National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pediatric Central Nervous System Cancers

Version 2.2023 — October 31, 2022

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Pediatric Central Nervous System Cancers

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NCCN Guidelines Panel Disclosures

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

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Pediatric Central Nervous System Cancers

Updates in Version 2.2023 of the NCCN Guidelines for Pediatric Central Nervous System Cancers from Version 1.2023 include:

MS-1

• The Discussion section, which reflects the recommendations in the algorithm, has been added.

INTRODUCTION TO PEDIATRIC DIFFUSE HIGH-GRADE GLIOMAS[1-4]

All patients with pediatric diffuse high-grade gliomas should be cared for by a multidisciplinary team with experience managing central nervous system (CNS) tumors.[a]

Epidemiology of Pediatric Diffuse High-Grade Gliomas

- 14.8% of all intracranial neoplasms are among children and adolescents (<19 years).
- The incidence of pediatric diffuse high-grade gliomas among children and adolescents is roughly 1.8 per 100,000 population.
- Incidence varies with age.
- 5-year overall survival is <20%.
- Prognostic features include age at presentation (<3 and >13 years), tumor location, sex, extent of resection, and genomic profile.

Risk Factors

- Inherited predispositions to cancer include, but are not limited to:
  - Neurofibromatosis type 1 (NF1)
  - Li-Fraumeni syndrome
  - Turcot syndrome/Lynch syndrome/constitutional mismatch repair deficiency (cMMRD):
    - ◊ Mutations in *APC*/familial adenomatous polyposis (FAP) locus (more often associated with medulloblastoma)
    - ◊ Mutations in mismatch repair (MMR) genes
- Exposure to ionizing radiation: Therapeutic cranial radiation treatments increase risk for pediatric diffuse high-grade gliomas.

Clinical Presentation

- The most common symptoms include effects of increased intracranial pressure, such as headache, nausea, and vomiting.
- Other presenting symptoms include seizure, hemiparesis, monoparesis, cranial nerve deficits, ataxia, hemisensory loss, dysphasia, aphasia, and memory impairment.
- Presenting symptoms among infants include increased head circumference and loss of developmental milestones.
- Shorter length of symptoms is associated with worse prognosis in older studies.

Treatment

- Treatment for pediatric diffuse high-grade gliomas frequently includes surgery, radiation therapy (RT), and chemotherapy.
- Goals of surgery include the safe reduction of tumor-associated mass effect and obtaining adequate tissue for histologic and molecular classification.
- Referral for cancer predisposition evaluation and/or genetic counseling should be considered.

[a] A multidisciplinary team that includes pediatric oncologists/neuro-oncologists, pediatric radiation oncologists, pathologists with expertise in neuropathology and molecular pathology, pediatric neuroradiologists, and pediatric neurosurgeons is strongly encouraged.

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INTRODUCTION TO PEDIATRIC DIFFUSE HIGH-GRADE GLIOMAS
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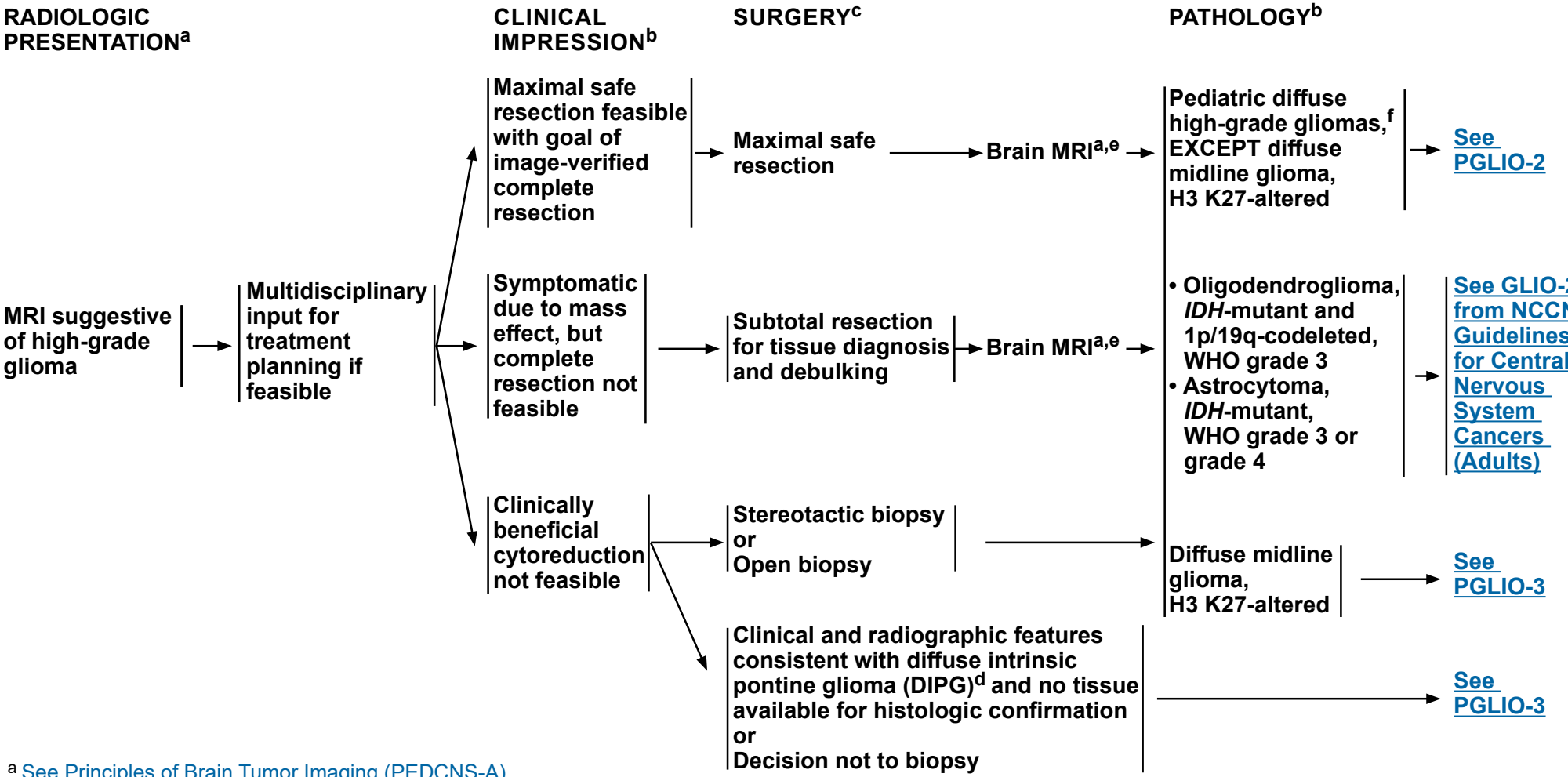

[a] See Principles of Brain Tumor Imaging (PEDCNS-A).
[b] See Principles of Brain Tumor Pathology (PEDCNS-B).
[c] The goals of surgery are to obtain a pathologic diagnosis and molecular genetic characterization, alleviate symptoms related to increased intracranial pressure or tumor mass effect, increase survival, and decrease corticosteroid dose requirements. See Principles of Surgery (PEDCNS-C).
[d] Encourage biopsy if atypical features on MRI are present, if patient is <3 years of age, or if standard of care at institution.
[e] Postoperative follow-up is ideally between 24–48 hours.
[f] Diagnoses include diffuse hemispheric glioma, H3 G34-mutant; pediatric diffuse high-grade glioma, *H3* wild-types and *IDH* wild-type; and infant-type hemispheric glioma, in addition to other high-grade glial entities.

