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Guideline

Guidelines for the Diagnosis and Treatment of Pediatric Low-Grade Gliomas in China (2024)

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Abstract

Pediatric low-grade gliomas (pLGGs) exhibit distinct biological and clinical characteristics compared to adult gliomas, and their treatment strategies differ substantially from those used in adults. Since the release of the 2016 World Health Organization Classification of Tumors of the Central Nervous System and its subsequent updates, significant advances have been made in understanding the diagnosis and management of pLGGs. Therefore, updated guidelines tailored to current clinical practice are needed. In this document, we present the consensus guidelines for the diagnosis and management of pLGGs in China. The recommendations were developed through a comprehensive review of relevant domestic and international guidelines and literature, combined with expert consensus meetings and external peer review to ensure rigorous validation. The guideline integrates the levels of evidence from published studies, expert consensus, and practical clinical considerations. All recommendations were reviewed and approved by a multidisciplinary panel of experts from the Pediatric Neurosurgery Group. This guideline is intended to serve as guidance for healthcare professionals involved in pediatric neuro-oncology, as well as for patients, caregivers, and other healthcare providers participating in the management of pLGGs.

Introduction

Gliomas are the most common central nervous system (CNS) tumors in children; among these, low-grade gliomas are the most prevalent subtype, accounting for approximately 25% to 40% of all pediatric CNS tumors.[1] Currently, there is a lack of comprehensive epidemiological survey reports that specifically focus on children in China. However, based on estimates derived from various domestic datasets, the annual incidence rate of pediatric CNS tumors is estimated to range from 2.10 to 2.59 per 100,000 population. Within this category, the annual incidence rate of pediatric low-grade gliomas (pLGGs) is estimated to be approximately 0.53 to 0.65 per 100,000 population.[2] Unlike adults, the nervous system in children is still developing; consequently, gliomas occurring in children exhibit unique molecular pathological characteristics and underlying mechanisms. Therefore, the 2021 World Health Organization (WHO) Classification of CNS Tumors specifically designated these entities as "Pediatric-type diffuse low-grade gliomas" and "Pediatric-type diffuse high-grade gliomas." Additionally, circumscribed gliomas and glioneuronal tumors, categories also included in the WHO classification, occur predominantly in children. These guidelines primarily address circumscribed gliomas, diffuse low-grade gliomas, and glioneuronal tumors, as defined in the 2021 WHO classification. Pediatric gliomas exhibit unique characteristics regarding their common sites of occurrence, clinical symptoms, molecular pathological mechanisms, clinical course, and imaging features. Consequently, the corresponding treatment strategies differ from those employed for adult gliomas.

Keywords: Pediatric low-grade glioma; Gliomas, Guideline; Consensus; Recommendation; Diagnosis; Treatment; Pediatric Neurosurgery Group.

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Table 1. GRADE system, quality, and strength of recommendation

Level of evidence	Specific description	Recommendation strength	Specific description
High	Future studies are highly unlikely to alter the credibility of the existing findings regarding efficacy	Strong	Clearly demonstrates that the benefits of the intervention outweigh its harms
Moderate	Future research may have a significant impact on the current assessment of efficacy, potentially altering the credibility of the evaluation results	Weak	The balance of benefits and harms is uncertain, or the benefits and harms are roughly equivalent
Low	Future research is highly likely to have a significant impact on existing assessments of efficacy, and there is a substantial possibility that it could alter the credibility of the assessment results		
Extremely low	Any assessment of efficacy is highly uncertain		

Furthermore, gliomas occurring in infants and toddlers are distinct from those found in children over the age of three. To standardize the diagnosis and treatment of pediatric gliomas, this guideline outlines the principles for imaging assessment, pathological diagnosis, surgery, radiotherapy, and systemic therapy of pLGGs, serving as a reference for healthcare professionals specializing in pediatric neuro-oncology. Recommendations within this guideline are formulated based on the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system, which classifies the quality of evidence and strength of recommendations (Table 1). These recommendations integrate the quality levels of the published literature, expert consensus, and practical clinical application. The recommendations were reviewed and approved by a multidisciplinary panel of 23 experts, and areas where evidence-based medicine remains insufficient require further validation and updates through future clinical trials.

Methods for guideline development

This guideline draws upon relevant domestic and international consensus statements and literature concerning pediatric gliomas and was finalized through a series of expert consensus meetings dedicated to the diagnosis and treatment of pediatric gliomas. The guidelines were primarily developed and formulated by a multidisciplinary panel of experts specializing in neurosurgery, neuropathology, neuroimaging, radiotherapy, and systemic therapy. This multidisciplinary expert panel was organized into two working groups, which proceeded through three distinct stages to draft and revise the guidelines' content, utilizing expert consensus meetings and external review processes for discussion and validation.

Stage 1

The Pediatric Neurosurgery Group of the Neurosurgery Branch of the Chinese Medical Association convened to discuss and determine the scope, breadth, and depth of the guidelines. Subsequently, the Editorial Committee for the Chinese Guidelines for the Diagnosis and Treatment of Pediatric Low-grade Gliomas (2024) was established, with specific responsibilities, including drafting, providing recommendations, and data collation, assigned to individual members.

Stage 2

A core working group for the guidelines was established to discuss, revise, and validate the initial draft. This process aimed to ensure that the guideline met the professional needs of physicians at various levels of practice, including the provision of specific explanations and instructions tailored for its application in primary care hospitals. The draft was finalized through an iterative process of internal review and discussion among editorial committee members.

Stage 3

An external expert review panel convened to critically appraise and vote on the guideline content that had been previously validated by the core working group.

All expert panel members involved in the development of this guideline declare that they have no conflicts of interest, nor was there any involvement of entities with financial or commercial interests in the subject matter. The development of this guideline was jointly funded by the National Key R&D Program and the National Natural Science Foundation of China.

Guideline contents

pLGGs encompass a diverse range of histopathological subtypes, with pilocytic astrocytoma being the most common one.[3–6] pLGGs predominantly occur in the hypothalamus, optic chiasm, and cerebellum. Among cases arising in the cerebral hemispheres, the temporal lobe is the most frequent site. Dysembryoplastic neuroepithelial tumors, which are frequently observed in children and often present with seizures, occur most commonly in the frontal lobe, followed by the parietal lobe.[3–6] pLGGs associated with genetic syndromes are relatively rare; examples include subependymal giant cell astrocytoma (SEGA) (WHO Grade I) occurring in conjunction with Tuberous Sclerosis Complex and optic pathway pilocytic astrocytoma seen in children with neurofibromatosis type 1 (NF1).

