulloblastoma and improves survival for at least 20% of the patients. Craniospinal irradiation (CSI) for primary disease is critical, regardless of molecular subtype, to achieve potential cure of medulloblastomas.[133,134] For high-risk subgroups, an elevated CSI dose is recommended whereas a lower dose is recommended for low-risk subgroups (Figure 3 and Figure 4). Using a lower dose of radiation, thought to have the same therapeutic efficacy while retaining neurocognitive outcomes, has not shown benefit when the molecular subtypes are analyzed as one group.[135] It is yet to be determined whether lower doses can be still be effective for certain molecular subtypes of medulloblastoma (eg, WNT); this is a topic of investigation in some clinical trials, including NCT02724579 (ClinicalTrials.gov identifier: NCT02724579) and NCT01878617 (ClinicalTrials.gov identifier: NCT01878617). In the recurrent setting, reirradiation is primarily based on clinical judgment, and a higher dose can be used especially if the patient did not receive any radiation (an unusual scenario) as part of adjuvant treatment.

Certain chemotherapy agents are thought to act as radiosensitizers. In a randomized phase III trial, treatment with carboplatin during radiation improved EFS by 19% only in children with high-risk group 3 medulloblastoma.[136] The authors did

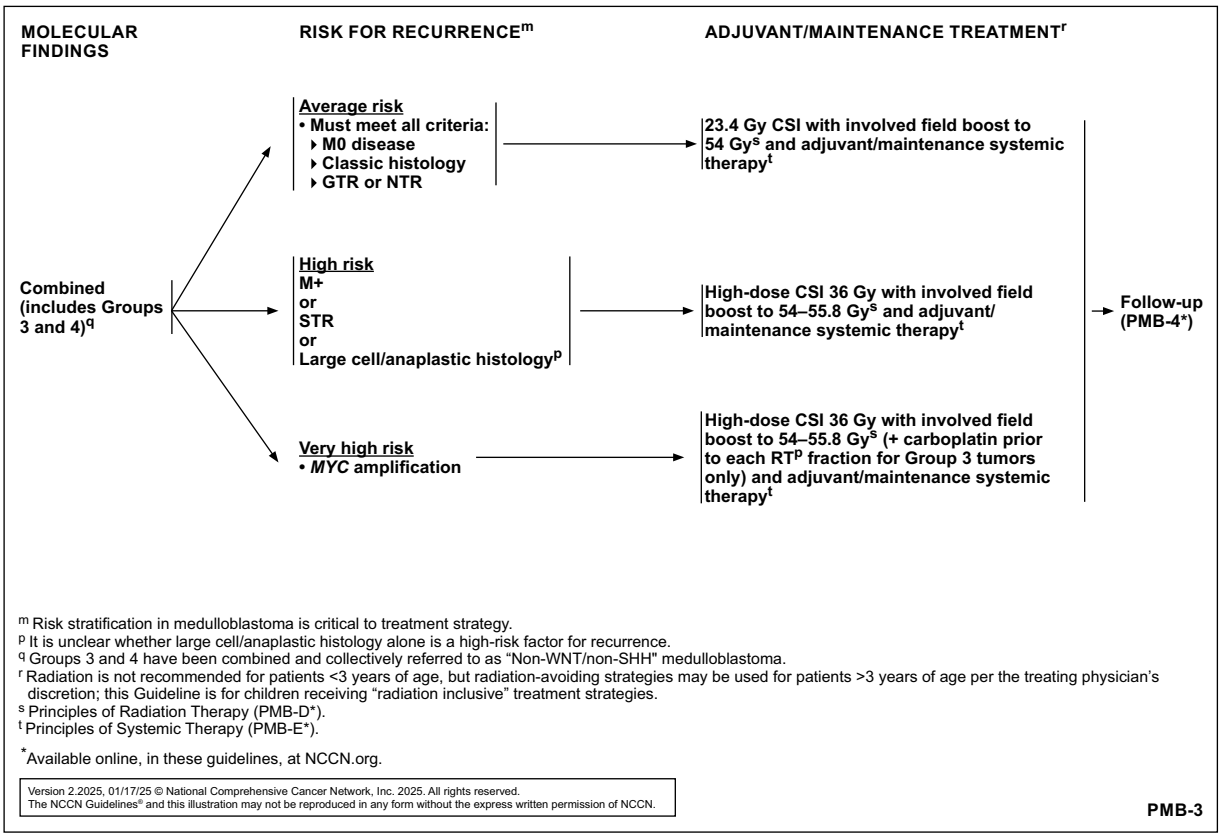

Figure 4. PMB-3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pediatric Central Nervous System Cancers, Version 2.2025.

observe higher toxicities in patients who received carboplatin during RT, which were attributed to an intense treatment schedule. Nevertheless, this study emphasizes the importance of molecular stratification, which can provide information about which patient subgroup is most likely to benefit from certain treatments. Based on the study, the panel recommends carboplatin before each RT fraction only for group 3 tumors with very high risk of recurrence (*MYC* amplification).