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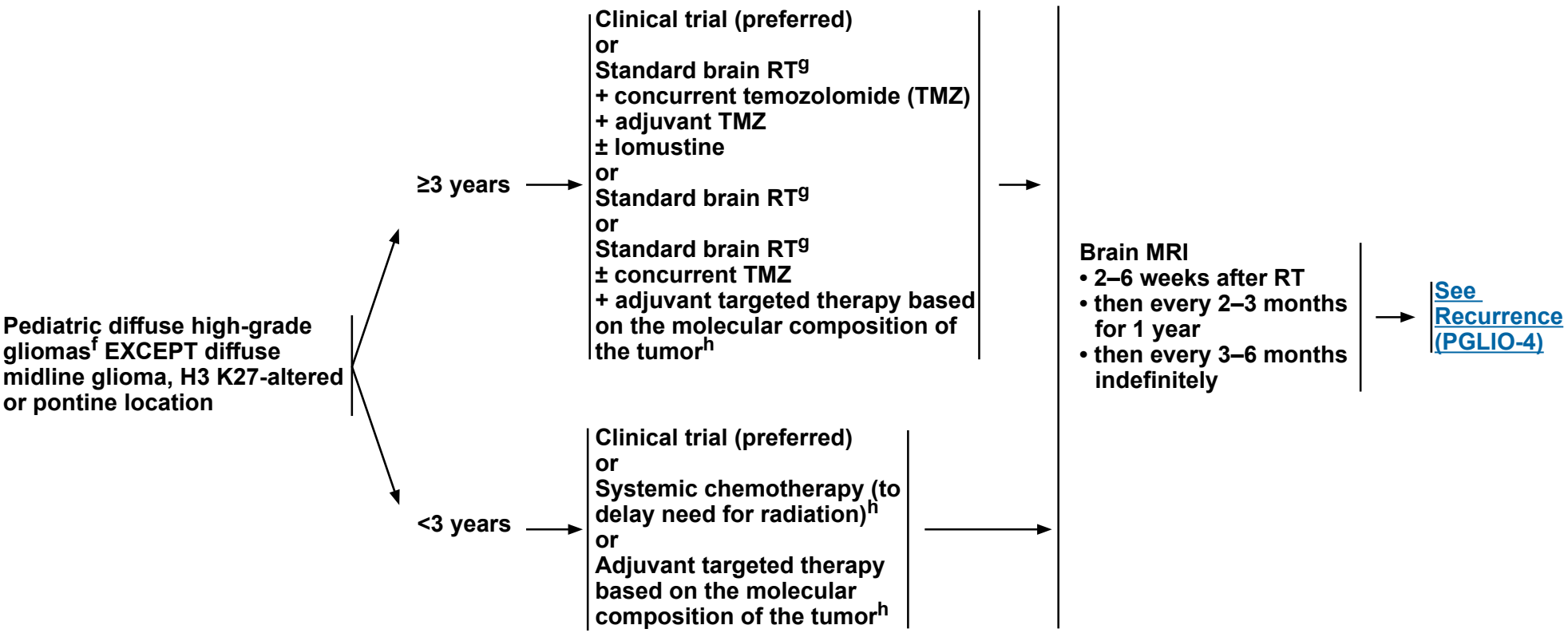

[a] See Principles of Brain Tumor Imaging (PEDCNS-A).
[b] See Principles of Brain Tumor Pathology (PEDCNS-B).
[f] Diagnoses include diffuse hemispheric glioma, H3 G34-mutant; pediatric diffuse high-grade glioma, *H3* wild-types and *IDH* wild-type; and infant-type hemispheric glioma, in addition to other high-grade glial entities.
[g] See Principles of Radiation Therapy Management (PEDCNS-D).
[h] See Principles of Systemic Therapy (PEDCNS-E).

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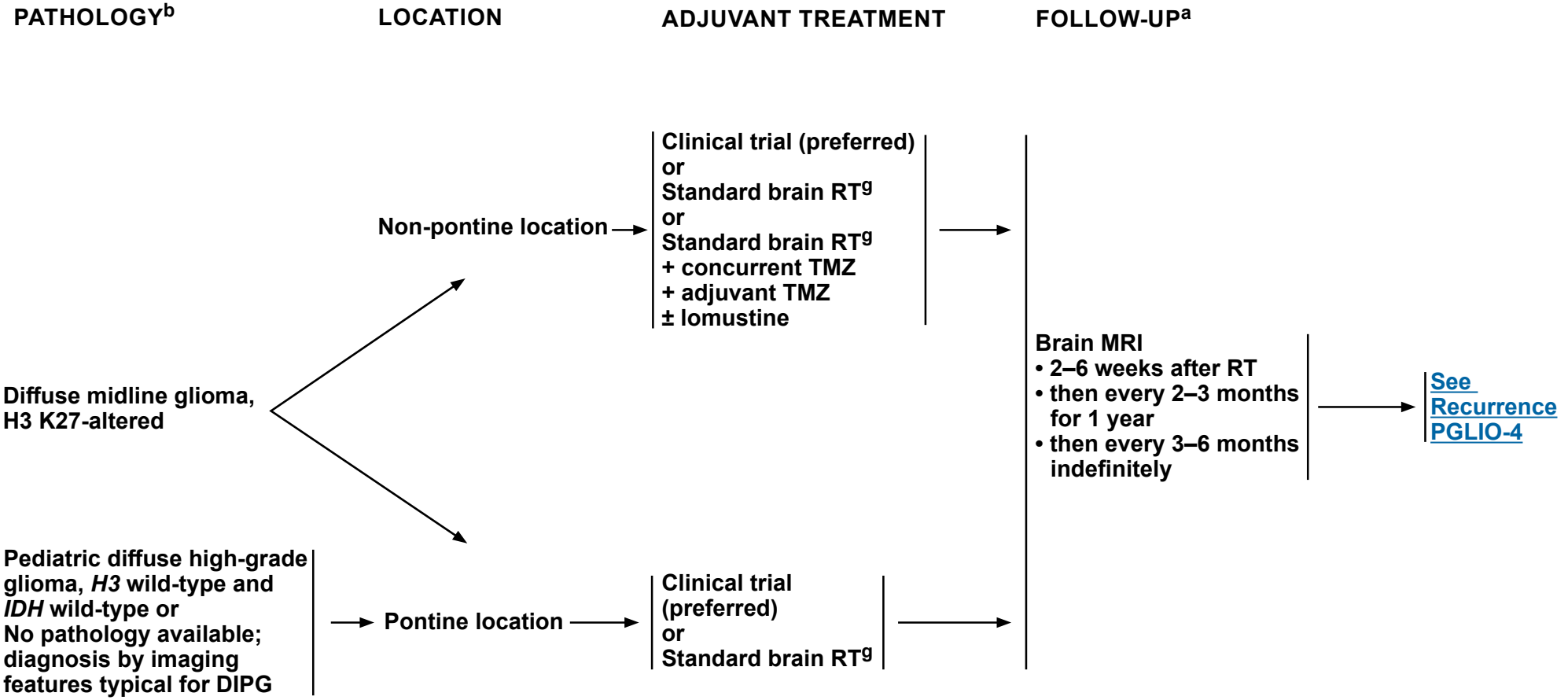

