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Treatment of pediatric low-grade gliomas

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Abstract

Purpose of review: Pediatric low-grade gliomas and glioneuronal tumors (pLGG) account for approximately 30% of pediatric CNS neoplasms, encompassing a heterogeneous group of tumors of primarily glial or mixed neuronal-glial histology. This article reviews the treatment of pLGG with emphasis on an individualized approach incorporating multidisciplinary input from surgery, radiation oncology, neuroradiology, neuropathology and pediatric oncology to carefully weigh the risks and benefits of specific interventions against tumor-related morbidity. Complete surgical resection can be curative for cerebellar and hemispheric lesions, while use of radiotherapy is restricted to older patients or those refractory to medical therapy. Chemotherapy remains the preferred first line therapy for adjuvant treatment of the majority of recurrent or progressive pLGG.

Recent findings: Technologic advances offer the potential to limit volume of normal brain exposed to low doses of radiation when treating pLGG with either conformal photon or proton RT. Recent neurosurgical techniques such as laser interstitial thermal therapy offer a ‘dual’ diagnostic and therapeutic treatment modality for pLGG in specific surgically inaccessible anatomical locations. The emergence of novel molecular diagnostic tools has enabled scientific discoveries elucidating driver alterations in mitogen activated protein kinase (MAPK) pathway components and enhanced our understanding of the natural history (oncogenic senescence). Molecular characterization strongly supplements the clinical risk stratification (age, extent of resection, histological grade) to improve diagnostic precision and accuracy, prognostication and can lead to the identification of patients who stand to benefit from precision medicine treatment approaches.

Summary: The success of molecular targeted therapy (BRAF inhibitors and/or MEK inhibitors) in the recurrent setting has led to a gradual and yet significant paradigm shift in the treatment of pLGG. Ongoing randomized trials comparing targeted therapy to standard of care chemotherapy are anticipated to further inform the approach to upfront management of pLGG patients.

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Keywords

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INTRODUCTION

Pediatric low-grade gliomas and glioneuronal tumors (subsequently referred to as pLGG) represent the most frequently encountered brain tumors accounting for nearly 30% of pediatric CNS neoplasms overall. pLGG are defined as grade 1 or 2 per the recent World Health Organization (WHO) 2021 classification (CNS5) and encompass a heterogeneous group of tumors of primarily glial histology, including astrocytic and/or oligodendroglial, as well as tumors of mixed neuronal-glial morphology (see Table 1) [1].

There are some important considerations which significantly impact the treatment approach to pLGG.

- First, overall survival (OS) is excellent for the majority of pLGG [2], with 20-year overall survival rates up to 87% [3]. However, patients can experience significant morbidity including vision loss, epilepsy, endocrine dysfunction, motor disability, neurocognitive dysfunction, and decreased quality of life [3, 4]. Therapy is indicated only in the event of sub-totally resected tumors with clinical progression or unequivocal non enhancing (T2/FLAIR MRI sequences) radiographic progression with likelihood of significant morbidity. Treatment goals should not only include long-term tumor control (i.e., radiographic responses), but also minimization of treatment-related morbidity and improvement in functional outcomes (such as visual acuity and motor abilities), quality of life, and neuro-psychological assessments.
- Devising an optimal clinical management plan is complex and requires multidisciplinary input from surgery, radiation oncology, neuroradiology and pediatric oncology and should carefully weigh the risks and benefits of tumor directed interventions against tumor related morbidity. Therefore, a one size fits all approach is unlikely to be effective.
- For some patients, the pLGG maybe represent the initial manifestation of an underlying tumor predisposition syndrome (neurofibromatosis type 1 [NF1], tuberous sclerosis [TS]) which carries important implications for genetic counseling, tumor surveillance and treatment choices.
- Extent of surgical resection, tumor location, histological grade/subtype and age at diagnosis were historically considered for clinical risk stratification and importantly, remain so to this day. However, it has long been recognized that differences in patient outcomes cannot be explained by clinical variables alone. The past two decades have witnessed the emergence of novel molecular diagnostic tools fueling seminal scientific discoveries which have shed light on the fundamental events contributing to gliomagenesis [5]. With few exceptions,

pLGG are exclusively driven by a diverse array of genetic alterations in mitogen activated protein kinase (MAPK) pathway components, resulting in constitutive activation of downstream effector signaling pathways including RAF/MEK/ERK and PI3K/AKT/mTOR [6, 7]. Molecular characterization is now an integral component of contemporary neuropathology and can strongly supplement the clinical risk stratification to improve diagnostic precision and accuracy [8, 9], prognostication (see Table 2) [10] and lead to the identification of patients who stand to benefit from precision medicine treatment approaches [11].

