



Pediatric Low-Grade Gliomas: A Continuous Evolution Toward Precision Medicine (Narrative Review)

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Abstract

Background: Pediatric low-grade gliomas (pLGG) represent the most common brain tumors in children. Although their overall prognosis is favorable, their often chronic course and considerable histo-molecular heterogeneity require an individualized management approach. Recent advances in neuroimaging, image-guided surgery, and molecular biology have profoundly reshaped the diagnostic and therapeutic paradigm of these tumors.

Objective: To provide a critical and up-to-date synthesis of current knowledge on pLGG, emphasizing the transition toward an integrated approach based on molecular biology and precision medicine.

Methods: A narrative review of the literature was conducted using PubMed, Scopus, and Web of Science databases, including articles published between 1991 and 2025. Studies addressing epidemiology, diagnosis, therapeutic innovations (surgery, chemotherapy, radiotherapy, targeted therapies), and long-term follow-up were analyzed.

Results: Advances in multimodal MRI have enabled more precise lesion characterization and improved surgical planning. Complete resection remains the main prognostic factor, but minimally invasive and neuronavigation-assisted techniques have enhanced surgical safety. Systemic treatments, historically based on vincristine and carboplatin, are gradually being replaced by targeted approaches directed against BRAF alterations or the MAPK/ERK pathway. Radiotherapy particularly proton therapy provides excellent tumor control while minimizing neuroendocrine sequelae.

Conclusion: Pediatric low-grade gliomas epitomize the ongoing shift in oncology toward precision medicine. The integration of histological, molecular, and radiological data paves the way for more effective and better-tolerated treatments. Future perspectives lie in tailoring therapeutic combinations, preventing late toxicities, and ensuring equitable access to molecular diagnostics across all clinical settings.

Introduction

Gliomas, whether low- or high-grade, represent the most common type of brain tumor in children. Among them, low-grade forms (pLGG) predominate, accounting for approximately 60–70% of all pediatric gliomas [1]. Their slow progression contrasts with the complexity of their management, which stems from their histomolecular heterogeneity and their frequent involvement of critical brain regions.

The 2021 revision of the World Health Organization (WHO) classification of tumours of the central nervous system (CNS), which integrates the specific genetic alterations of the MAPK/BRAF signaling pathway, has profoundly reshaped both the diagnostic and therapeutic approach to these tumors [2]. Surgery remains the standard of care, yet recent advances in neuroimaging, conformal radiotherapy, and targeted therapies are redefining current management paradigms.

Through this narrative review, we aim to provide a synthesis of recent advances in the understanding, diagnosis, and treatment of pLGG, in light of the emerging framework of precision medicine.

Methodology

This narrative review was conducted through a comprehensive literature search focusing on pediatric low-grade gliomas (pLGG). The PubMed, Scopus, and Web of Science databases were queried to identify relevant publications published between 1993 and 2025.

The keywords used included “pediatric low-grade glioma,” “pilocytic astrocytoma,” “BRAF mutation,” “MAPK pathway,” “targeted therapy,” “Packer protocol,” and “proton therapy.” Eligible studies encompassed clinical trials, observational studies, literature reviews, and meta-analyses addressing diagnostic, histomolecular, and therapeutic aspects of pLGG.

The selected data were analyzed descriptively and critically, emphasizing the evolution of diagnostic approaches (imaging, WHO 2021 classification), therapeutic strategies (surgery, chemotherapy, radiotherapy, targeted therapies), and recent trends toward more individualized management of pLGG.

Nosological Framework and the 2021 WHO Classification of tumours of CNS

Pediatric low-grade gliomas (pLGG) are now defined within a nosological framework established by the 2021 WHO integrated classification, which combines histological and molecular criteria [2]. This approach has profoundly reshaped the understanding of glial tumors, being the first to highlight age-specific features and to recognize pediatric gliomas as distinct entities from their adult counterparts. This distinction relies on histological, clinical, and, most importantly, molecular differences, acknowledging that pediatric low-grade gliomas are not merely the low-grade equivalents of adult gliomas, but biologically distinct entities.

Based on these criteria, pLGG are divided into two major subgroups:

1. Circumscribed astrocytic gliomas, including pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, and subependymal giant cell astrocytoma. These tumors are generally well demarcated and characterized by slow, localized growth.
2. Pediatric diffuse low-grade gliomas, mainly encompassing diffuse astrocytomas with MYB, MYBL1, or other gene alterations involving the MAPK/ERK signaling pathway.