[a] See Principles of Brain Tumor Imaging (PEDCNS-A).
[b] See Principles of Brain Tumor Pathology (PEDCNS-B).
[g] See Principles of Radiation Therapy Management (PEDCNS-D).

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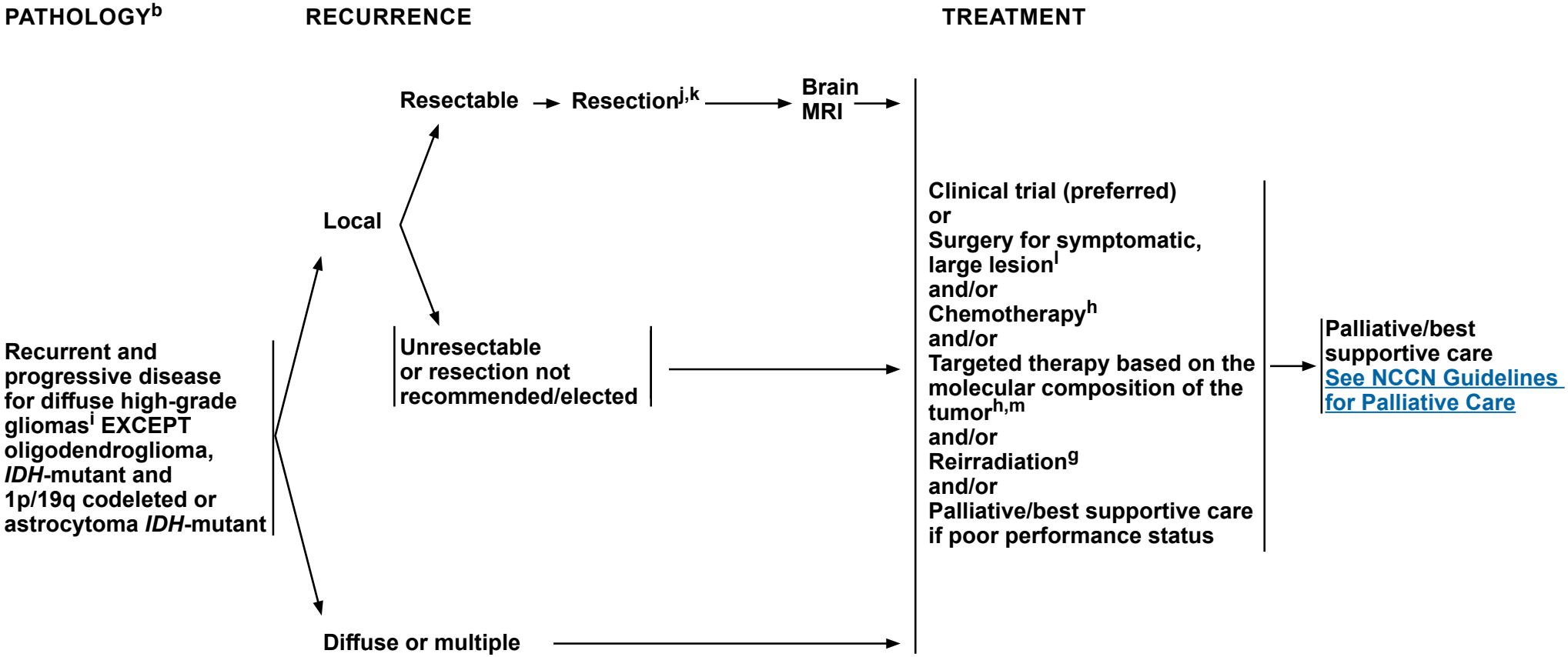

[b] See Principles of Brain Tumor Pathology (PEDCNS-B).
[g] See Principles of Radiation Therapy Management (PEDCNS-D).
[h] See Principles of Systemic Therapy (PEDCNS-E).
[i] Diagnoses include diffuse hemispheric glioma, H3 G34-mutant; pediatric diffuse high-grade glioma, *H3* wild-types and *IDH* wild-type; and infant-type hemispheric glioma; diffuse midline glioma, H3 K27-altered, in addition to other high-grade glial entities.
[j] See Principles of Surgery PEDCNS-C.
[k] Consider enrollment in phase 0 or preoperative clinical trials before resection.
[l] Re-resection at the time of recurrence may improve outcomes. As in adult patients with diffuse high-grade glioma, tumor involvement in specific critical brain areas and poor KPS score may be associated with unfavorable re-resection outcomes.
[m] For high tumor mutational burden (TMB) or personal or family history of cMMRD, consider checkpoint blockade; RAF and MEK inhibition for tumors with *BRAF* V600E mutation, and TRK inhibitors for tumors with *NTRK* gene fusion are recommended.

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PRINCIPLES OF BRAIN AND SPINE TUMOR IMAGING[a]

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. Below is a list of imaging modalities available and used in neuro-oncology to make treatment decisions.