- Mutations in MAPK pathway component genes (*RAS*, *RAF* and *NF1)* can trigger cellular senescence. This phenomenon, termed oncogene induced senescence (OIS) likely accounts for the relatively benign behavior of pLGG and lack of transformation to higher-grade gliomas (with specific exceptions such as *BRAFV600E*) in the absence of additional cooperating mutations [12].
- For pLGG, a specific genetic alteration may either be disease defining (*MYB-QKI* fusion in angiocentric glioma) or play only a supporting role in diagnosis because of its enrichment in specific tumor histologies (*BRAFV600E* mutation in PXA) (see Table 1).
- Despite the common theme of constitutively activated MAPK signaling, there exists substantial molecular heterogeneity. The specific underlying alteration may variably activate different MAPK downstream effector pathways (PI3K/mTOR pathway in SEGA and the RAF/MEK/ERK pathway in *BRAF*/*NF1* altered pLGG). Even the mechanisms driving signaling via a common effector pathway (RAF/MEK/ERK) can be distinct based on -
    - **a.** the type of molecular alteration (BRAFV600E mutant pLGG signal as monomers while BRAF fusion pLGG signal as dimers) which carries important therapeutic implications (BRAF monomer inhibitors cause paradoxical activation and accelerate tumor growth in BRAF fused pLGG and should be avoided)
    - **b.** which specific nodes in the MAPK pathway are disrupted because of complex feedback loops that exist between these nodes and effector pathways
- While pLGG usually appear fairly circumscribed on imaging compared to pediatric high-grade gliomas (pHGGs), some lesions demonstrate a more diffuse growth pattern. These “pediatric-type” diffuse gliomas [1] constitute a new group including 4 entities with some histological overlap but distinct molecular features [1, 13]. They should be differentiated from “adult-type” diffuse gliomas which are more aggressive and require a different approach to diagnosis and management.

Keeping these principles in mind, a brief overview of the management options, including surgery, radiation therapy (RT), and chemotherapy, is discussed in this review. In addition, our growing understanding of the molecular underpinnings of pLGG is leading to the increasing utilization of novel targeted molecular agents mostly in the recurrent, and in

specific scenarios, in the upfront setting, signaling a gradual, yet significant paradigm shift [14, 15]. Therefore, we emphasize the relevant pathophysiology and genetics that significantly impact the clinical approach within the framework of the most frequently encountered pLGG.

Surgery

The surgical treatment of pLGG is complex and requires multi-disciplinary involvement to delineate the goals of surgery. Often, these lesions are discovered incidentally or in the setting of seizure or headache without significant neurological deficit present. In pLGG, maximal safe excision with an intent to cure is the preferred treatment approach and should always be considered. However, this is not always feasible due to location, infiltrative nature, or molecular phenotype of the lesion. Surgical objectives fall into the broad categories of total tumor extirpation, cytoreduction, or biopsy (stereotactic needle and endoscopic).

To address the questions of efficacy and specific type of surgical intervention, clinical, radiographic, diagnostic, and treatment factors must be considered. Currently, there is no validated diagnostic imaging or biomarker available that can predict the clinical grade of the lesion. In pLGG, goals of surgical intervention include symptom palliation and improvement of neurological condition, obtainment of tissue for molecular and histological diagnosis, and reduction in risk of continued tumor growth or malignant transformation. [16] For symptomatic or asymptomatic non-infiltrative and surgically accessible lesions with confidence around a WHO grade 1 diagnosis for which resection is associated with acceptable risk, maximal safe surgical intervention with intent to cure is the preferred treatment approach. Gross total resection of pLGG is significantly associated with improved overall survival (OS), with 10-year OS rates approximating 90%, and is the main predictor of PFS [2, 17–20]. Notably, over 50% of children with residual tumor volume after resection have no disease progression at 5 years, and these patients have excellent long-term survival. Therefore, even though complete resection should be a goal, the benefit of possibly prolonging PFS should be carefully weighed with the risk of neurologic deficit caused by an aggressive resection. While the rates of malignant transformation of pLGG are estimated to be less than 10%, this can be a source of lifelong concern for the patient and their families, and require frequent and longitudinal monitoring.[21]

For lesions that are surgically inaccessible principally being defined by an infiltrative growth pattern on imaging, have known biological behavior that would not warrant resection, or for which resection would leave an unacceptable functional outcome (optic pathway gliomas), the surgical objectives narrow to tissue sampling for diagnosis and molecular classification and debulking in the setting of mass effect and hydrocephalus. Further research is needed to quantify the minimal amount of tissue that is required for histological and molecular analysis in order to better understand if stereotactic or endoscopic biopsies are sufficient for providing diagnostic tissue samples. Laser interstitial thermal therapy is another surgical tool to target focal, surgically inaccessible tumors, such as lesions in the dominant temporal lobe, medial to the internal capsule, or cerebral peduncle [22, 23].