A cohort study of patients with medulloblastoma showed that proton radiotherapy may be associated with more favorable intellectual outcomes, measured by global intelligence quotient, perceptual reasoning, and working memory scores, compared with photon radiotherapy.[137] The authors noted that modern photon radiotherapy techniques can result in intellectual benefits; however, they still favored proton radiotherapy. Photon radiotherapy is also associated with side effects.[138–140] The panel notes that it is important to remain vigilant regarding potential radiotherapy related morbidities, such as brainstem injury, as data mature for the modern techniques. Regardless of the type of therapy used, the panel emphasizes the need for utilizing optimal normal tissue-sparing techniques during radiotherapy planning and administration.

There is some concern about secondary malignancies due to RT; however, the panel feels that such risk can be largely attributed to germline mutations, including *TP53*, that predispose individuals to certain cancers. Finally, the panel encourages clinical trial enrollment; if a patient is enrolled in a clinical trial, the protocol recommendations and normal tissue dose constraints of the trial should be met.

Principles of Systemic Therapy

Adjuvant Chemoradiation Followed by Maintenance Chemotherapy

The therapy for all risk categories consists of chemoradiation followed by maintenance chemotherapy. The maintenance treatment schedule from the Children's Oncology Group (COG) or St. Jude protocol can be used. However, these protocols are not interchangeable. Toxicity should be monitored during treatment, including neuropathy associated with vincristine and ototoxicity associated with cisplatin. The panel recommends slightly different chemoradiation regimens for low-/average-risk and high-/very-high-risk categories.

Low and Average Risk

A randomized phase III trial (n=464 eligible and evaluable patients) conducted by the COG studied weekly vincristine with radiotherapy; after 6 weeks patients received maintenance chemotherapy that cycled between cisplatin/lomustine/vincristine and cisplatin/cyclophosphamide/vincristine.[135] All the molecular subtypes of medulloblastoma were represented in this study with group 4 tumors comprising the largest subgroup. In all patients, outcomes including EFS and OS were comparable between posterior fossa and involved-field RT. However, the study showed that using low-dose CSI may not be as efficient as using standard-dose CSI. Another study conducted by investigators at St. Jude (n=330) used a similar dosing strategy for CSI and primary chemotherapy, while maintenance consisted of vincristine/cisplatin/cyclophosphamide.[141] Group 4 tumors were the largest proportion of subtypes among the molecular subtypes in

this study. In general, the outcomes of this trial were comparable to previously performed prospective studies. Based on these 2 studies, the panel recommends weekly vincristine with RT (COG) that can be followed by maintenance therapy from either the COG or St. Jude trial as options for low-/average-risk disease.

High and Very High Risk

Studies have investigated potential radiosensitizing effects of carboplatin.[136,142] The addition of carboplatin during radiotherapy improved clinical outcomes in high-risk group 3 tumors. Therefore, the panel recommends carboplatin prior to each RT fraction for group 3 tumors with very high risk for recurrence (*MYC* amplification). The panel recommends using the St. Jude trial protocol or the ACNS0332 protocol (consisting of 6 cycles of chemotherapy including cisplatin, cyclophosphamide, and vincristine) as maintenance options for high- and very-high-risk disease.

Recurrent or Progressive Disease

Recurrent or progressive disease after first-line therapy is observed in approximately one-third of the patients and is associated with significantly lower survival rates of <10%. Given the low survival rates, recurrent/progressive medulloblastoma is thought of as high-risk disease. Therefore, a combination of systemic therapies based on existing data, described subsequently, are options for aggressively treating recurrence/progressive disease. The panel also encourages patients with recurrent or progressive disease to participate in clinical trials.

TMZ and Irinotecan + Bevacizumab

The addition of bevacizumab to TMZ and irinotecan demonstrated a 3-month benefit to EFS (6 months without bevacizumab vs 9 months with bevacizumab) in a phase II screening trial of patients with recurrent medulloblastoma or CNS primitive neuroectodermal tumor.[143] Both arms had similar toxicity profiles. Therefore, this regimen is included as an option to treat recurrent or progressive disease. The panel notes that bevacizumab initiation can be delayed to ensure appropriate wound healing in patients who recently had surgery.