MRI[1-4] of the Brain and/or Spine (entire neural axis) (with and without IV contrast)

- **Benefits: excellent soft tissue contrast and depiction of neoplasms through a combination of standard, universally available pulse sequences; typically infiltrative growth pattern; higher grade components commonly enhance and demonstrate restricted diffusion; no ionizing radiation**
- **Limitations: relatively long examinations; sensitive to patient motion so younger children generally require deep sedation/anesthesia; metal from surgery and implants cause artifact; some implants are unsafe in MRI environment**
- **Basic MRI sequences of the brain should include T1-weighted images before contrast, T1-weighted images in two planes after contrast (one of which would ideally be acquired as a 3D sequence), T2-weighted, T2-FLAIR, and diffusion-weighted imaging (DWI) and gradient echo or susceptibility-weighted (blood-sensitive) imaging.**
  - **These should be utilized for preliminary diagnostic evaluation and immediate postoperative follow-up (ideally within 24–48 hours post-op, if clinically feasible) to evaluate disease burden (measurable and non-measurable disease) on initial exam and extent of resection on immediate postoperative scan.**
  - **2D acquisitions should be ≤4-mm slices; 3D acquisitions should be nearly isotropic.**
  - **Post-contrast 3D sequence can be obtained as either 3D T1-weighted gradient echo or turbo spin echo (TSE) acquisitions for planar reconstructions and/or volumetric analysis of tumors.**
- **Group II gadolinium-based contrast agents (GBCAs) are recommended for use given the potential of higher gadolinium retention with linear GBCAs.**
- **Basic MRI imaging of the spine should include post-contrast sagittal and axial T1-weighted images of the entire neural axis. Additional sequences such as heavily T2-weighted images and/or DWI may be helpful.**
  - **These should be utilized to evaluate for leptomeningeal spread of neoplasm.**
  - **Sagittal slices should be 3 mm and axial slices may be 3- to 4-mm slices.**
  - **Preoperative spine imaging should be performed at the time of brain imaging since many children require sedation to tolerate the exam.**
  - **Postoperative spine MRIs should be delayed to occur at least 10 days after surgery if evaluating for leptomeningeal spread of neoplasm to avoid confusion with blood byproducts.**
- **Follow-up studies of the brain and spine should be performed at intervals defined by the treatment algorithms. More frequent imaging may be necessary if indicated by the treating physician 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 if those techniques are available.**

[a] Some imaging modalities or techniques may not be available at all institutions.

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PRINCIPLES OF BRAIN AND SPINE TUMOR IMAGING[a]

CT of the Brain (with contrast or with and without contrast):
- Can be used for rapid assessment in the acute setting and for the evaluation of acute intracranial hemorrhage, ventriculomegaly, and shunt-related issues.
- Should be used in those patients in whom an MRI is contraindicated because of unsafe implants or foreign bodies.
- Benefits: shorter acquisition; generally no sedation is needed; ideal in acute or immediate postoperative setting; sensitive to acute blood and calcium
- Limitations: ionizing radiation; limited soft tissue contrast; metal causes artifact

MR Perfusion[5-7]: Measures cerebral blood volume and/or cerebral blood flow in neoplasms; choice of various techniques (dynamic susceptibility contrast-enhanced [DSC] vs. dynamic contrast-enhanced [DCE] vs. arterial spin labeling [ASL] perfusion) will depend upon user availability and preference
- May be helpful for grading neoplasms, assessing response to therapy, identifying malignant degeneration and pseudoprogression, distinguishing radiation necrosis from recurrent neoplasm, and choosing biopsy site
- Limitations: reliability degraded by adjacent metal, blood byproducts, air, and bone/soft tissue interface; other general limitations of MRI are as listed above

MR Spectroscopy[7,8]: Assess metabolites of neoplasms (choice of single voxel vs. multivoxel spectroscopy will depend on user preference and availability)
- May be helpful for grading neoplasms, assessing response to therapy, identifying malignant degeneration and pseudoprogression, distinguishing radiation necrosis from recurrent neoplasm, and choosing biopsy site
- Limitations: complex acquisition; long acquisitions; nonstandard acquisition and post-processing; reliability degraded by adjacent metal, blood byproducts, and bone/soft tissue/air interfaces

Brain PET Studies: Assess brain tissue metabolism with radiopharmaceutical
- May be useful in differentiating between neoplasm and radiation necrosis, tumor grading, or identifying more aggressive focus for biopsy
- Limitations: spatial resolution; availability of radioisotopes; additional radiation exposure

Supplemental Imaging for Preoperative Planning:
- Isotropic volumetric MRI 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 (DTI) may also be used to localize major white matter tracts underlying the eloquent cortex that could also compromise vital functions if injured during surgery

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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[1]): 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.**

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PRINCIPLES OF BRAIN TUMOR PATHOLOGY

Molecular Characterization

- **Pediatric diffuse high-grade gliomas comprise a rare, but biologically diverse group of tumors. In adults, molecular workup has remained relatively simple, with focus on distinguishing *IDH*-mutant from *IDH*-wild-type gliomas. However, in the majority of pediatric tumors, there exists a high degree of histologic overlap and non-specificity of histologic features amongst the numerous recognized pathologic entities, and underlying molecular alterations in pediatric gliomas are distinct from those seen in adults. This 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[2-7] (See Table 1 PEDCNS-B 3 of 4).**
  - **While targeted therapies are still limited, clinical trial stratification is becoming increasingly dependent on molecular characterization.**
- **In light of the 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:**
  - **Copy number and fusion detection:**
    - **NGS with fusion detection (*ROS1*, *MET*, *NTRK1/2/3*, *ALK*, *FGFR1/2/3*)**
    - **RNA sequencing**
    - **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.[8,9]**

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PRINCIPLES OF BRAIN TUMOR PATHOLOGY

Table 1[a,6,7]

Molecular Alterations of Significance in Pediatric Gliomas	Molecular Alterations Consistent with "High Grade" in Pediatric Diffuse Gliomas
• *IDH1/2* mutations with or without 1p/19q co-deletion (adult type gliomas) • H3 K27Me3 loss (epigenetic loss of trimethylation at this site) • *H3-3A K28M* mutation (historic synonyms H3.3 K27M, H3F3A p.K28M) • *H3C2* p.K28M mutation (historic synonyms H3.1 K27M and HIST1H3B K27M) • *H3C3 p.K28M* mutation (historic synonym HIST1H3C K27M) • *H3 G34* mutation • *MYB* fusion • *MYBL1* fusion • *BRAF* V600E mutation • *BRAF* fusion • *BCOR* internal tandem duplication • *EGFR* mutations • *FGFR1* TKD-duplicated • *FGFR1* mutation • *FGFR1* fusion • *FGFR2* fusion • *NTRK1/2/3* fusion • *ALK* fusion • *ROS1* fusion • *MET* fusion • Other MAPK pathway alterations	• Homozygous deletion of *CDKN2A/2B* • *TP53* mutation • Amplification of *PDGFRA*, *EGFR*, *MET*, or *MYCN* • Complex karyotype • H3 K27Me3 loss by *IHC/H3* K27M mutation by sequencing–informs a grade IV neoplasm in appropriate context

[a] Human gene nomenclature evolves over time. For a current list of gene nomenclature, please refer to the HGNC database, Human Genome Organization (HUGO) Gene Nomenclature Committee site: https://www.genenames.org/