With molecular classification increasing in the role of therapeutic management, tissue sampling should be performed early in diagnosis. In general, the benefits of accurate molecular diagnosis far outweigh the risks of surgical intervention and can often act synergistically with other surgical goals of symptom palliation, restoration of neurological function, or decreasing risk of tumor growth or transformation. However, for certain slow growing pathologies with a well-understood natural history, exposing children to the risk of surgical intervention involving highly functional structures may not be necessary. A reappraisal of the need for surgical intervention in these cases is warranted. In the case of optic pathway and hypothalamic gliomas, surgical intervention is rarely indicated except when the treating team is requesting tissue for diagnosis prior to initiating treatment or to debulk the lesion due to significant mass effect. Given the risks involved with tissue sampling including vision loss, the field should investigate the role of upfront chemotherapy or molecular targeted therapy.[24, 25]

Radiation Therapy

Radiation therapy (RT) is an effective management strategy in both the upfront and salvage treatment settings for pLGG. Historically, RT was the preferred primary treatment for rapidly progressive or unresectable tumors, with 10-year progression-free (PFS) and overall survival (OS) rates of 70% and 80%, respectively.[26–29] RT has also been used in the adjuvant setting, particularly when surgery is limited to partial resection or biopsy for tumors located in the optic pathway, hypothalamus, deep midline structures, and brainstem.[18, 19] Since PFS is significantly reduced after incomplete resections,[18, 30, 31] adjuvant RT is considered for this scenario; however, there is a lack of consensus for this use due in part to the absence of randomized prospective trials.[18, 20, 32] One randomized prospective phase 3 trial sought to evaluate neurosurgical and radiotherapeutic treatments of pLGG;[33] however, the trial was closed early due to practitioner bias in treatment selection. Our current understanding is therefore built upon conflicting retrospective studies, which have suggested that while adjuvant RT may improve PFS, this benefit does not necessarily translate into improved OS.[18, 31, 34] For instance, while one study demonstrated that adjuvant RT improved PFS when complete resection was not achieved (89% vs. 49%, $P < 0.003$), others showed no improvement in PFS with postoperative RT.[20, 32] This unclear PFS benefit suggests that RT could be delayed until the time of progression.[35] However, Tsang *et al* found initial RT improved event-free survival for optic pathway and hypothalamic gliomas, suggesting that delaying RT with chemotherapy may not be without consequence for certain high risk patients.[36] Therefore, in the adjuvant setting, RT is used for patients with symptomatic residual tumors or for those who have radiologic or symptomatic progression.[18]

RT is also favored as part of the management strategy in older children who have failed multiple lines of systemic agents. Historically, the rationale for delaying RT revolved around concern for RT-associated toxicities, namely cognitive decline,[37, 38] endocrine dysfunction,[39] secondary malignancies,[36] vascular damage,[36, 40] and growth abnormalities,[41] the severity of which is highly dependent on the location of the tumor and patient age (<10-years-old).[36–38] Much of the concern about RT-associated toxicity is based on long-term toxicity data derived from trials performed in

the 1970s-1990s, which used 2-dimensional RT techniques that did not enable conformal radiation dose delivery. Major technological advancements have since been made to reduce the radiation dose delivered to normal structures surrounding the tumor: first with 3-dimensional conformal external beam RT (3D-CRT) followed in the 2000s by intensity-modulated RT (IMRT). Importantly, the introduction of proton therapy minimized radiation exit dose,[42, 43] largely contributing to its increasing role in pediatric patients. Some studies suggest that proton therapy may even improve both patient quality of life and cost effectiveness of treatment for pediatric brain tumors.[44, 45] Moreover, outcomes with proton therapy are excellent, with one institutional review over a median follow-up of 11 years reporting 8-year PFS and OS rates of 83% and 100%, respectively.[46] In this study, neurocognitive function was not shown to decline overall; however, there was significant cognitive decline in young children (<7-years-old) and in patients who received significant dose to the left temporal lobe or hippocampus. Endocrine dysfunction was identified in those with higher doses to the hypothalamus or pituitary, and two patients developed moya moya disease. Second cancers are a rare, but feared, potential long-term toxicity after RT. In a large single-institutional study of 1,713 children treated with proton therapy (1,040 for central nervous system [CNS] tumors) over a median follow up of 3.3 years, 5- and 10-year cumulative incidences of second tumors were 0.8% and 3.1%, respectively.[47] Importantly, all but one patient who developed a second tumor were irradiated at age 5 years or younger, and there was a significant relationship between tumor predisposition syndromes and second tumor development. A recent report of 945 pediatric patients treated with proton therapy for CNS tumors reported a low 5-year cumulative incidence of secondary neoplasms of 2.4%.[48] In a recently published prospective study of 174 pediatric patients with LGG treated with proton therapy, 5-year PFS and OS rates were 84% and 92%, respectively, at a median follow-up of 4.4 years.[49] Severe late toxicities (brainstem necrosis, symptomatic vasculopathy, radiation retinopathy, and fatal secondary malignancy) occurred in four patients. While radiation-related toxicity must be acknowledged, studies performed in the modern era have encouraging results and the long latency of toxicity must therefore be appreciated within the context of rapid advances in the field.[50]

In addition to radiation planning advances, improvements in neuroimaging (such as multiparametric magnetic resonance imaging) and patient immobilization have further contributed to accurate delivery of highly conformal radiation dose with smaller target margins. Specifically, planning margins can be safely limited to 10 mm or less to protect adjacent normal structures when delivering the typical dose of 54 Gray (Gy) in 30 fractions.[38] Stereotactic RT is a technique that has demonstrated excellent local control for patients with small (<5 cm) tumors. Dana Farber Cancer Institute reported their 5-year results with this technique using a median dose of 52.5 Gy in 1.8 Gy fractions, demonstrating PFS and OS rates of 83% and 98%, respectively.[51] Importantly, in this study there were no marginal (“near miss”) disease recurrences, meaning that treatment margins can be minimized to reduce radiation-related toxicities without compromising local control.