At the molecular level, all these tumors share a common oncogenic mechanism; the constitutive activation of the MAPK/ERK signaling pathway, which is now considered the major biological hallmark of pLGG [3].

This activation results from various genetic alterations depending on the histologic subtype:

- In circumscribed forms, the most frequent events include KIAA1549–BRAF fusions, BRAF V600E mutations, and, more rarely, alterations in FGFR1, RAF1, NTRK, or TSC1/TSC2;
- In diffuse forms, alterations typically involve MYB, MYBL1, or FGFR1, leading to the same downstream activation of the MAPK pathway.

This new nosological framework forms the foundation of precision medicine in pediatric neuro-oncology, paving the way for prognostic stratification and targeted therapies tailored to tumor biology.

Tumor type	Key alteration	anatomical distribution
Pilocytic astrocytoma	KIAA1549–BRAF fusion (50–70%), BRAF V600E (extracerebellar), FGFR1 (midline), BRAF V600E + NTRK	Cerebellum, optic pathways, brainstem (in Neurofibromatosis type 1 (NF1) cases)
Diffuse astrocytoma with MYB/MYBL1 alteration	MYB or MYBL1 mutations/fusions, MYBL1 gain 8q13.1, MYB–QKI	Cerebral hemispheres (supratentorial)
Subependymal giant cell astrocytoma	TSC1/TSC2 inactivation (≈80%), PI3K pathway activation	Intraventricular
Diffuse low-grade glioma – MAPK pathway altered	BRAF V600E and FGFR1 mutations	Variable (supratentorial regions)
Angiocentric glioma	MYB–QKI fusion (≈90%)	Frontal cortex
Dysembryoplastic neuroepithelial tumor (DNET)	BRAF V600E (reported), partial loss of Chr22	Temporal cortex
Pleomorphic xanthoastrocytoma	BRAF V600E (≈50%)	Temporal, parietal, or occipital lobes

Figure 1: Main genetic alterations and anatomical distribution of pLGG [4]

Integrated Therapeutic Approaches for Pediatric Low-Grade Gliomas: From Conventional Surgery to Precision Medicine.

1. Surgery: Cornerstone of Initial Treatment

Surgery remains the fundamental cornerstone in the management of pediatric low-grade gliomas (pLGG). The surgical indication is determined by the tumor's location, radiological characteristics, and histopathological features. Technological advances such as neuronavigation, cortical stimulation, and intraoperative imaging have significantly enhanced the precision and safety of surgical procedures, thereby increasing rates of gross total resection while minimizing neurological sequelae [5].

When complete resection is not feasible, a biopsy is recommended, particularly for symptomatic tumors, except in certain cases associated with NF1, where initial observation may be preferred [6]. Even in situations where a watch-and-wait strategy is adopted, molecular characterization of the tumor is becoming a key element in guiding future therapeutic decisions. Modern biopsy techniques, including neuroendoscopic, stereotactic, and robot-assisted approaches, now allow for the collection of sufficient tissue to perform comprehensive histo-molecular analyses.

In a prospective multicenter study conducted by the Children's Oncology Group (Wisoff et al., Neurosurgery, 2011) involving more than 500 children, the 10-year overall survival exceeded 95%, confirming the critical role of initial complete resection in tumor control and long-term survival. The study also demonstrated a direct correlation between the extent of resection and progression-free survival, reinforcing the central role of surgery as the first-line therapeutic step [7].

Despite its major importance, surgery alone is not always sufficient to control the disease, particularly when complete resection is precluded by deep or functionally eloquent tumor locations. In such cases, the risk of recurrence or progression justifies close monitoring and consideration of adjuvant therapy whether chemotherapy, radiotherapy, or, more recently, targeted therapies tailored to the tumor's molecular profile.

2. Chemotherapy: A Tool for Disease Control and Functional Preservation

In the therapeutic management of pLGG, chemotherapy plays a pivotal role, particularly when surgical resection is not feasible or when gross total removal cannot be achieved. It serves as a key treatment strategy aimed at controlling tumor growth while delaying the need for radiotherapy; especially in younger children, in order to preserve neurocognitive and endocrine development.