The median age of onset for pLGGs is 6–8 years.[7] Clinical symptoms typically correlate with the specific subtype and anatomical location; common presentations include visual impairment, visual field deficits, and cerebellar signs, such as ataxia. pLGGs in the cerebral hemispheres may manifest as seizures. Conversely, somatosensory and motor deficits are relatively uncommon, as are symptoms associated with elevated intracranial pressure. In cases co-occurring with other congenital syndromes, such as NF1, patients may exhibit associated cutaneous manifestations and comorbidities. Infants and toddlers may also present with rare clinical manifestations, such as diencephalic syndrome. The onset of pLGGs is typically insidious; with the exception of cerebral hemispheric pLGGs presenting with seizures, patients of-

ten initially seek medical attention from other departments because of minor visual disturbances or gastrointestinal symptoms, or the tumor may even remain asymptomatic for extended periods and be discovered incidentally.[7]

For pLGG cases not associated with NF1, surgical intervention constitutes the preferred primary mode of treatment.[6] The objectives of surgery are to achieve complete tumor resection or maximal cytoreduction, establish a definitive histopathological diagnosis, and identify potential molecular targets for therapeutic intervention. Adjuvant chemotherapy is administered in cases of postoperative residual tumor or disease progression; however, radiotherapy is generally not considered the first-line adjuvant treatment modality, as it has the potential to adversely affect neurological development and cognitive function in children.[3–6] In recent years, driven by the widespread adoption of genomic sequencing technologies, characteristic molecular targets associated with pLGGs have been progressively identified. Clinical trials have confirmed that targeted therapies directed against BRAF gene mutations in pLGGs demonstrate significant efficacy.[6] However, aspects such as the optimal duration of targeted therapy, how best to combine it with conventional chemotherapy, and the appropriate timing and sequence of combination treatments remain to be fully elucidated.[6,8]

Children with pLGGs generally have a favorable prognosis and prolonged survival, with five-year and ten-year overall survival rates exceeding 90% and 70%, respectively. However, precisely because these patients experience long postoperative survival—coupled with the fact that their tumors are often relatively insensitive to chemotherapy or radiotherapy, and these treatments carry adverse effects—long-term adjuvant therapy is associated with a high rate of morbidity; patients may be left with residual visual, sensory, or motor impairments resulting from either the tumor itself or the associated treatments.[3–6] Beyond postoperative neurological deficits, the impact of the tumor itself—as well as its associated treatments—on a child's psychological well-being, behavior, learning abilities, and even social integration represents a critical area requiring greater attention within the long-term postoperative management of pLGG patients. Currently, however, the assessment of tumor treatment response and progression remains largely confined to changes observed via imaging and neurological function.[6–8] Furthermore, the treatment response manifested on imaging may not necessarily correlate with changes in neurological function. Consequently, postoperative treatment assessment and long-term management of children with pLGGs continue to present numerous challenges.

I. Imaging assessment

(I) Imaging characteristics of pLGGs

Magnetic resonance imaging (MRI) is a crucial imaging modality for evaluating pLGGs. Routine T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), fluid-attenuated inversion recovery (FLAIR) sequences, and contrast-enhanced T1WI scans provide information regarding the tumor's location, size, presence of hemorrhage, necrosis, cystic changes, and extent of surrounding edema.[9–11] On MRI, pLGGs typically present as low signal intensity on T1WI and high signal intensity on T2WI and FLAIR sequences. Peritumoral edema is typically absent or mild; contrast-enhanced T1WI scans usually demonstrate no enhancement or only mild enhancement, although cystic components may be present. Certain subtypes, specifically pilocytic astrocytoma, pleomorphic xanthoastrocytoma, some diffuse cerebellar astrocytomas, and a minority of gangliogliomas, may exhibit significant contrast enhancement.[12]

Recommendation 1: Routine T1WI, T2WI, FLAIR, and contrast-enhanced T1WI are recommended. When conditions permit, the addition of a multimodal MRI protocol incorporating techniques such as diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), susceptibility-weighted imaging (SWI), magnetic resonance spectroscopy (MRS), and perfusion-weighted imaging (PWI) is suggested to acquire multidimensional information regarding the tumor's cellular density, its spatial relationship with critical white matter tracts (e.g., the corticospinal tract), hemorrhage, metabolic profile, and blood perfusion status (Level of Evidence: Moderate; Recommendation Strength: Strong).[1]

(II) Imaging assessment of treatment response in pLGGs

In 2020, the International Society of Paediatric Neuro-Oncology Response Assessment Committee formulated and published a consensus document on the evaluation of treatment response in pLGGs, which is recommended for use in the management of pLGGs.[13]

1. Noncystic pLGGs

Routine non-contrast and contrast-enhanced MRI scans should be performed. The non-contrast MRI protocol includes T1WI, T2WI, FLAIR, and DWI sequences, and a three-dimensional acquisition sequence is recommended following the administration of contrast medium.[14] For children with primary intracranial pLGGs who are highly suspected of having spinal metastases (e.g., those with pleomorphic xanthoastrocytoma or pilocytic astrocytoma) or who present with spinal symptoms (e.g., back pain or urinary retention), preoperative spinal MRI screening is recommended to establish a baseline tumor assessment.[14,15] A follow-up spinal MRI scan should be performed within 10 to 14 days postoperatively to evaluate spinal metastases.[15] For children with confirmed spinal metastases, spinal MRI should be incorporated into routine postoperative surveillance,[13,16,17] and the follow-up interval may be aligned with cranial MRI surveillance according to disease status and clinical need. For children highly suspected of having intracranial metastases, preoperative cranial MRI scanning is recommended to establish baseline tumor assessment. A follow-up cranial MRI scan should be performed within 10–14 days postoperatively to evaluate intracranial metastases. If intracranial metastases are confirmed, routine postoperative follow-up cranial MRI scans are recommended, with intervals consistent with those used for spinal MRI.[18–20]

2. pLGGs with cystic components

(1) If the solid component of the tumor increases by ≥25% relative to the baseline, disease progression should be considered, regardless of the size of the cystic component. (2) If the solid component remains stable or increases by <25% relative to the baseline but the tumor-associated cystic component shows progression, a follow-up MRI scan should be considered within four to six weeks or based on clinical indications. If a follow-up scan reveals progressive enhancement of the cyst wall or progression of the solid component, disease progression should be considered. Conversely, if cyst wall enhancement remains stable and no progression of

the solid component is observed, this suggests stable disease, and follow-up should proceed at standard intervals (i.e., an MRI scan every three months). (3) If the solid component remains stable or increases by <25% relative to the baseline, but the cystic component expands, close monitoring of the mass effect of the cyst and the patient's clinical symptoms is required. If the cyst does not exert a mass effect and the patient's clinical condition remains stable, periodic follow-up is appropriate. If the cystic component causes a mass effect or symptoms of elevated intracranial pressure, surgical decompression may be performed, followed by routine postoperative MRI examinations.[21]

Recommendation 2: For primary intracranial pLGGs, a routine preoperative cranial MRI examination is recommended, and a postoperative cranial MRI scan should be completed within 72 h of surgery. If a residual tumor cannot be clearly identified due to interference from hemorrhage, hemostatic materials, or other factors, a follow-up cranial MRI examination should be performed two to three weeks postoperatively. During the course of treatment, cranial MRI scans should be conducted at least once every three months to assess the child's treatment response (Evidence Level: High; Recommendation Strength: Strong).