In summary, technologic advances offer the potential to limit volume of normal brain exposed to low doses of radiation when treating pLGG with either conformal photon[52] or proton[49] RT. The severity of radiation-related toxicities is most often dependent on the age at the time of RT and the location of the tumor. Given the chronic nature of this disease and

long latency of treatment-related toxicities, long-term data are needed, but RT in the modern era offers a safe, effective strategy for local tumor control.

Chemotherapy

Over the past 3 decades multiple prospective clinical trials (single arm or randomized) in children with progressive LGGs were completed (see Table 3). Most patients had diencephalic tumors (optic nerves/chiasm/hypothalamus/optic tracks/optic radiations) with more recent studies including a higher proportion of non-diencephalic tumors including brainstem tumors. Inconsistencies in the inclusion criteria and imaging criteria for response assessment (enhancing versus non enhancing, central vs local review), lack of correlation between radiographic responses and PFS and the long duration of follow up resulting in delayed reporting of results hamper the ability to directly compare results across studies. Nonetheless, these studies demonstrate very similar 5-year PFS rates and better 5-year disease control in children with NF1 compared to those without.

Chemotherapy regimens in newly-diagnosed pLGG achieve 3-year PFS between 50–80% depending on the regimen. Frequently used chemotherapy regimens include i) carboplatin alone or in combination with vincristine (CV), ii) thioguanine, procarbazine, CCNU and vincristine (TPCV) and iii) vinblastine alone. Although carboplatin and vincristine may offer slightly inferior PFS compared to TPCV (not statistically significant) [53], the combination avoids the risks of secondary malignancy and infertility posed by the TPCV regimen and is therefore preferred given the indolent nature of pLGG to mitigate long term sequelae. Carboplatin monotherapy affords the advantage of monthly administration (as opposed to weekly administration with CV regimen) obviating the need for a central line and carries reduced risk of chemotherapy hypersensitivity reactions and infections.

Molecular genetics and targeted therapy

The most common alterations in pLGG are loss of neurofibromin in the context of patients with NF1, and in non-NF1-related pLGG, the fusion and tandem duplication of *BRAF* with *KIAA1549* (class II BRAF alteration which signals as BRAF dimers) and the $BRAF^{V600E}$ mutation (class I BRAF alteration which signals as BRAF monomers), respectively [5, 7, 54]. These seminal discoveries opened the door to precision oncology trials targeting the RAS-MAP kinase pathway with MEK inhibitors (MEKi) (which function downstream of RAF) and BRAF inhibitors (BRAFi) (first generation=BRAF monomer inhibitors and second generation=BRAF dimer inhibitors or pan-RAF inhibitors) [11, 55].

A) pLGG associated with tumor predisposition syndromes (TPS)

Neurofibromatosis type 1 (NF1)—NF1 is an autosomal dominant (AD) tumor predisposition syndrome and affected individuals develop a combination of dermatologic, skeletal, ophthalmic, and neurologic findings at typical ages of onset. Optic pathway gliomas (OPGs) and brainstem low-grade gliomas (LGGs) are the most common intracranial neoplasms found in NF1. Nearly a third of children with OPG have germline mutations in NF1. Conversely, OPGs are detectable in approximately 15% of NF1 patients, usually before the age of 7 years and bilateral OPGs are detected exclusively in NF1. Most of these tumors are WHO grade 1 pilocytic astrocytomas (PA), although most patients are diagnosed

based on imaging without a biopsy. Brainstem gliomas present in late childhood (mean age 7 years), exhibit mass effect on T2 and increased signal on T1 weighted images (unlike UBOs), are more indolent than sporadic brainstem gliomas, and may regress spontaneously. Patients with NF1 also often exhibit multiple T2 hyperintense lesions, mainly in the basal ganglia and brainstem which are referred to as unidentified bright objects (UBOs) and undergo spontaneous regression.

The *NF1* locus maps to chromosome 17q11.2 and encodes neurofibromin, a protein which harbors a GTPase–activating protein domain that functions to silence *RAS* in its activated form. Biallelic inactivation of the *NF1* gene leads to deregulated *RAS* activity, which initiates downstream signaling by activating the RAF/MEK/ERK and the Akt/mTOR pathways.[56] A comprehensive molecular profiling study in NF1 patients using WES of tumor and matched blood germline DNA demonstrated that LGGs have a low mutational burden and primarily exhibit loss of heterozygosity (LOH) in the *NF1* region along with alterations in genes (*FGFR1, PIK3CA*) encoding component of the MAPK pathway [57].