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PRINCIPLES OF BRAIN TUMOR PATHOLOGY
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PRINCIPLES OF SURGERY

Preoperative Assessment

- Labs, imaging, multidisciplinary consult
- Treat emergent situations prior to further investigative studies or interventions
- Consider medical management to treat focal neurologic deficits, seizure, and pain (ie, dexamethasone, anti-epileptics, acetaminophen)
- Avoid medications that may alter the patient's neurologic examination or increase surgical risks (eg, narcotics)
- Patients should undergo neuro-axis imaging if clinically indicated.
- Consider advanced imaging in cases where patients may benefit from it
- Consider appropriate ancillary testing
- Outside of emergent clinical presentations, multidisciplinary case discussion should be utilized for treatment planning and optimization of patient care. Treatment decision planning should include radiation oncology, neurosurgery, radiology, and oncology/neuro-oncology.
- Consider physical therapy/occupational therapy and sleep and swallow assessments to assist with comorbidity management.
- Consider referral to a child life social worker for family/patient support

Surgical Procedure

- Alleviate symptoms related to increased intracranial pressure or tumor mass effect, increase survival, and decrease corticosteroid dose requirements.
- Obtain adequate and optimal tissue for a pathologic diagnosis and molecular genetic characterization.
- In pediatric diffuse high-grade gliomas, a small number of prospective and retrospective studies have demonstrated an association between greater extent of resection and improved overall survival and progression-free survival (PFS).
- Nearly all diffuse high-grade gliomas recur. Re-resection at the time of recurrence may improve outcomes. As in adult patients with diffuse high-grade gliomas, tumor involvement in specific critical brain areas and poor Karnofsky Performance Status (KPS) score may be associated with unfavorable re-resection outcomes.

Postoperative Management

- Monitor for signs and symptoms of increased intracranial pressure
- Monitor sodium and serum osmolarity
- Avoid fluctuations in blood pressure – hypo or hypertension
- Consider the following:
  - Seizure prophylaxis[1]
  - Antibiotics for infection prophylaxis
  - Deep vein thrombosis (DVT) prophylaxis

[1] Greenhalgh J, Weston J, Dendar Y, et al. Antiepileptic drugs as prophylaxis for postcraniotomy seizures. Cochrane Database Syst Rev 2020;4:CD007286.

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF RADIATION THERAPY MANAGEMENT

Pediatric Diffuse High-Grade Glioma (except diffuse midline glioma and diffuse intrinsic pontine glioma)

- **Adjuvant (Dose, timing)**
  - **50.4–54 Gy with a cone-down to 59.4 to 60 Gy in 1.8 to 2.0 Gy fractions for newly diagnosed disease.**
    - **◊ Simultaneous integrated boost (SIB) techniques can be considered, to deliver 1.8 and 2.0 Gy x 30 fractions concurrently to 54 and 60 Gy.**
  - **Initiation of RT is recommended whenever a patient has recovered from surgery and within 4–8 weeks after surgical resection.**

- **Re-irradiation (Dose, timing)**
  - **The majority of data are from adult HGG studies of recurrent glioblastoma multiforme (GBM)**
  - **Studies have suggested improvements in PFS, but limited overall survival gains**
  - **Multiple dosing schedules have been reported for re-irradiation and should be performed with a conformal technique**
    - **◊ 30–35 Gy in 5–15 fractions (eg, 30 Gy in 5 fractions, or 35 Gy in 10 fractions)**
    - **◊ 54–60 Gy in 30 fractions (long interval from prior RT)**
    - **◊ Stereotactic radiosurgery (SRS) with a median marginal dose of 16 Gy**

- **Principles of Radiation Therapy (Include simulation, treatment planning, normal tissue RT constraints)**
  - **Child life specialists, audio and video distraction techniques, and other pediatric-friendly interventions can improve pediatric tolerance of RT without anesthesia.**
  - **Proton therapy may be considered for patients with better prognoses (eg, *IDH1*-mutated tumors, 1p/19q-codeleted, younger age).**
  - **In most instances intensity-modulated RT (IMRT) allows reduction of risk or magnitude of side effects from treatment.**
  - **Patients should be placed supine with immobilization. CT simulation for treatment planning should include ≤0.25 cm slice thickness. Volumetric CT simulation for treatment planning is recommended.**
  - **Image-guided RT (IGRT) may be used to ensure daily setup accuracy.**
  - **Tumor volumes are best defined using pre- and postoperative MRI imaging using both post-contrast T1 volumetric and T2/FLAIR sequences to define GTV. Volumetric T2/FLAIR and DTI (for white matter tracts) are optional but can be helpful sequences to define GTV.**
  - **GTV1 includes the enhancing and non-enhancing areas of tumor both pre- and post-resection. GTV1 should take into account changes in brain anatomy post-resection and surgical tracts for deep tumors may be excluded if not involved pre-surgery.**
  - **GTV2 will include residual tumor post-resection. It will typically include the resection bed. For no residual tumor GTV1 = GTV2.**
  - **CTV1 is an isotropic 1- to 2-cm expansion of GTV1, with the larger margins along white matter tracts.**
  - **CTV2 is an isotropic expansion of 0.5–1 cm on GTV2.**
  - **PTV1/2 is an isotropic expansion that is institution-specific, but typically 3–5 mm, and dependent on frequency and modality of imaging, and size of the targets. PTV definition in proton therapy may be beam-specific or replaced by robustness testing.**
  - **PTV1 = 50.4–54 Gy**
  - **PTV2 = 59.4–60 Gy**
  - **Maximal PTV coverage should be balanced against normal tissue tolerances** **(See PEDCNS-D 3 of 3)****.**
  - **Accepted normal tissue constraints should be used, and although the prognosis of these patients often is poor, ALARA (as low as reasonably achievable) principles still applies to the lenses, retina, pituitary gland/hypothalamus, cochlea, lacrimal glands, hippocampi, temporal lobes, spinal cord, and uninvolved brain.**

Note: All recommendations are category 2A unless otherwise indicated.
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.