Recommendation 3: For primary spinal pLGGs, a routine preoperative spinal MRI examination is recommended, and a postoperative spinal MRI scan should be completed within 72 h. If a residual tumor cannot be definitively identified, a follow-up spinal MRI examination should be performed two to three weeks postoperatively. During the course of treatment, spinal MRI scans should be conducted at least once every three months to assess treatment response (Evidence Level: High; Recommendation Strength: Strong).

Recommendation 4: For tumors associated with cystic changes, preoperative and postoperative assessments must distinguish between a mixed cystic-solid tumor and true cystic degeneration within the tumor. The criteria for true cystic degeneration include: (1) Cystic changes located within the solid component, presenting a "soap-bubble" appearance; (2) Absence of a clear demarcation between the cystic changes and the solid tumor component (excluding cystic cavities formed between the tumor and surrounding brain tissue, as well as postoperative residual surgical cavities surrounding the residual tumor), or the presence of thick, enhancing cyst walls, or both; (3) The presence of multiple microscopic cystic changes within the tumor; and (4) Imaging manifestations characterized by a large cystic component accompanied by a distinctly enhancing mural nodule (if the cyst wall shows no significant enhancement, the cystic component is not included in the assessment of disease progression) (Evidence Level: High; Recommendation Strength: Strong).

II. Pathological diagnosis

(I) Overview of pathological classification in pLGGs

The 5th Edition of the WHO Classification of Tumors of the CNS classifies diffuse gliomas into two groups—"adult-type" and "pediatric-type"—based on information regarding age, histology, and molecular genetic features. Pediatric-type diffuse gliomas are further subdivided into four types of diffuse low-grade gliomas and four types of diffuse high-grade gliomas.[22] Pediatric-type diffuse low-grade gliomas include diffuse astrocytoma (MYB- or MYBL1-altered), angiocentric glioma, polymorphous low-grade neuroepithelial tumor of the young, and diffuse low-grade glioma (MAPK pathway-altered). Although pediatric-type diffuse gliomas occur primarily in children, they are not exclusively found in this population.[23] Children may also develop adult-type diffuse gliomas; for instance, IDH-mutant diffuse gliomas occur in pediatric patients.[24] Furthermore, circumscribed gliomas, glioneuronal tumors, and neuronal tumors are predominantly low-grade and constitute a significant component of pLGGs.[25]

(II) Principles of pathological examination

Diagnosis requires the integration of both histological and molecular genetic features. Histological diagnosis remains the foundation of the diagnostic process, whereas molecular genetic features serve as a crucial supplement, providing additional diagnostic and prognostic information. This enhances diagnostic accuracy and aids in the selection of appropriate treatments and clinical trials.[22] There is a substantial overlap in the molecular genetic features among pediatric-type diffuse low-grade gliomas, circumscribed gliomas, and glioneuronal tumors; therefore, molecular genetic alterations must not be interpreted in isolation from histological features. Relatively speaking, circumscribed gliomas and glioneuronal tumors are more readily distinguishable based on their histological morphology.[26,27]

The pathological diagnosis of a glioma that lacks adequate molecular genetic information is considered incomplete. This is because, compared to the variability in histological morphology, the molecular genetic characteristics within a single tumor tend to be highly conserved.[28,29] Furthermore, only through a comprehensive assessment of molecular genetic characteristics is it possible to accurately diagnose certain tumors exhibiting significant morphological heterogeneity while simultaneously obtaining crucial information regarding prognosis and treatment.[30] In pLGGs, histological and molecular genetic features do not always correspond directly to specific tumor types[31]; consequently, even after thorough histological examination and molecular testing, precise diagnosis can sometimes remain elusive. In such cases, DNA methylation clustering analysis can serve as a valuable adjunct to the diagnostic process.[32] pLGGs are typically driven by genetic alterations in the RAS/MAPK pathway. Moreover, the specific patterns of these driver gene alterations are frequently correlated with patient age at onset, histological grade, and prognosis. Based on factors such as patient age, tumor location, and the specific pattern of driver gene alterations, pLGGs can be stratified into low-, intermediate-, and high-risk groups.[33]

DNA methylation profiling enables the detection of alterations at the molecular epigenetic level, thereby serving as an essential complement to standard molecular genetic testing methods. DNA methylation clustering analysis has emerged as an effective auxiliary tool for the classification of CNS tumors.[34] In the 5th Edition of the WHO Classification of CNS Tumors, the relationship between DNA methylation clustering analysis and tumor diagnostic criteria is categorized into three tiers: essential diagnostic criteria, desirable diagnostic criteria, or non-essential diagnostic criteria. Currently, DNA methylation clustering analysis is recommended for a select group of pediatric patients for whom other testing methods fail to yield a precise diagnosis, for tumor types where identifying the specific molecular subtype is critical for guiding treatment, or for tumor types where the WHO Classification of CNS Tumors designates DNA methylation profiling as an essential diagnostic criterion.[32] However, the application of DNA methylation clustering analysis is constrained by various resource and technical limitations (including, but not limited to, tissue availability, equipment access, financial

Table 2. Characteristics and detection methods for low-grade gliomas of different histological subtypes in children