Treatment: Patients with asymptomatic OPG or LGG are managed conservatively, with imaging surveillance and close clinical/ophthalmological follow-up [58]. Surveillance neuroimaging in asymptomatic children with NF1 has not been shown to reduce the incidence of visual loss, with MRI recommended only for patients with ophthalmological findings suggestive of an OPG, such as proptosis, optic disc pallor or vision loss.[58] Only a third of patients with NF1-OPG require treatment, with the primary goal to preserve vision. Radiotherapy is generally avoided given the increased risk of secondary neoplasms [59] and moya moya disease [60], with carboplatin or vinblastine based regimens most commonly used. Recently, molecular targeted therapy with MEK inhibitors has demonstrated impressive anti-tumor effects and is increasingly being considered as second-line therapy for NF1-associated LGGs.[11] The current COG (children's oncology group) study ACNS1831 is a randomized phase 3 trial testing anti-tumor efficacy and visual outcomes during treatment with selumetinib (MEK inhibitor) compared with standard chemotherapy and may alter the current treatment paradigm for NF1-associated LGG (NCT03871257).

Tuberous sclerosis complex (TSC)—TSC is an autosomal dominant multisystem condition characterized by the triad of adenoma sebaceum, epilepsy and mental retardation [61–63]. CNS lesions are the major cause for TSC-related morbidity and mortality.[64] The vast majority of TSC patients develop cortical tubers before birth and subependymal nodules during the first years of life [64–66]. Cortical tubers are benign hamartomas resulting from abnormal neuronal migration and disordered differentiation and demonstrate dysplastic neurons along with giant eosinophilic cells of mixed glioneuronal lineage. Subependymal nodules are hamartomatous lesions growing indolently along the walls of the lateral ventricles. These are WHO grade 1 tumors of mixed glioneuronal lineage and may cause symptomatic obstructive hydrocephalus secondary to their oft occurrence at the Foramen of Monroe. Subependymal giant cell astrocytoma (SEGA) is the most common brain tumor in patients with TSC, observed in 5–15% of confirmed cases and usually occurs in the first 2 decades of life. Size >10 mm, location, growth on serial neuroimaging studies,

and development of hydrocephalus are helpful to distinguish SEGA from a subependymal nodule [66].

The genes responsible are *TSC1*, also known as *Hamartin*, located on chromosome 9q34 and *TSC2* or *Tuberin* on chromosome 16p13 [67] and *de novo* mutations account for approximately 80% of cases [68]. The AKT/mTOR pathway is a key driver of tumorigenesis in TS patients and an important therapeutic target [69, 70].

Treatment: In TS patients, surveillance neuroimaging should be obtained annually during childhood and adolescence, when the risk for SEGA development is greatest.[71] The two main approaches to treatment include surgical resection and targeted medical therapy with mTOR inhibitors such as everolimus. Indications for surgical resection of SEGAs include obstructive hydrocephalus, increased intracranial pressure, tumor progression, and the presence of focal neurologic deficits. Although potentially curative, gross total resection (GTR) is seldom feasible given their intra-ventricular location [72, 73]. TS represents a prototype disease in which biological discoveries have led to the successful development of effective targeted therapies, with profound consequences on clinical management. First-generation mTOR inhibitors (termed rapamycin analogs or rapalogs, including rapamycin) are mTOR complex 1 (mTORC1) specific inhibitors, acting downstream of TSC 1 and 2. Clinical trials using rapalogs have revealed striking tumor regression of virtually all SEGAs in treated TS patients [74–76], and some benefit for neurological symptoms including improved seizure control [77, 78]. Everolimus is FDA approved for pediatric and adult patients with TSC associated SEGAs deemed unresectable. Furthermore, prevention strategies and protocols for long-term therapy with rapalogs are currently being developed for these patients.[79]

B) BRAF fused pLGG

Nearly 30–40% of pLGG harbor focal gains at 7q34 due to a tandem duplication leading to the formation of a novel oncogenic fusion, KIAA1549-BRAF, which represents the most frequent molecular alteration encountered [5, 80, 81]. This rearrangement results in loss of the N-terminal regulatory domain of BRAF and constitutive activation of the RAS/MAPK signaling pathway [5, 81]. KIAA1549-BRAF is enriched in specific histologies (pilocytic astrocytomas which are highly circumscribed) and in tumors arising in the posterior fossa/cerebellum (amenable to gross total resection) resulting in excellent PFS and OS [7, 82–84]. BRAF rearrangements involving non canonical fusion partners including SRGAP [80], FAM131B [85], among others [54, 86, 87] are frequently observed in hemispheric and/or brainstem lesions and tend to arise in older children and adolescents. Given their rarity, impact on patient outcome is difficult to ascertain with some data suggesting lower PFS [7] but requires validation in larger cohorts.

Molecular targeted therapy—Several studies have been completed evaluating MEKi (selumetinib, binimetinib, trametinib) which have demonstrated impressive anti-tumor efficacy across multiple pLGG subtypes [11, 88–92]. Importantly, visual outcomes were reported and improved or stabilized in most patients [89]. Consequently, the COG launched a randomized clinical trial to compare the ORR and functional outcomes for newly

diagnosed pLGG treated upfront with either MEKi (Selumetinib) or standard of care (SOC) chemotherapy in non NF1 pLGG (NCT04166409).