TMZ/Topotecan

In a phase 2 basket trial, treatment with TMZ/topotecan led to a 28% overall ORR in a small cohort of pediatric patients with recurrent/refractory medulloblastoma.[144] Hematologic toxicities were frequently observed in patients treated with TMZ/topotecan.

MEMMAT Regimen

Metronomic antiangiogenic therapies are low doses of anticancer drugs that are administered on a regular basis over long periods of time.[145] Two potential advantages of such low-dose regimens include lowering side effects and readministering drugs previously given at high doses to circumvent tumor resistance.[145] A few phase II trials and a retrospective analysis showed the benefit of MEMMAT or "MEMMAT-like" regimens in treating pediatric medulloblastoma.[146,147] Phase II trials in pediatric patients with recurrent or progressive CNS tumors evaluated disease progression after treatment with these regimens for up to 7 months.[148,149] These trials showed acceptable toxicity profiles and promising clinical activity in a subset of patients.

Carboplatin/Etoposide

A phase II window-of-opportunity trial that included patients with recurrent medulloblastoma (n=93) investigated the efficacy of 3 arms (nonrandomized): carboplatin/etoposide, oral chemotherapy with TMZ, and a documentation arm that included patients not treated with the 2 regimens.[150] Patients on the carboplatin/etoposide arm had better ORRs compared with those who received TMZ (51.8% vs 18.2%). The authors noted that both hematologic and nonhematologic toxicities were observed but were manageable. The clinical outcomes of this trial were comparable to trials that investigated TOTEM or TMZ/irinotecan/bevacizumab.

Brief Summary of NCCN Recommendations for Medulloblastoma

Radiologic Presentation and Multidisciplinary Review

A contrast-enhanced MRI compatible with primary brain tumor is the preferred method to perform radiologic evaluation of medulloblastoma. The panel recommends that multidisciplinary review be conducted once pathology reports are evaluated, and this should be performed before surgery.

Primary Treatment

The primary treatment consists of surgery followed by adjuvant therapy. The goals of surgery include GTR; if that is not possible then maximal safe resection is an option. The panel strongly recommends referring the patient to a pediatric brain tumor center for evaluation of possible more complete surgical resection when open biopsy or STR are being considered. STR may be warranted only if the patient has gross leptomeningeal disease and no detectable primary site. Postoperative staging includes brain/spine MRI, cerebrospinal fluid, and molecular analysis. Postoperative imaging is required for the brain only and is ideally obtained within the first 24–72 hours (within 24 hours preferred). If spine MRI is not performed before surgery, imaging should wait 10 to 14 days postoperatively to get an accurate image. The panel notes that rapid-sequence MRI is not a substitute for a full brain and spine MRI when staging or assessing for response evaluation. Timely molecular testing of medulloblastoma is recommended, which informs risk stratification before adjuvant treatment.

Adjuvant Therapy

Adjuvant treatment consists of chemoradiation followed by maintenance chemotherapy. CSI and chemotherapy recommendations differ for low-/average-risk and high-/very-high–risk disease.

Follow-up and Recurrence

The algorithm lists details of recommended follow-up tests and surveillance methods. This includes endocrine tests at least annually for 5 years to ensure institutions and doctors can best follow-up with patients on an individualized basis. If thyroid-stimulating hormone or growth failure is suspected, endocrine tests can be performed more frequently. The oncologist may also refer to an endocrinologist if any of the endocrine test results raise suspicion. Recurrent/progressive disease can be treated with combined chemotherapy regimens. The panel encourages enrollment in clinical trials. Palliative/supportive care that includes radiation and additional resection are also included as options for recurrent/progressive disease.

Summary

Pediatric CNS cancers are the leading cause of cancer-related death in children. Referral for cancer predisposition evaluation and/or genetic counseling should be considered for patients with pediatric diffuse high-grade gliomas/medulloblastoma linked to certain inherited cancer predisposition syndromes. All patients should be cared for by a multidisciplinary team with experience managing pediatric CNS tumors. Advances in molecular profiling have expanded the use of targeted therapies in patients whose tumors harbor certain alterations in diffuse high-grade gliomas. However, nearly all patients will experience recurrent disease, which has limited treatment options. For medulloblastomas, the panel notes that molecular subgrouping is an evolving field that will perhaps affect the clinical management of this disease. Subsequent versions of the NCCN Guidelines will address additional tumor types.

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