Tumor type	WHO grade	Key molecular/genetic features	Recommended testing methods	Remarks
Pilocytic astrocytoma	1	IDH-wildtype; KIAA1549-BRAF fusion; mutations in MAPK pathway genes such as BRAF, NF1, etc.	IHC, FISH, qPCR, Sanger sequencing, NGS, DNA-MC	Pilomyxoid astrocytoma is described as a subtype of this entity; it occurs more frequently in young children as a lesion in the sellar region (hypothalamus or optic chiasm)
Diffuse astrocytoma, MYB- or MYBL1-altered	1	IDH-wildtype; MYB or MYBL1 alteration	FISH, NGS, DNA-MC	Tumor cells: GFAP-positive; Olig2, MAP2, and CD34-negative
Angiocentric glioma	1	IDH-wildtype, MYB-mutant	FISH, NGS, DNA-MC	The MYB rearrangement partner gene is most frequently QKI; tumor cells are positive for GFAP, negative for Olig2 and CD34, and show paranuclear punctate positivity for EMA
Polymorphous low-grade neuroepithelial tumor of the young	1	IDH-wildtype; BRAF, FGFR family, or MAPK pathway gene alterations	IHC, qPCR, Sanger Sequencing, NGS, DNA-MC	CD34 expression is frequently observed in tumor cells and the surrounding neuronal components, often associated with BRAF V600E mutations and FGFR2/3 gene fusions
Diffuse low-grade glioma, MAPK pathway-altered	/	IDH-wildtype; FGFR1 or BRAF mutation, or MAPK pathway gene alteration	IHC, FISH, qPCR, Sanger Sequencing, NGS, DNA-MC	Commonly observed in children, adolescents, or adults aged 20 to 40 years; characterized by IDH/H3 wildtype status and the absence of homozygous CDKN2A deletion, with FGFR and BRAF alterations being the most frequent genetic variants; a formal WHO CNS classification has not yet been established
Ganglioglioma	1	IDH-wildtype; Mutations in MAPK pathway-related genes, such as BRAF.	IHC, FISH, qPCR, Sanger Sequencing, NGS, DNA-MC	The 5th Edition of the WHO Classification of CNS Tumors does not establish diagnostic criteria for anaplastic ganglioglioma; as this entity requires further research for validation, it warrants close attention in clinical practice
Dysembryoplastic neuroepithelial tumor	1	IDH-wildtype; FGFR1-mutated (internal tandem repeat, fusion, or nonsense mutation)	IHC, FISH, qPCR, Sanger Sequencing, NGS, DNA-MC	Commonly observed in children and adolescents, this epilepsy-associated tumor is characterized by a multinodular growth pattern within the cortex, in which oligodendroglia-like cells form columnar structures

BRAF, V-Raf murine sarcoma viral oncogene homolog B; CDKN2A, cyclin dependent kinase inhibitor 2A; CNS, central nervous system; DNA-MC, DNA methylation clustering analysis; EMA, epithelial membrane antigen; FGFR, fibroblast growth factor receptor; FISH, fluorescence in situ hybridization; GFAP, glial fibrillary acidic protein; IDH, isocitrate dehydrogenase; IHC, immunohistochemistry; MAP2, microtubule-associated protein 2; MAPK, mitogen-activated protein kinase; MYB, myeloblastosis; MYBL1, MYB proto-oncogene like 1; NF1, neurofibromatosis type 1; NGS, next-generation sequencing; Olig2, oligodendrocyte transcription factor 2; QKI, Quaking I; qPCR, quantitative polymerase chain reaction; WHO, World Health Organization.

resources, and depth of accumulated database references). Furthermore, for certain tumors, DNA methylation clustering analysis may fail to assign them to a specific subtype, potentially indicating the existence of novel tumor entities.[35,36] Consequently, the diagnostic process should involve the comprehensive synthesis of DNA methylation clustering results, other molecular genetic data, and morphological features to arrive at a precise diagnosis. In cases where the molecular classification results are discordant, it is recommended to seek institutional multidisciplinary consultation or to refer the case to a specialized neuropathology center equipped with advanced diagnostic capabilities. The molecular genetic features, diagnostic pathways, and key differential points for the various types of pLGGs are detailed in Table 2.

Recommendation 5: Histological examination and immunohistochemical analysis should be performed on all tumors. Regardless of whether the facilities are available to conduct relevant molecular testing, every effort should be made to histologically distinguish—at a preliminary level—between diffuse gliomas and other low-grade neuroepithelial tumors, appending the designation "NOS" (Not Otherwise Specified) where appropriate (Evidence Level: High; Recommendation Strength: Strong).

Recommendation 6: Whenever possible, comprehensive molecular genetic profiling should be performed on brain tumors to facilitate an integrated diagnosis. Strict pathological quality control measures must be implemented prior to molecular testing (Evidence Level: High; Recommendation Strength: Strong).

Recommendation 7: In cases where histological and molecular genetic features do not permit definitive classification, DNA methylation profiling can aid in differential diagnosis or in the identification of novel tumor entities (Evidence Level: High; Recommendation Strength: Weak).

(III) Standardized pathological terminology

The pathological diagnosis of gliomas should be standardized and formalized, adhering to the principles of integrated diagnosis out-

lined in the 5th Edition of the WHO Classification of CNS Tumors. Hierarchical diagnostic information should include[22]: (1) Integrated Diagnosis, (2) Histopathological Diagnosis, (3) WHO Grade, and (4) Molecular Genetic Information. Key details, such as tumor location, specimen type, testing methodology, and specific variant types, should be explicitly stated.

The grading system for glioma malignancy differs from that used for tumors in other parts of the body; consequently, the WHO recommends using the specific terminology "CNS WHO Grade" to denote this classification. The grading system for gliomas in the 5th Edition of the WHO Classification is an "intra-tumor-type" grading system, emphasizing the biological similarities shared among tumors of the same specific type.[22] The CNS WHO Grade reflects the prognostic outcome based on the tumor's natural history, rather than the clinical outcome following standardized treatment.[22]

If, during the diagnostic process, specific diagnostic information mandated by the WHO cannot be obtained, or if the diagnosis of a specific tumor type remains uncertain, the diagnostic conclusion should be appended with the suffix "NOS" (Not Otherwise Specified) or "NEC" (Not Elsewhere Classified).[37] The suffix "NOS" specifically indicates that comprehensive molecular testing has not yet been performed or that such testing was unsuccessful. The suffix "NEC" indicates that, despite the successful completion of adequate testing and the acquisition of reliable results, those results do not meet the diagnostic criteria for any of the specific tumor entities currently recognized and included in the WHO classification.

Recommendation 8: In clinical practice, the morphological features, key immunohistochemical markers, and molecular alterations of pLGGs should be thoroughly interpreted. When sufficient evidence is available, every effort should be made to achieve precise diagnostic classification and grading. It is not always necessary to perform large-panel gene sequencing to complete an integrated diagnosis (Evidence Level: High; Recommendation Strength: Strong).
Recommendation 9: For "descriptive diagnoses" bearing the suffixes "NOS" or "NEC", the assigned pathological grade may be described as "equivalent to histological grade" (Evidence Level: Moderate; Recommendation Strength: Strong).