Tovorafenib, a second generation BRAFi (blocks BRAF dimers and causes less paradoxical activation) demonstrated impressive ORR in recurrent/refractory BRAF fusion driven pLGG (FIREFLY-1, NCT04775485) and a global phase 3 randomized trial comparing Tovorafenib vs SOC chemotherapy for newly diagnosed BRAF fused pLGG is planned.

Another important question concerns the durability of the observed responses and whether acquired resistance developed off treatment. The PBTC conducted a re-treatment study (NCT01089101) evaluating selumetinib in patients who previously enrolled on PBTC-029 (MEKi naïve patients) and maintained SD for ≥12 courses or had a sustained PR or CR during their first exposure to selumetinib but later progressed after coming off treatment [93]. Re-treatment with selumetinib (n=35) appeared to be effective with 80% of patients again achieving response or prolonged stable disease.

At present, MEKi or BRAFi (second generation) appear similarly efficacious in BRAF fused pLGG. The results of the above referenced randomized phase III studies may potentially alter the standard treatment paradigm for upfront management of non NF1/BRAF fused pLGG.

C) BRAF V600E

Mutations in BRAF resulting from a single amino acid substitution (valine is replaced with a glutamic acid at position 600 (p.V600E) or infrequently, alternate codon 600 substitutions (V600K/R/D/L), located near the activation segment. These alterations act as a phosphomimetic resulting in constitutive activation of MAPK signaling [94, 95]. BRAF p.V600E mutations are histologically and spatially enriched in with pleomorphic xanthoastrocytoma (40–80%) [96, 97], diffuse astrocytoma (30– 40%) and ganglioglioma (25–45%) and supratentorial lesions demonstrating a high frequency of BRAF V600E alterations, respectively [96–98]. BRAF V600E mutant pLGG have worse PFS and OS compared to other pLGG [99, 100]. This is driven in part by the increased propensity for anaplastic/malignant transformation to HGG in specific histological entities (ganglioglioma and PXA) and may occur several years from initial diagnosis, especially when co-occurring with CDKN2A deletions [101, 102]. These anaplastic GGs and “pleomorphic xanthoastrocytoma like” HGG fare better compared to other HGG but are still significantly worse when compared to pLGG [102, 103].

Molecular targeted therapy—Based on impressive results noted in the phase II ROAR trial [104] and NCI-MATCH ‘basket’ trials [105], the Dabrafenib (BRAFi) and Trametinib (MEKi) combination received tumor agnostic approval for adult and pediatric patients with solid tumors harboring a *BRAFV600E* mutation. For patients with *BRAFV600E* mutant pLGG, preliminary results of a randomized phase II study (Dabrafenib/Trametinib versus chemotherapy) support the use of combined BRAFi and MEKi molecular targeted therapy for front line treatment in lieu of chemotherapy [106]. The combination is associated with less dermatological toxicity than that seen with MEKi alone.

Molecular targeted therapy versus chemotherapy—As is to be expected, BRAFi and MEKi offer distinct advantages to chemotherapy (oral administration, less myelosuppression) but harbor unique toxicity profiles which include rashes, skin and nail infections and rarely, but significantly, cardiac dysfunction and ocular retinal toxicity which require periodic monitoring, supportive care and drug interruption in severe cases. In addition, the importance of tailoring therapy for pLGG based on a thorough understanding of the distinct signaling mechanisms underlying different *BRAF* alterations cannot be overstated. First-generation BRAFi (vemurafenib, dabrafenib) which target the monomeric forms of BRAF should not be used for tumors with BRAF fusion which function as dimers given paradoxical ERK activation resulting in tumor progression as demonstrated in a prior study [107, 108].

Receptor tyrosine kinase (RTK) altered pLGG

Besides *BRAF*, additional fusion genes involving upstream receptor tyrosine kinases (RTKs) have been identified in pLGG including *FGFR1/2/3* (fibroblast growth factor receptor), *NTRK2* (neurotrophic tropomyosin-related kinase), *ROS1* (protein tyrosine kinase encoded by the ROS1 gene), or *ALK* (anaplastic lymphoma kinase), *RAF1, MET* or *PDGFRA* (platelet derived growth factor alpha) [6, 87]. These kinase fusion positive tumors respond to targeted therapy clinically [109]. In pediatric glioma specifically, both entrectinib (*ALK*/*ROS*/*TRK*) and larotrectinib (*TRK* only) have shown potent anti-tumor effects (NCT02637687, NCT02576431) and the latter was recently approved in the treatment of pediatric and adult patients with TRK-altered cancers (NCT02122913).