Continued

PRINCIPLES OF RADIATION THERAPY MANAGEMENT

Diffuse Midline Glioma (DMG)/Diffuse Intrinsic Pontine Glioma (DIPG)

- **Initiation of RT should be considered as soon as possible after diagnosis, given the highly effective nature of this modality for symptom management.**
- **Recommend using IMRT; 3D conformal RT is an acceptable option.**
- **54 Gy in 1.8 Gy fractions (30 total fractions) is recommended; higher doses are now considered non-standard.**
- **An option of hypofractionated RT (39 Gy in 3 Gy fractions [13 total fractions]) is emerging as an alternative treatment to standard fractionation, although data are limited and studies are ongoing to assess the benefit/safety of this approach. This is also being tested in the re-irradiation setting.**
- **Palliative re-irradiation of 20–30 Gy has been shown to alleviate symptoms related to tumor progression.**
- **Tumor volumes**
  - **Gross tumor volume (GTV): Defined as the tumor best demonstrated on MRI. The MRI sequence that best defines the extent of disease should be used. The T2 sequence is usually the most appropriate image to use for GTV definition for these patients.**
  - **Clinical target volume (CTV): Shall include the GTV with a 1-cm margin in all directions, respecting anatomic barriers to spread.**
  - **Planning target volume (PTV): Shall include the CTV with a 0.3–0.5 cm margin dependent on immobilization techniques. Exact margins will be left up to the discretion of the treating radiation oncologist and may not be uniform in all dimensions. The clinician should consider the effects of the beam penumbra when designing the treatment apertures.**

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Continue

PRINCIPLES OF RADIATION THERAPY MANAGEMENT
NORMAL TISSUE CONSTRAINTS[a]

Organs at Risk (OAR)[b]	Constraints
Cochlea	D50% ≤35 Gy
Optic globes	D50% ≤10 Gy D10% ≤35 Gy
Optic nerves and chiasm	D50% ≤54 Gy D10% ≤56 Gy
Spinal cord	D50% ≤26 Gy D10% ≤57 Gy
Brainstem	• Cannot exceed 60 Gy max ▸ For 60 Gy <0.3 cc, mean dose <56.1 Gy • If protons are used for a non-brainstem primary in patient with good prognosis: ▸ Max brainstem dose <56.6 Gy ▸ D50% <52.4 Gy
Pituitary gland/hypothalamus	Mean dose <25 Gy
Hippocampi	Mean <30 Gy
Temporal lobes	No more than 1 cc exceeding 60 Gy, maximum dose of 65 Gy
Uninvolved brain (Brain – PTV)	No more than 1% or 1 cc of the tissue outside of either PTV receiving more than 110% of the prescribed dose.
Lenses	As low as possible

[a] The noted normal tissue constraints are per COG ACNS0831 and ARAR0331.
[b] In general all normal tissues should be as low as reasonably achievable even if the constraint is achieved (ALARA principle).

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PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(PARTICIPATION IN A CLINICAL TRIAL IS STRONGLY ENCOURAGED)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant Therapy	RT + concurrent TMZ + adjuvant TMZ + lomustine[1]	RT + concurrent TMZ + adjuvant TMZ[2] Age <3 years: • Chemotherapy only ▸ Cyclophosphamide/vincristine/cisplatin/etoposide[3] ▸ Vincristine/carboplatin/TMZ[4] • Targeted therapy only ▸ Targeted therapy including, but not limited to the following: – If *BRAF* V600E mutated: ▪ Dabrafenib/trametinib[5] ▪ Vemurafenib[6] – If *TRK* fusion-positive: ▪ Larotrectinib[7] ▪ Entrectinib[8] – If hypermutant tumor: ▪ Nivolumab[9,10] ▪ Pembrolizumab[11]	RT ± concurrent TMZ[1,2] + adjuvant targeted therapy including, but not limited to the following: If *BRAF* V600E mutated: • Dabrafenib/trametinib[5] • Vemurafenib[6] If *TRK* fusion-positive: • Larotrectinib[7] • Entrectinib[8] If hypermutant tumor: • Nivolumab[9,10] • Pembrolizumab[11]
Recurrent or Progressive Disease	Targeted therapy including, but not limited to the following: If *BRAF* V600E mutated: • Dabrafenib/trametinib[5] • Vemurafenib[6] If *TRK*-fusion positive: • Larotrectinib[7] • Entrectinib[8] If hypermutant tumor: • Nivolumab[9,10] • Pembrolizumab[11]	Reirradiation if feasible	For palliation: • Oral etoposide[12] • Bevacizumab[13,c] • Nitrosoureas (lomustine or carmustine)[1]

[a] Regimens and recommendations on this page are for those patients who elect not to participate in clinical trials.
[b] Monitor (labs and/or imaging) as clinically indicated.
[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

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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.

Continued

PRINCIPLES OF SYSTEMIC THERAPY
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ABBREVIATIONS

ALARA	as low as reasonably achievable
APC	adenomatous polyposis coli
ASL	arterial spin labeling
cMMRD	constitutional mismatch repair deficiency
CNS	central nervous system
COG	Children's Oncology Group
CT	computed tomography
CTV	clinical target volume
DCE	dynamic contrast-enhanced
DIPG	diffuse intrinsic pontine glioma
DMG	diffuse midline glioma
DNA	deoxyribonucleic acid
DSC	dynamic susceptibility contrast-enhanced
DTI	diffusion tensor imaging
DVT	deep vein thrombosis
DWI	diffusion-weighted imaging
FAP	familial adenomatous polyposis
FDA	U.S. Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GBCA	gadolinium-based contrast agent
GBM	glioblastoma multiforme
GTV	gross tumor volume
H&E	hematoxylin and eosin
HGG	High grade glioma
IDH	isocitrate dehydrogenase
IGRT	image-guided radiation therapy
IHC	immunohistochemistry
IMRT	intensity-modulated radiation therapy
IV	intravenous
KPS	Karnofsky Performance Status
MAPK	mitogen-activated protein kinase
MMR	mismatch repair
MR	magnetic resonance
MRI	magnetic resonance imaging
NF1	neurofibromatosis type 1
NGS	next-generation sequencing
OAR	organ at risk
PET	positron emission tomography
PFS	progression-free survival
PTV	planning target volume
RNA	ribonucleic acid
RT	radiation therapy
SIB	simultaneous integrated boost
SRS	stereotactic radiosurgery
TKD	tyrosine kinase domain
TMB	tumor mutational burden
TMZ	temozolomide
TRK	tropomyosin receptor kinase
TSE	turbo spin echo
WHO	World Health Organization

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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Pediatric Central Nervous System Cancers

Discussion

This discussion corresponds to the NCCN Guidelines for Pediatric Central Nervous System Cancers. Last updated on October 31, 2022.