In primary care hospitals or other institutions lacking the necessary infrastructure for specialized neuropathological diagnosis, pathologists must continue to prioritize training for morphological diagnoses. Building upon a foundation of morphological diagnosis, they should fully comprehend the implications and hierarchical relationships of essential diagnostic information, accurately utilize the "NOS" and "NEC" suffixes, and provide recommendations for further testing required to complete the diagnosis; when necessary, they should seek assistance from specialized neuropathologists or recommend referral to a higher-level hospital for consultation. Pathological grading described as "equivalent to histological grade"—assigned to "descriptive diagnoses" bearing the "NOS" or "NEC" suffixes—carries inherent limitations, as it is constrained by available testing resources or current levels of diagnostic expertise. Therefore, when utilizing such reports as a basis for clinical management, clinicians must fully consider factors such as tumor location, growth pattern, extent of surgical resection, and disease course, and multidisciplinary discussion is strongly recommended.

(IV) Pathological examination considerations for pLGGs

Pathological diagnosis requires that all tumors undergo both histological and immunohistochemical examinations. In cases where the specimen volume is limited, to ensure that sufficient tissue remains available for molecular genetic analysis, immunohistochemical staining for specific molecular markers (e.g., IDH1 R132H, BRAF V600E, ATRX, H3K27M, etc.) may be omitted in favor of proceeding directly to molecular testing. Particular attention must be paid to the fact that all fresh or paraffin-embedded tissue specimens designated for molecular testing must undergo rigorous pathological quality control before analysis.

Pediatric gliomas may be associated with hereditary tumor predisposition syndromes. In addition to diagnosis based on clinical features and family history, high-throughput genetic sequencing can be used to identify the underlying heritable pathogenic gene variants.[38] When the clinical history suggests the presence of a genetic syndrome associated with brain tumors, further investigation of germline genetic variants is warranted. Identifying the specific hereditary tumor predisposition syndrome not only facilitates the monitoring and prevention of multifocal lesions—whether in the brain or other organs—for the affected child, but also provides the entire family with guidance regarding genetic disease surveillance and reproductive planning.[39] Regarding DNA methylation clustering analysis, it is crucial to note that adequate intraoperative acquisition of brain tumor specimens remains a prerequisite for obtaining accurate DNA methylation profiles. Furthermore, such clustering analyses must account for tumor heterogeneity, which is intrinsically linked to the purity of tumor components within the analyzed sample and the degree of variation in their biological activity.[40,41] Moreover, current applications of DNA methylation clustering analysis primarily focus on classification, specifically, identifying diagnostically challenging or rare tumor types, or delineating specific molecular tumor subtypes that inform therapeutic strategies. Given national regulations governing the cross-border transfer of genetic data, it is strongly advised that—should DNA methylation clustering analysis be deemed necessary—the patient's genetic data should not be uploaded in bulk to foreign websites for analysis; instead, such analyses should be conducted domestically through consultation with specialized neuropathology centers equipped with the requisite capabilities.

III. Principles of surgical management

pLGGs are often discovered incidentally or present with associated seizures, and affected children may exhibit no obvious neurological deficits. Prior to surgery, the risks associated with aggressive tumor resection must be carefully weighed against the potential risk of postoperative neurological impairment. For children with pLGGs who undergo gross total resection (GTR), the 10-year overall survival rate can reach 90%. Furthermore, GTR is a primary predictor of progression-free survival. However, there is currently a lack of effective imaging modalities or biomarkers that can aid in the preoperative diagnosis of pLGGs. For tumors that are preliminarily assessed preoperatively as low-grade, non-infiltrative, and situated in surgically accessible locations with low and controllable operative risks, the primary objective of surgical treatment is GTR to achieve cure.[6] Among cases of pLGGs where GTR is not achieved and residual tumor remains, approximately 50% show no progression within five years; the long-term survival prognosis for this subgroup of patients remains excellent.[6,7,13] The rate of malignant transformation of pLGGs to a high-grade malignancy is less than 10%[6,7,13]; nevertheless, the necessity for long-

term—or even lifelong—follow-up examinations can still impose significant psychological stress on both children and their parents.

Given the variability in tumor location and growth characteristics, for children with tumors exhibiting infiltrative growth or situated in surgically challenging locations, particularly those likely to result in significant neurological deficits (e.g., gliomas involving the visual pathways or diffuse brainstem gliomas), the objectives of surgery are expanded to include tumor debulking, alleviation of hydrocephalus, symptom relief, reduction of the risk of malignant transformation, and establishment of a definitive pathological diagnosis.[6,7,13]

For low-grade gliomas of the visual pathways and hypothalamus that present with typical imaging features and a relatively definitive diagnosis, surgical intervention is generally not recommended because surgery or biopsy carries the risk of inducing corresponding neurological deficits. However, surgical resection or biopsy may be considered in cases where the tumor is massive, exerts a significant mass effect, is associated with hydrocephalus, or demonstrates progression during observation, necessitating the initiation of treatment. In such cases, the aim is to obtain a histological and molecular pathological diagnosis to guide the formulation of an appropriate systemic treatment plan.[1,31,33,42] For cortical or subcortical pLGGs accompanied by epilepsy, surgical principles for epilepsy management may be applied; specifically, intraoperative electrophysiological monitoring techniques should be utilized to localize the epileptogenic focus while simultaneously strengthening the prevention, control, and management of seizures during the perioperative period.[6,43,44]

Recommendation 10: It is recommended that the surgical objective and extent of resection be determined through multidisciplinary discussion prior to surgery (Level of Evidence: High; Recommendation Strength: Strong).[6,7]
Recommendation 11: Laser interstitial thermal therapy may serve as a therapeutic option for tumors located in areas that are surgically difficult to access (Level of Evidence: Moderate; Recommendation Strength: Weak).[45–48]
Recommendation 12: The role of molecular pathological diagnosis in the current diagnosis, treatment, and prognostic assessment of pLGGs is becoming increasingly important. Biopsy procedures performed to obtain tissue specimens carry a low risk and are therefore recommended for pediatric patients whose tumors are difficult to resect (Level of Evidence: Moderate; Recommendation Strength: Strong).[1,31,33,42]