FGFR altered pLGG

The molecular landscape of FGFR alterations in pLGG can be divided into 2 groups: 1) Single structural variants (SNVs) or 2) rearrangements that result in the expression of a fusion protein. *FGFR1* mutations represent the second most common point mutations in pLGG after *BRAF V600* and are most frequently reported in DNETs, RGNTs and a subset of PAs which occur predominantly in extracerebellar, midline locations [6, 87, 110]. These are hotspot alterations affecting *p.N546* or *p.K656* in the kinase domain and frequently co-occur with a second event in *FGFR1* (“dual hit”) and *NF1* alterations or additional mutations in components of *RAS/MAPK/PI3K* pathway [7, 111]. Rearrangement driven pLGG include fusions of FGFR genes with members of the TACC protein family (*TACC1*, *TACC2*, and *TACC3*) or other partners and internal tandem duplications (ITDs). *FGFR3:TACC3* fusions are reported in pLGG [6, 112]. *FGFR1-TACC1* fusions have been reported in extraventricular neurocytoma [EVN] while several fusions (*FGFR2–KIAA1598*, *FGFR2–CTNNA3* and *FGFR3–TACC3*) have been observed in polymorphous low-grade neuroepithelial tumor of the young (PLNTY) [113]. Other novel mechanisms resulting in constitutive FGFR1 activation include duplication of the entire kinase domain (TKD) called ITD which is frequently demonstrated in DNET or tumors with oligodendroglial-like histology [6, 87, 114].

A small single center study reported the promising efficacy of FGFR targeted therapy in recurrent/refractory FGFR altered pediatric gliomas [115]. Interestingly, skeletal toxicities not encountered in adults were reported in skeletally immature patients including

acceleration of linear growth velocity and slipped capital femoral epiphyses, both of which represent on target effects given the critical role of FGFR3 in bone growth [115].

MYB altered pLGG

MYB alterations are histologically restricted to angiocentric (87%) and diffuse gliomas (41%). Angiocentric gliomas demonstrate characteristic MYB-QKI gene fusion [114, 116] which function via a tripartite mechanism of MYB protein activation, MYB overexpression and the loss-of-function of QKI [116]. Within the same MYB gene family of transcriptional regulators is MYBL1 with similar structure and function [117, 118]. The category of “diffuse astrocytoma, MYB or MYBL1-altered” includes pLGG not bearing the characteristic histologic features of angiocentric glioma but demonstrating recurrent amplifications and structural variants of MYB and MYBL1 [6, 117], including fusions with various gene partners. These tumors arise in young children predominantly in the cerebral hemispheres, although infrequently they occurred in the diencephalon or brainstem [119–121]. Reported 10-year OS and PFS are 90% and 95%, respectively, suggesting that these lesions are indolent [120].

Tectal gliomas

Tectal gliomas *a*rising in the dorsal midbrain typically cause aqueductal obstruction with resultant hydrocephalus [122–124]. These tumors are usually indolent [125, 126] and biopsy is not indicated unless atypical features are present. When biopsied, the majority are WHO grade I PA and frequently harbor KRAS mutations and/or BRAF alterations [127], while histone H3 K27M mutations are absent [124]. Patients can be safely observed post CSF diversion (VP shunt or endoscopic third ventriculostomy) to relieve hydrocephalus and remain progression free without further therapy. Ten-year progression-free and overall survival were 49 and 84 percent, respectively [124, 126, 128].

Cystic pLGG

Some pLGG present with cystic components wherein their biologic behavior may be independent of the solid component of the tumor. These cysts can be symptomatic, necessitating drainage. Approaches to treatment of reaccumulated fluid include repeated drainage via intracavitary ommaya placement, cyst fenestration, bevacizumab or focal RT [129, 130].

Spinal cord pLGG

A recent study reported outcomes in a large cohort (n = 128) of pediatric spinal LGG patients and reported favorable 10-year OS (93 ± 2%) but low 10-year EFS (38 ± 5%), demonstrating a high rate of tumor recurrence and treatment related morbidities resulting in a significant neurological and orthopedic sequela, including kyphoscoliosis, motor disability, pain, and decreased quality of life [131]. An important observation was the excellent disease control rate for patients with localized disease when treated with first-line RT (5-year PFS of 92 ± 8%), whereas patients receiving first-line chemotherapy had 5-year PFS rates of 62 ± 11% which suggest that RT merits serious consideration when adjuvant therapy is required, especially in older, skeletally mature children [131]. Whereas concerns of long-

term neurocognitive and endocrine sequelae from RT are of great importance when choosing adjuvant therapy for intracranial LGGs, these are seemingly less relevant to patients with spinal cord tumors where proton irradiation may help limit exposure of unaffected tissues and subsequent morbidity.

CONCLUSIONS

It is important to individualize the timing and selection of tumor-directed interventions for each patient with pLGG based on clinical (age, extent of resection) and molecular characteristics, severity of clinical symptoms, and functional status at presentation. The low mortality but high morbidity rates highlight the need to focus on functional outcomes rather than survival alone. Accordingly, future clinical trials should include systematic evaluation of late toxicities (particularly with respect to molecular targeted therapies where such data is unavailable currently), while incorporating functional outcomes (such as motor abilities), quality of life, and neuro-psychological assessments. Moreover, several important questions remain unresolved, including the role, timing (front line versus relapse) and durability of responses with molecularly targeted agents. It is paramount that future prospective studies will build on the observations made, and ultimately lead to further improvements in both tumor control and functional outcomes for pLGG.