Table of Contents

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.[2] They account for 26% of all pediatric tumors and are the leading cause of cancer-related death in children.[3] More than 4000 brain and spinal cord tumors are diagnosed each year in children and teens, and the incidence rate has remained stagnant in recent years.[2] According to the Central Brain Tumor Registry of the United States (CBTRUS) Statistical Report, the incidence rate of primary CNS tumors in children younger than 14 years was 5.83 per 100,000 population between 2013 and 2017.[4] The most common malignant pediatric CNS tumors are gliomas, embryonal tumors consisting of predominately medulloblastomas, and germ cell tumors.[4]

Literature Search Criteria and Guidelines Update Methodology

Prior to the publication of the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Pediatric Central Nervous System Cancers, an electronic search of the PubMed database was performed to obtain key literature in the field of neuro-oncology, using the following search terms: pediatric diffuse high-grade glioma. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[5]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Guidelines; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.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 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. 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 the *Principles of Systemic Therapy*; 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 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (WHO CNS5).[1,6] 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 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 four 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).[6]

The NCCN Guidelines for Pediatric CNS Cancers currently include recommendations for the management of the four types of pediatric-type diffuse high-grade gliomas recognized in WHO CNS5[6]:

- diffuse hemispheric glioma, H3 G34-mutant
- diffuse pediatric-type high-grade glioma, *H3*-wildtypes and *IDH*-wildtype
- infant-type hemispheric glioma
- diffuse midline glioma (DMG), H3 K27-altered

The first three 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 wildtype 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*. While not a new entity, the nomenclature was changed from DMG, H3 K27-mutant to DMG, H3 K27-altered in order to include subtypes with a different mechanism for the loss of H3K27 trimethylation (eg, EZHIP protein overexpression).[1,6]

Introduction

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 younger than 19 years.[2,7] Although incidence rates generally decrease with age from 0 to 19 years, they are highest for age groups 0 to 4 years (6.18 per 100,000 population) and 15 to 19 years (7.09 per 100,000 population).[4] The prognosis for these highly aggressive tumors is generally poor with 5-year survival rates of less than 20% despite the use of combined modality therapies of surgery, RT, and systemic therapy.[7] Prognosis and survival rates depend on multiple factors including the age at presentation, tumor location, sex, extent of resection, histological subtype and genomic profile.[8] While diagnosis is more common in females, males typically have higher mortality rates from CNS tumors.[4]

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 (NF-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.[9-11] 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] Estimated risk is higher for younger children, and the estimated 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.[4,8,9,13]

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 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.[2] 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.[2]

Treatment Overview

Treatment for 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.[2] The main treatment paradigm includes surgery followed by systemic therapy with or without radiation therapy. The goals of surgery include the safe reduction of tumor-associated mass effect and obtaining adequate tissue for histological 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 it is reasonable to omit RT in children younger than 3 years.[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. Below is a list of imaging modalities used in neuro-oncology to make treatment decisions.

MRI of the Brain and/or Spine

Conventional MRI of the entire neural axis (with and without intravenous [IV] contrast) is the imaging modality of choice for the evaluation of pediatric diffuse high-grade gliomas.[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 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 or spread through the corpus callosum into the other hemisphere.[8] They may demonstrate mass effect on surrounding structures, hemorrhage, increased perfusion, vasogenic edema, and a variable degree of contrast enhancement.[17] Higher grade components commonly enhance and demonstrate restricted diffusion, which is a key feature that reflects the high-grade nature of the tumor.[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 to 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 (FLAIR) 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.[17] Therefore, basic MRI sequences of the brain should include T1-weighted images before contrast, T1-weighted images in two planes after contrast (one of which would ideally be acquired as a 3D sequence), T2-weighted, T2-FLAIR, and diffusion-weighted imaging (DWI) and gradient echo or susceptibility-weighted (blood-sensitive) imaging. These images should be utilized 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 non-measurable disease) on initial examination and extent of resection on immediate postoperative scan.[18-21]

Basic MRI imaging of the spine should include post-contrast 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 utilized 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.

Follow-up studies of the brain and spine should be performed at intervals defined by the treatment algorithms (see *NCCN Recommendations* below). 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, pseudo-progression, 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 (CBV) 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.[22-24] Limitations of MR perfusion include the degradation of reliability by adjacent metal, blood by-products, air, and bone/soft tissue interface; and other general limitations of MRI as listed above. Generally, most high-grade gliomas show higher perfusion (increased CBV and/or CBF) than low-grade gliomas.[17,25]

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 upon user availability and preference. DSC perfusion is the most commonly used technique. Due to the need for power injectors and large-bore IV access, DSC is challenging to perform on infants but is feasible in young children.[17] Other limitations include calcification and hemorrhage-induced susceptibility within the tumor and contrast leakage due to breakdown of the blood-brain barrier.[17] DCE can be used as an alternative or complementary technique to DSC, although few studies have assessed its use in children.[26,27] 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[28]; 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 post-processing; and post-processing 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.[2] 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 anatomical 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 co-registering 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 (DTI) 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 Pathology

There are major molecular and genetic differences between pediatric and adult CNS tumors, which is established in WHO CNS5.[1,6,17] 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.[1,6] The NCCN Guidelines describe guiding principles for the diagnosis of pediatric CNS tumors according to the parameters of WHO CNS5.[1,6] A general workflow for processing of tissue and tumor characterization using histologic, immunohistochemical (IHC), and molecular data is presented in the *Principles of Pathology* section of the algorithm. 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.[6] 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 *Commonly Used IHC Markers for High-Grade Glial Tumors*). 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* below).

Molecular Characterization

Pediatric diffuse high-grade gliomas comprise a biologically diverse group of tumors. There is a high degree of histologic overlap and non-specificity of histologic features amongst 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 in the algorithm for molecular alterations of significance in pediatric gliomas.

In light of 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. Broad molecular testing should include detection of copy number and gene fusions via next-generation sequencing (NGS) with fusion detection (*ROS1, MET, NTRK1/2/3, ALK, 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.[43,44]

Limited Tissue Sample/Specimen

In cases where there is limited tissue available for processing, care should be taken to prioritize obtaining the following tests: hematoxylin and eosin (H&E) 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 non-pontine 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. The histology and location of the tumor, as well as the extent of possible resection, are significant prognostic factors which influence the decision for surgical management.[45] Surgical resection is not feasible for patients with DMG of the pons (previously called diffuse intrinsic pontine glioma [DIPG]) 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 prior to further investigative studies or interventions. Consider medical management to treat focal neurologic deficits, seizure, and pain (ie, dexamethasone, anti-epileptics, 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 utilized 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 (PFS) in patients with pediatric diffuse high-grade gliomas.[46-53] In the HIT-GBM study of 85 pediatric patients with malignant non-pontine gliomas, gross total resection (GTR) was the strongest predictor of OS and event-free survival (EFS).[52] 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 to historical controls (17%; *P* = .003).[51]

Nearly all diffuse high-grade gliomas recur. Re-resection at the time of recurrence may improve outcomes, although evidence varies widely.[48,54] 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 re-resection outcomes.[54]

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 (DVT) can be considered.[55]

Principles of Radiation Therapy Management

RT plays an essential role in the adjuvant treatment of patients with pediatric diffuse high-grade gliomas who are aged 3 years and older.[56,57] Out of concern for long-term complications with brain development, it is reasonable to omit RT in patients younger than 3 years.[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 *Principles of Radiation Therapy Management* in the algorithm for specific information.