IV. Principles of radiotherapy

(I) Indications for radiotherapy

Although radiotherapy demonstrates proven efficacy against pLGGs,[49] its application is often restricted by the associated long-term adverse effects and impact on quality of life, factors that are particularly pertinent given the favorable prognosis and long survival duration typical of children with pLGGs.[50] Research data indicate that the scope and dose of radiotherapy are associated with an increased risk of cognitive decline,[51,52] endocrine dysfunction,[53] vascular pathologies,[54,55] growth retardation, and secondary malignancies.[56] Furthermore, the younger the patient is at the time of radiotherapy, the higher these risks tend to be. However, existing data regarding the incidence of radiotherapy-related adverse effects are largely derived from conventional two-dimensional or three-dimensional conformal radiotherapy techniques. Newer precision radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) and proton therapy, are capable of significantly reducing radiation exposure to normal tissues.[57] Therefore, new clinical studies are warranted to re-evaluate the benefit-to-risk ratio of radiotherapy (weighing therapeutic gains against the incremental risk of adverse effects) to provide updated guidance for radiotherapy protocols. Currently, for unresectable pLGGs, chemotherapy or targeted therapy is typically administered first, based on the assumption that delaying radiotherapy does not adversely affect disease outcomes,[58,59] with radiotherapy considered only upon disease progression. Children with NF1-associated optic pathway gliomas face an increased risk of adverse effects following radiotherapy, such as vascular complications (e.g., Moyamoya disease), secondary malignancies, or cognitive decline, compared to children without NF1[56,60,61]; consequently, chemotherapy is generally the preferred initial treatment.[60] However, for children presenting with high-risk factors, such as a histological diagnosis of diffuse astrocytoma or a tumor located in the midbrain or thalamus, delaying radiotherapy may compromise overall survival.[62] Therefore, the risk of mortality associated with disease progression must be carefully weighed against the risk of adverse effects of radiotherapy; radiotherapy should not be indefinitely postponed or entirely avoided.[63] Furthermore, for pLGG cases that fail to respond to chemotherapy or targeted therapy, radiotherapy should be actively considered as a means to control disease progression.

Recommendation 13: Radiotherapy is primarily indicated for the following groups of children: (1) those aged >3 years with incompletely resected tumors accompanied by neurological symptoms, (2) those with continuously progressing tumors, and (3) those who have failed multiple lines of therapy. For children aged ≤3 years, it is recommended that radiotherapy be delayed or avoided through the use of chemotherapy (Level of Evidence: Moderate; Recommendation Strength: Strong).
Recommendation 14: For NF1-associated optic pathway gliomas, radiotherapy should not be selected as the initial treatment[64]; rather, it should be reserved as salvage therapy only when the tumor remains uncontrolled or continues to progress following multiple lines of chemotherapy.[65] Conversely, for non-NF1-associated optic pathway gliomas, radiotherapy can effectively control the tumor and preserve—or even improve—the child's visual acuity (Level of Evidence: Low; Recommendation Strength: Strong).[61]
Recommendation 15: For children with a histological diagnosis of diffuse astrocytoma or those with tumors located in the midbrain or thalamus, early initiation of radiotherapy may confer a survival benefit (Level of Evidence: Moderate; Recommendation Strength: Weak).[62]

(II) Radiotherapy techniques

To better protect normal brain tissue and minimize late adverse effects associated with radiotherapy, IMRT is the preferred technique for patients with pLGGs[66]; where resources permit, proton therapy may also be utilized.[67] During simulation and localization, in addition to the traditional method of head immobilization using a thermoplastic mask combined with a body board, a head immobilization system comprising a novel carbon-fiber composite frame, elastic headrest, and head positioning membrane may also be employed. This system enhances immobilization precision, improves conformity of the head mold fit, and increases patient comfort. For spinal

pLGGs, an appropriate immobilization device should be selected during localization based on the specific tumor site (the cervical, thoracic, or lumbosacral region). Given that children, particularly younger patients, are prone to crying and agitation, often exhibiting poor compliance with radiotherapy localization procedures and presenting difficulties in immobilization, the judicious use of pharmacological sedation or anesthesia administered by an anesthesiologist is appropriate.[68] Studies indicate that children are susceptible to developing anxiety and fear regarding radiotherapy; therefore, medical institutions with necessary resources are encouraged to provide proactive psychological counseling and interventions to both the child and their family, thereby facilitating the child's effective cooperation throughout the radiotherapy course.[69,70]

Recommendation 16: Radiotherapy techniques should utilize either three-dimensional conformal radiotherapy or IMRT (Evidence Level: High; Recommendation Strength: Strong).
Recommendation 17: Radiotherapy localization typically involves head immobilization using a thermoplastic mask combined with a body board, utilizing non-contrast CT scanning for simulation. Institutions with the necessary capabilities may additionally employ MRI for simulation and localization (Evidence Level: Moderate; Recommendation Strength: Strong).
Recommendation 18: For certain children who are unable to cooperate with radiotherapy localization procedures, sedative-hypnotic agents, such as chloral hydrate, may be administered, or intravenous anesthesia may be performed by an anesthesiologist (Evidence Level: Moderate; Recommendation Strength: Strong).

(III) Radiotherapy target volumes and dosing strategies

Regarding the delineation of target volumes for pLGGs, fusion of CT and MRI is strongly recommended. As low-grade gliomas typically exhibit minimal contrast enhancement, it is necessary to additionally reference FLAIR or T2WI sequences to accurately define the gross tumor volume (GTV).[71] If positron emission tomography (PET) imaging data are available, incorporating PET image fusion can further assist in precisely delineating the extent of the GTV.[72] When delineating the clinical target volume (CTV), the expansion margin of the CTV may be appropriately reduced to mitigate radiation-induced injury to normal brain tissue. Studies have indicated that the CTV expansion margin can be safely reduced to as little as 5 mm without increasing the rate of marginal recurrence.[73]

Regarding radiation dosage, the total prescribed dose varies depending on the tumor's anatomical location. For spinal pLGGs, considering the radiation tolerance of the normal spinal cord, the prescribed dose is typically 45 Gy; conversely, for intracranial tumors, the dose may be increased to 54 Gy. Given the significant correlation between long-term neurological sequelae and higher fractional doses, hypofractionated regimens are not recommended for pLGGs; instead, conventional fractionation—typically 1.8 to 2.0 Gy per fraction—remains the current standard fractionation regimen.[62]

Recommendation 19: Delineation of the radiation target volume should be guided by both pre- and post-operative MRI images; for pLGGs, the CTV is typically defined as a 10 mm expansion beyond the GTV (Level of Evidence: Moderate; Recommendation Strength: Strong).
Recommendation 20: The prescribed radiation dose for pLGGs typically ranges from 45 to 54 Gy, administered using a conventional fractionation regimen of 1.8 to 2.0 Gy per fraction (Level of Evidence: Moderate; Recommendation Strength: Strong).