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Table 1.

WHO 2021 classification of pediatric low grade gliomas/glioneuronal tumors [1, 13, 54], tumor histologies and associated molecular alterations

WHO classification	Molecular alteration
Pediatric-type diffuse low-grade gliomas	
Diffuse astrocytoma, MYB- or MYBL1-altered	MYB- or MYBL1-altered
Angiocentric glioma	MYB-altered
Polymorphous low-grade neuroepithelial tumor of the young	FGFR2/3 Fusions (30-40%) BRAF p.V600E (30-40%)
Diffuse low-grade glioma, MAPK pathway-altered	-
Circumscribed astrocytic gliomas	
Pilocytic astrocytoma	KIAA1549-BRAF (70-80%) FGFR1-TACC1 (3-5%) FGFR1 SNV (3-5%) BRAF p.V600E (3-5%) Other BRAF Fusions (2-5%) CRAF Fusions (2-5%) PTPN11 SNV (2-5%) KRAS/HRAS SNV (2-5%)
High-grade astrocytoma with piloid features	BRAF p.V600E TSC1/2 SNV (85-95%)
Pleomorphic xanthoastrocytoma	PRKCA SNV (80-90%)
Subependymal giant cell astrocytoma	MN1
Chordoid glioma	
Astroblastoma, MN1-altered	
Glioneuronal and neuronal tumors	
Ganglioglioma	BRAF p.V600E (40-50%) KIAA1549-BRAF (10-15%) BRAF pV600E/D (40-60%)
Desmoplastic infantile ganglioglioma/astrocytoma	FGFR1 SNV (5-10%) KIAA1549-BRAF (2-5%) FGFR1-TKD duplication (20-30%)
Dysembryoplastic neuroepithelial tumor	FGFR1 SNV (20-30%) FGFR1-TACC1 (10-15%) Other RTK SNV/Fusions (5-10%) BRAF p.V600E (5-10)
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters	SLC44A1-PRKCA (80-90%) PIK3CA SNV (20-30%) KIAA1549-BRAF (20-30%) FGFR1 SNV (20-30%)
Papillary glioneuronal tumor	
Rosette-forming glioneuronal tumor	MAP2K1 SNV/Indel (50-60%) BRAF p.V600E (5-10%) Other BRAF SNV (5-10%)
Myxoid glioneuronal tumor	FGFR2 Fusions (3-5%)
Diffuse leptomeningeal glioneuronal tumor	
Gangliocytoma	
Multinodular and vacuolating neuronal tumor	
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	
Central neurocytoma	
Extraventricular neurocytoma	
Cerebellar liponeurocytoma	

Table 2.

Molecular-Based Risk Stratification of pLGG [7]

Risk group	Alteration type	Outcomes
Low	Gene fusions (*BRAF-KIAA1549*, *FGFR1-TACC1*) Germline *NF1* mutations	10-year PFS of 67% and OS of 98% 20-year PFS and OS of 58% and 96%, respectively. [7]
Intermediate	*BRAF p.V600E* without *CDKN2A* deletion, *FGFR1* SNV or *MET* mutations Co-occur with other alterations	10-year PFS and OS of 35% and 90% 20-year PFS of 27% and 20-year OS of 81%, respectively. [7]
High	*H3.3 p.K27M*, or *BRAF p.V600E* with *CDKN2A* deletion	10-year PFS and OS of 0% and 35% 10-year PFS and OS of 0% and 60%, respectively. [7]

Table 3.

Results of prospective clinical trials for newly diagnosed sporadic pLGG

Study	Design	Chemotherapy	N	EFS/PFS
Packer et al [132]	Single arm, multicenter	CV	63 NF1 (n=15)	2-y 79 ± 11% 2-y 79 ± 11%
POG [133]	Single arm	C	29 NF1 (n=21)	3-yr 51 ± 9% 5-y 61 ± 12%
SFOP [134]	Single arm	PCV/CARBO; VP16/CPDD VCR/CYTOX	62 NF1 (n=23)	3-yr 42 ± 12% 3-y 62 ± 13%
HIT-LGG-1996 [135]	Single arm	CV	161 NF1 (n=55)	5-yr 47% 5-y 68%
COG A9952 [53]	Randomized multicenter	TPCV CV	137 137 NF1 – single arm – CV only (n=127)	5-yr 52% ± 5% 5-yr 39% ± 4% (ns) 5-yr 69 ± 4%
COG (ACNS0223) [136]	Single arm	CV + TMZ	66	5-yr 46 ± 13%
(SIOP European Brain Tumor Committee) [137]	Randomized multicenter	CV CV + VP-16	497	5-yr 46% 5-yr 45% (ns)
[138]	Single arm	Vinblastine	54 NF1 (n=15)	5-yr 42% 5-yr 85%