Following surgery, patients aged 3 years and older with pediatric diffuse high-grade gliomas (except for those with pontine DMG) are treated with RT combined with concurrent and/or adjuvant systemic therapy.[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 (ALARA) 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 the *Principles of Radiation Therapy Management* in the algorithm. 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.[58-62]

The majority of studies on re-irradiation are from adult high-grade glioma studies of recurrent glioblastoma multiforme (GBM) and have suggested improvements in PFS, but limited OS gains.[54,63-66] Multiple dosing schedules have been reported for re-irradiation, including stereotactic radiosurgery (SRS).[54,64-67] One of the few pediatric studies conducted was a retrospective cohort study of 40 children with recurrent supratentorial high-grade glioma who had received at least one course of RT.[68] Of the 40 children, 14 received re-irradiation and had improved median survival from the time of first disease progression when compared with the 26 patients who were not offered re-irradiation (9.4 vs. 3.8 months; P =.005), suggesting that re-irradiation 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.[16] Dose-escalated RT and concurrent or adjuvant systemic therapy have produced disappointing results in patients with pontine DMG, and are therefore not recommended.[16,69-73] The panel recommends using IMRT, but 3D conformal RT is an also acceptable option.[15] Hypofractionated RT has been evaluated as an alternative to standard fractionation in the first-line and re-irradiation 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 following initial RT have poor prognosis and limited treatment options. Palliative re-irradiation 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 aged 3 years 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 following maximal surgical resection.[56] The 3-year EFS and OS were significantly improved compared to 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).[56,57] The addition of lomustine also resulted in significantly better EFS and OS in participants without gross-total resection (P = .019 and P =.00085, respectively). Although the addition of lomustine resulted in modest outcome benefits compared to TMZ alone, survival rates remained low. Therefore, use of this regimen without lomustine is also an option for adjuvant therapy.[57]

Chemotherapy

It is reasonable to avoid RT in patients younger than 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.[82,83] A Pediatric Oncology Group study showed that high-grade gliomas in children younger than 3 years are sensitive to chemotherapy.[82] In this study, 18 children younger than 3 years with malignant gliomas were treated with postoperative chemotherapy with cyclophosphamide and vincristine for two 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 younger than 6 years with newly-diagnosed high-grade gliomas were treated with four cycles of

induction chemotherapy with vincristine, carboplatin, and TMZ followed by myeloablative chemotherapy and stem cell rescue.[83] The 5-year EFS and OS rates were 25% and 36%, respectively. Children younger than 3 years had improved 5-year EFS and OS (44% and 63%, respectively) compared to older children (31% and 38% for children aged 36–71 months and 0% and 13% for children 72 months and older).

Targeted Therapy

Recent advances in molecular technology have enabled the development of molecular agents capable of targeting the biological drivers of pediatric diffuse high-grade gliomas.[84] 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 below.

BRAF V600E Mutated Tumor

The *BRAF* V600E point mutation, which results in constitutive activation of the MEK/ERK pathway, is detected in approximately 10% to 15% of pediatric high-grade gliomas.[85-87] Many tumors that initially respond to BRAF inhibition eventually develop resistance due to reactivation of the MAPK pathway.[88,89] Combined therapy targeting BRAF and downstream MEK has shown success in several clinical trials in adults with cancer.[88-90] However, data on this regimen in the pediatric population are limited to small case series and reports.[91,92] In one such case series, three pediatric patients with *BRAF* V600E mutated high-grade gliomas exhibited clinical responses to combined BRAF/MEK blockade using dabrafenib and trametinib.[91] 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 two 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.[84,93,94] 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.[84] 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 anti-tumor activity and manageable toxicities, the phase II part of the trial is currently ongoing (NCT01748149).

TRK-Fusion Positive Tumor

Gene fusions involving *NTRK1*, *NTRK2*, or *NTRK3* encode for TRK fusion proteins (TRKA, TRKB, TRKC) that 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.[99] In patients with TRK-fusion positive tumors, the objective response rate (ORR) was 93% compared to 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 and recruiting patients (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.[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 four 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 (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, two siblings with recurrent hypermutant pediatric diffuse high-grade gliomas were treated with the anti-programmed death-1 (PD-1) inhibitor nivolumab, which resulted in significant clinical and radiologic responses in both children following several months of treatment.[101] 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.[103]

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.[101] Patients with recurrent or progressive disease have a median OS of less than 6 months, and no effective therapies currently exist.[101] 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. This includes but is not limited to the following: checkpoint blockade for high tumor mutational burden (TMB) 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. See *Targeted Therapy* above for more information about these therapy options.

Patients with poor performance status may receive palliative chemotherapy with oral etoposide,[104] bevacizumab (or an U.S. Food and Drug Administration [FDA]-approved biosimilar),[105] or single-agent nitrosoureas (lomustine or carmustine).[56] 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.[104] Three out of the four patients with medulloblastoma exhibited a partial response and two of the five patients with ependymoma responded (one with a complete response and one with a partial response), demonstrating activity for etoposide in recurrent brain tumors. Toxicity was manageable with only one hospitalization for neutropenic fever and two 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 non-pontine high-grade gliomas.[105] Median EFS did not differ significantly between the treatment groups and the addition of bevacizumab did not reduce the risk of death. Since adding BEV to RT+TMZ did not improve EFS in pediatric

patients with newly diagnosed high-grade gliomas, 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. 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.[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. 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 aged 3 years and older 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).[56,57] Standard brain RT alone and standard brain RT with concurrent TMZ and adjuvant targeted therapy based upon the molecular composition of the tumor are also options in this setting. Patients younger than 3 years can receive systemic chemotherapy with either cyclophosphamide, vincristine, cisplatin, and etoposide[82] or vincristine, carboplatin, and TMZ[83] to delay the need for RT or with adjuvant targeted therapy based upon the molecular composition of the tumor. See *Targeted Therapy* above for more information on specific recommendations.

Patients with non-pontine 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 with recurrent or progressive disease should be followed closely with brain MRI scans starting at 2 to 6 weeks post-irradiation, then every 2 to 3 months for 1 year, then every 3 to 6 months indefinitely after the completion of

treatment for 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 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. 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. Re-resection 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 re-resection outcomes.

Preferred systemic therapy options for recurrent disease include but are not limited to dabrafenib/trametinib[91] or vemurafenib[84] for *BRAF* V600E-mutated tumors, larotrectinib[99] or entrectinib[98] for *TRK*-fusion positive tumors, and nivolumab[101,102] or pembrolizumab[103] for hypermutant tumors. Re-irradiation, 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. Pediatric diffuse high-grade gliomas are highly aggressive tumors with poor prognoses. 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. Clinical trial participation is recommended 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 radiation therapy. 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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