V. Principles of systemic therapy

Most pLGGs of the brain and spinal cord exhibit non-aggressive clinical behavior and rarely undergo malignant transformation (<10%). GTR is the most important prognostic factor for pLGGs[74]; adjuvant therapy is not required following GTR, and the recurrence rate in such patients is less than 20%. However, GTR is often not feasible for pLGGs involving deep midline structures, optic pathways, brainstem, or those accompanied by disseminated disease.[75] Chemotherapy is the preferred treatment for pLGGs in cases of clinical deterioration or radiologic progression.[76,77] Given the rapid growth rate of low-grade gliomas in infants and toddlers, and the associated high risk of disease-related mortality, chemotherapy should be initiated immediately upon diagnosis; a "watch-and-wait" approach is not appropriate.[78] For pLGGs in children aged >3 years, if symptoms are mild or absent, a period of clinical observation and follow-up may be appropriate; however, chemotherapy is initiated if the tumor progresses or symptoms emerge during this observation period.

Recommendation 21: For infants and toddlers with pLGGs who have not undergone surgery or for whom surgery resulted in only partial resection, a period of observation is not recommended; chemotherapy should be initiated immediately. For children >3 years of age with pLGGs who have undergone only partial resection and are symptomatic or whose tumor demonstrates progression during follow-up observation, chemotherapy is indicated (Evidence Level: High; Recommendation Strength: Strong).

(I) First-line treatment regimens

1. Conventional chemotherapy

The most commonly used first-line chemotherapy regimens for pLGGs are the CV and TPCV regimens. The CV regimen comprises carboplatin (CBP) plus vincristine (VCR). The TPCV regimen comprises thioguanine, procarbazine, lomustine, and VCR. These two regimens have comparable efficacy, with an objective response rate of approximately 50%.[79] However, because the TPCV regimen contains multiple alkylating agents, it carries a higher long-term risk of secondary malignancies and is therefore not recommended for children with NF1. Furthermore, the TPCV regimen involves the administration of multiple oral tablets, which can be difficult for young children to take.

CV or TPCV chemotherapy regimens are ineffective in approximately 50% of patients. In a randomized controlled clinical trial designed to optimize the CV regimen, the addition of etoposide to the standard CV regimen did not improve efficacy compared to the CV regimen alone; the objective response rates were 46.4% and 41%, respectively. Moreover, treatment with the etoposide combination resulted in higher rates of grade 4 hematologic toxicity (64% vs. 76%) and grade 3/4 infections (18% vs. 30%).[80] Furthermore, studies have

indicated that the multi-targeted anti-angiogenic agent recombinant human endostatin, when combined with the CV regimen, helps to improve the response rate and shorten the time to response.[81,82]

A single-arm Phase II study demonstrated that in patients with previously untreated pLGGs, monotherapy with vinblastine yielded an objective response rate of approximately 26% and a five-year progression-free survival rate of 53%. Based on the results of this trial, vinblastine has been adopted as a first-line treatment in certain countries or institutions.[83]

Recommendation 22: The recommended first-line chemotherapy regimens for pLGGs are the CV or TPCV regimens (Evidence Level: High; Recommendation Strength: Strong). Vinblastine is an optional chemotherapy regimen for pLGGs (Evidence Level: Moderate; Recommendation Strength: Weak). The addition of etoposide to the CV regimen is not recommended (Evidence Level: High; Recommendation Strength: Strong).

2. Targeted Therapy

Activation of the RAS/MAPK pathway is a predominant feature of pLGGs.[27,42,84] Children with corresponding molecular target alterations may be candidates for targeted therapy. A randomized controlled Phase II study indicated that the combination of the first-generation BRAF inhibitor dabrafenib and the MEK inhibitor trametinib, used as a first-line treatment for BRAF-mutated pLGGs, may yield superior objective response rates and progression-free survival compared to the CV regimen.[85] The combination of dabrafenib and trametinib has been approved by the U.S. Food and Drug Administration for the treatment of pLGGs harboring the BRAF V600E mutation.[86]

For pLGG cases characterized by BRAF fusions, the MEK inhibitor trametinib demonstrates some degree of activity.[87] First-generation BRAF inhibitors, such as dabrafenib and vemurafenib, are unsuitable for the treatment of children with BRAF-fusion tumors because they are unable to target RAF kinase dimers and may instead lead to the aberrant activation of the MAPK pathway, thereby promoting accelerated tumor growth.[88] In contrast, the second-generation BRAF inhibitor tovorafenib can block BRAF dimers and reduce aberrant pathway activation. In patients with relapsed/refractory BRAF-fusion pLGGs, treatment with tovorafenib has demonstrated an objective response rate of up to 50%. Studies are currently underway to investigate the potential use of tovorafenib as a first-line treatment option for BRAF-fusion pLGGs.[89]

Approximately 85% to 95% of children with SEGA associated with tuberous sclerosis complex (TSC) harbor mutations in the TSC1 or TSC2 genes, resulting in aberrant activation of the mTOR pathway. The selective mTOR inhibitor, everolimus, has proven effective in the treatment of SEGA and is recommended for patients with unresectable TSC-associated SEGA.[90]

Larotrectinib is indicated for patients of all ages with solid tumors harboring NTRK fusions. Entrectinib is indicated for children aged ≥12 years with solid tumors harboring NTRK fusions; during treatment with entrectinib, clinicians should remain vigilant for the occurrence of fractures.[91,92]

Recommendation 23: The use of BRAF inhibitors and/or MEK inhibitors may be considered for patients with BRAF-mutated pLGGs; however, the use of first-generation BRAF inhibitors is not recommended for patients with BRAF-fusion pLGGs (Level of Evidence: High; Recommendation Strength: Strong).

Recommendation 24: Patients with SEGA harboring TSC1/2 gene mutations may be treated with selective mTOR inhibitors (Level of Evidence: High; Recommendation Strength: Strong).

Recommendation 25: The use of TRK inhibitors, such as larotrectinib and entrectinib, may be considered for patients with TRK-fusion-positive pLGGs (Level of Evidence: High; Recommendation Strength: Strong).

(II) Treatment at relapse or progression

Following first-line treatment, approximately 50% of pediatric patients experience relapse or disease progression.[76,77] Currently, there is no standard systemic treatment regimen for patients with relapsed or progressive disease; treatment plans should be formulated based on the patient's prior treatment history, general condition, tumor burden, and genetic testing results.