The first validated protocols were based on the carboplatin–vincristine (CV) combination proposed by Packer et al. in a multicenter phase II study published in *The Journal of Clinical Oncology* in 1993. This regimen

demonstrated an objective response rate of approximately 50% in children with unresectable gliomas, establishing the foundation of standard therapy for newly diagnosed, inoperable, symptomatic, or progressive forms [8].

These findings were later reinforced by a phase III trial conducted by the Children's Oncology Group and led by Ater et al. (JCO, 2012), which compared the CV regimen with the TPCV protocol (thioguanine, procarbazine, lomustine, vincristine). The study, which included 274 children under 10 years of age, showed similar overall survival between the two groups (86% vs 87%), but superior progression-free survival with the TPCV regimen (52% vs 39%), at the cost of increased neurotoxicity and more frequent allergic reactions to carboplatin [9].

More recently, the European phase III trial conducted by Gnekow et al. (*European Journal of Cancer*, 2017) evaluated the addition of etoposide (VCE: vincristine, carboplatin, etoposide) to the standard VC regimen. Conducted in nearly 500 children under 16 years of age with unresectable or progressive gliomas, the study did not demonstrate any significant improvement in progression-free survival (46.1% for VC vs 45.3% for VCE) but reported a higher incidence of hematologic toxicity in the VCE arm [10].

Thus, despite multiple attempts at treatment intensification, the CV regimen remains the standard of care for unresectable pLGG due to its proven efficacy, acceptable tolerability, and its capacity to delay irradiation while maintaining long-term functional preservation.

3. Radiotherapy: From 2D Techniques to Proton Therapy

Radiotherapy, long regarded as a cornerstone in the management of pLGG, continues to play a major role, particularly in cases of progression following surgery or chemotherapy. While it provides excellent tumor control, its use in children remains guided by the need to balance oncologic efficacy with long-term functional preservation.

Early studies, including those by Jenkin et al. (*Int J Radiat Oncol Biol Phys*, 1993) and Pollack et al. (*Cancer*, 2003), reported 5- to 10-year OS rates ranging from 79% to 84%, and PFS rates between 63% and 68%, achieved with conventional two-dimensional (2D) techniques using wide radiation fields at doses of 50–55 Gy. However, these approaches were associated with significant morbidity, characterized by neurocognitive and endocrine sequelae resulting from irradiation of the developing brain [11,12].

The introduction of three-dimensional conformal radiotherapy (3D-CRT) represented a major advance. In the study by Merchant et al. (*J Clin Oncol*, 2009), which included 78 children with symptomatic or progressive disease, the 5-year PFS reached 87.4%, demonstrating the high efficacy of conformal techniques for local control [13]. Nevertheless, the same group showed that the mean dose to normal brain tissue and younger age

at treatment were the main predictors of cognitive decline, evidenced by a progressive reduction in intelligence quotient (IQ) over time.

Endocrine toxicities remain frequent. Merchant and colleagues reported central hypothyroidism in 70% of patients, growth hormone deficiency in 50%, and precocious puberty in 40%. In addition, hearing impairments occurred in 5–6% of cases, correlated with cochlear radiation dose. Although these adverse effects are better controlled with modern techniques, they still warrant long-term, multidisciplinary follow-up [14].

The advent of intensity-modulated radiotherapy (IMRT) and proton therapy has marked a new era, further reducing treatment-related toxicity without compromising tumor control. In the study by Paulino et al. (*Cancer*, 2013), involving 39 children treated with IMRT, the 8-year OS was 93.7% and PFS 78.2%, confirming the precision and safety of this approach [15].

Similarly, a retrospective cohort from the University of Florida, reported by Indelicato et al. (*Int J Radiat Oncol Biol Phys*, 2019), including 174 children treated with proton therapy following surgery or chemotherapy, demonstrated excellent local control rates (85–90% at 5 years), with severe toxicity limited to 4% and central hormonal deficits in 22% of cases [16].

Collectively, these data confirm that proton therapy significantly reduces radiation exposure to surrounding healthy brain structures, decreases both acute and late toxicities, and maintains a high level of tumor control. It therefore represents the treatment of choice whenever available, particularly for younger patients or for tumors located near critical functional areas.

Interestingly, despite the technological advances achieved over the past decades—from conventional 2D techniques to intensity-modulated radiotherapy and proton therapy—the prescribed total radiation dose has remained relatively stable, with a median dose of approximately 54 Gy, typically ranging from 50.4 to 59.4 Gy. This consistency underscores that progress in radiotherapy for pediatric low-grade gliomas has primarily relied on improving dose conformality and sparing of healthy tissue, rather than on escalating radiation intensity.

4. Targeted Therapies: A Revolution Toward Precision Medicine, Limitations, and Future Challenges

The advent of molecular biology has profoundly reshaped the management of pediatric low-grade gliomas (pLGG), paving the way for a more rational and personalized therapeutic approach. A refined understanding of the genetic alterations underlying these tumors (particularly MAPK/ERK pathway abnormalities such as KIAA1549–BRAF fusions, BRAF V600E mutations, and FGFR1 or NF1 alterations) has enabled the identification of specific therapeutic targets, thereby transforming the traditional treatment paradigm [3, 4].

MEK inhibitors (selumetinib, trametinib, binimetinib) and BRAF inhibitors (dabrafenib, vemurafenib) have emerged as promising agents capable of selectively modulating the signaling cascades driving tumor proliferation. Multicenter clinical trials conducted by the Children's Oncology Group (COG) and the Pacific Pediatric Neuro-Oncology Consortium (PNOC) have reported substantial response rates, often exceeding those achieved with conventional chemotherapy. In the PBTC-029B trial, selumetinib demonstrated a disease control rate of 78%, whereas in the PNOC002 study, vemurafenib achieved a 6-month progression-free survival (PFS) rate of 63% among patients with recurrent BRAF V600E-mutant tumors [17,18,19].

Similarly, évérolimus, an mTOR inhibitor, has shown clinical benefit in refractory or NF1-associated cases, contributing to disease stabilization and improvement in quality of life [20]. These orally administered, better-tolerated therapies often allow the delay (or even avoidance) of radiotherapy, which is particularly detrimental in young children.

Nevertheless, several limitations remain. The optimal duration of therapy has yet to be established, and tumor regrowth may occur upon treatment discontinuation. Adverse effects, although generally manageable, require close monitoring and include dermatologic reactions, ocular toxicities, and metabolic disturbances depending on the therapeutic class. Furthermore, access to these agents remains restricted, frequently limited to clinical trial settings and dependent on the availability of comprehensive molecular profiling.

Future challenges involve defining the optimal therapeutic sequencing (first-line versus relapse), exploring rational drug combinations (MEK/mTOR or MEK/BRAF) to overcome resistance, and conducting long-term follow-up to assess neurocognitive and endocrine outcomes.

Thus, despite their current limitations, targeted therapies represent a major advance toward a personalized, effective, and better-tolerated management strategy for pediatric low-grade gliomas.

Author's Perspective

As a clinician involved in the management of pediatric brain tumors, I believe that the future of low-grade gliomas lies in true therapeutic personalization integrating molecular biology, advanced neuroimaging, and preservation of neurological function. Radiotherapy, once approached with caution in children, now holds a more balanced role thanks to the advent of conformal techniques and the emergence of targeted therapies that allow its indication to be delayed or even avoided.

Recent advances, though remarkable, demand continuous vigilance regarding late toxicities and long-term quality of life. The primary challenge remains to translate these therapeutic successes into lasting cures—achieved without major functional or cognitive compromise—through a multidisciplinary, child-centered approach.

Conclusion

pLGG represent a heterogeneous group of slowly evolving tumors whose management relies on a multidisciplinary approach integrating surgery, oncology, radiotherapy, and long-term functional follow-up. Complete surgical resection remains the gold standard when achievable without significant morbidity, while conformal radiotherapy and proton therapy offer effective alternatives with reduced toxicity.

At the same time, the rise of targeted therapies driven by a deeper understanding of the underlying molecular alterations has opened the door to a promising era of precision medicine. The current challenge lies in optimizing therapeutic strategies to achieve durable tumor control while preserving neurological function and ensuring the best possible long-term quality of life.

Abbreviations

pLGG: Pediatric low-grade gliomas

WHO: World Health Organization

CNS: Central nervous system

NF1: Neurofibromatosis type 1

CV: Carboplatin, Vincristine

TPCV: Thioguanine, Procarbazine, Lomustine, Vincristine

VCE: Vincristine, Carboplatin, Etoposide

OS: Overall survival

PFS: Progression-free survival

3D-CRT: Three-dimensional conformal radiotherapy

IQ: Intelligence quotient

IMRT: Intensity-modulated radiotherapy

2D : Two-dimensional

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