1. Targeted drug therapy

Patients with BRAF mutations may be treated with BRAF inhibitors (e.g., vemurafenib, dabrafenib, tovorafenib) and/or MEK inhibitors (e.g., trametinib, selumetinib). During treatment, clinicians must remain vigilant for the occurrence of ocular toxicity, cardiac toxicity, and intracranial hemorrhage.[85,93–99] For patients in whom the disease progresses following discontinuation of prior BRAF inhibitor treatment, re-administration of this agent may still be effective, with 90% of patients achieving an objective response.[100] For patients with BRAF fusions, MEK inhibitors or second-generation BRAF inhibitors (e.g., tovorafenib) may be considered.[1,95] Subependymal giant cell astrocytomas harboring TSC1/2 gene mutations may be treated with mTOR inhibitors (e.g., everolimus).[90] For pLGG cases positive for TRK fusions, TRK inhibitors, such as entrectinib and larotrectinib, may be considered.[91,92]

Recommendation 26: Treatment with appropriate molecularly targeted agents is recommended for relapsed or progressive pLGGs harboring BRAF gene alterations or TRK fusions, or for SEGAs harboring TSC1/2 gene mutations (Evidence Level: High; Recommendation Strength: Strong).

2. Other medications

Temozolomide, an alkylating agent used to treat diffuse low-grade gliomas in adults, demonstrates limited efficacy in pLGGs and is therefore not recommended for use as a first-line agent. For pLGG that has progressed, 30 pediatric patients were treated with temozolomide; among them, four (13%) experienced tumor shrinkage exceeding 25%, and 13 (43%) maintained stable disease, suggesting that temozolomide may serve as a second-line option for pLGGs.[101]

Treatment with bevacizumab for recurrent or progressive pLGGs can induce a rapid tumor response (with an efficacy rate of 86% at nine weeks), which helps alleviate acute visual impairment or other neurological deterioration[102]; however, following discontinuation of the drug, 93% of tumors progress again within a short period, with a median time to progression of four months.[103,104] Furthermore, clinicians must remain vigilant regarding the risks of

adverse reactions, such as proteinuria, rheumatoid arthritis, somnolence, and premature ovarian insufficiency.

Studies have shown that among 37 patients with progressive pLGGs treated with a combination of cisplatin and etoposide, 24 (65%) experienced a reduction in tumor volume, with therapeutic effects lasting up to 12 months.[105] In a cohort of 16 patients with progressive optic pathway gliomas treated with a three-drug combination regimen of cisplatin, etoposide, and vinblastine, four patients experienced tumor shrinkage, and five achieved stable disease, resulting in an objective response rate of 25% and a disease control rate of 56.3%.[106] Another study analyzed the efficacy of re-treatment with the CV regimen, carboplatin monotherapy, and vinblastine monotherapy for progressive, surgically unresectable pLGGs; the objective response rates for these three regimens were 58.8%, 27%, and 46.4%, respectively.[107]

Recommendation 27: Chemotherapy regimens available for recurrent or progressive pLGGs include re-treatment with the CV regimen, temozolomide, bevacizumab, cisplatin combined with etoposide, and vinblastine (Evidence Level: Moderate; Recommendation Strength: Weak).

Discussion

The revision of the WHO Classification of CNS Tumors has led to major changes in the routine diagnosis and treatment of patients with gliomas. In this study, we present consensus guidelines for the diagnosis and management of pediatric gliomas in China. These guidelines integrate levels of evidence from published studies, expert consensus, and practical clinical considerations. They are also anchored by high-level evidence for foundational diagnostics, including standardized imaging surveillance and molecular genetic profiling. They suggest that diagnosis and management plans should follow multidisciplinary tumor board recommendations throughout the course of the disease.

Strong evidence also supports the efficacy of first-line chemotherapy and targeted inhibitors (e.g., mTOR and TRK inhibitors). These recommendations are grounded in a comprehensive review of the literature, supported by expert consensus and peer review. The recommendations establish a multidisciplinary framework that shifts the field toward integrated molecular diagnostics and personalized therapy. Central to this approach is the prioritization of multimodal imaging and molecular profiling (e.g., BRAF and TRK) to guide the use of precision inhibitors. A critical clinical directive is the age-appropriate de-escalation of treatment, specifically the avoidance or delay of radiotherapy in children aged <3 years to minimize long-term neurocognitive and endocrine morbidity. However, limitations remain due to the immaturity of the current clinical evidence. Advanced local therapies, such as laser interstitial thermal therapy and specific radiotherapy localization techniques, currently rely on moderate evidence, and there is no high-level evidence supporting the use of salvage chemotherapy in recurrent disease. Guidelines reflect knowledge and consensus at a given time. For many of the newly defined disease entities in the latest WHO classification, data on specific treatments and outcomes are not yet available; extrapolating data from clinical trials to these novel entities remains challenging. Well-designed, molecularly enriched randomized controlled trials are necessary to substantiate some of the treatment recommendations of the present guidelines.

To further refine clinical outcomes, research must prioritize the optimization of radiotherapy margins and long-term safety monitoring of molecularly targeted agents. Additionally, the field faces significant ongoing hurdles, including the development of more accurate preclinical pLGG models to better predict human responses and the standardization of early-phase clinical trials to ensure comparable and high-quality data. Addressing the complex phenomena of treatment resistance, tumor rebound, and recurrence continues to challenge the long-term management of these patients.

Conclusions

Our consensus guidelines provide a robust, evidence-based roadmap for the multidisciplinary management of pLGGs. By integrating molecular drivers into the diagnostic and therapeutic workflow, these guidelines aim to maximize tumor control while safeguarding the developmental potential of the child. While foundational standards are now well-established, addressing the remaining gaps in preclinical modeling and trial standardization is essential for the next generation of precision neuro-oncology.

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Conflict of interest

Jie Ma has been an executive associate editor of the journal *Neurosurgical Subspecialties* since 2024. The authors declare no other conflicts of interest.

Author contributions

JM and FW conceived and designed the project; FW, JZ, SD, XQ, HL, YZ, and JW contributed to the development and writing of the Chinese guideline; LZ drafted the English version; ST, QW and QL revised the manuscript. All authors have made significant contributions to this study and have approved the final manuscript.

Disclaimer

This guideline is based on existing literature and expert consensus and is intended to aid clinical decision-making; however, it cannot substitute for individualized treatment tailored to specific patient circumstances and should not be construed as a legal basis for medical practice.

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