Pediatric Low-Grade Gliomas: Diagnosis, Treatment, and Future Directions

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Angela J. Waanders, Jane E. Minturn, and Michael J. Fisher

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Abstract

Low-grade gliomas are the most common brain tumor in children, accounting for 30–50% of central nervous system tumors in the pediatric age group. They can arise anywhere along the neuraxis and are a heterogeneous group of neoplasms with treatments and outcomes that vary widely by age, tumor location, and extent of surgical resection. Treatment ranges from expectant observation to surgery, chemotherapy, and radiotherapy as single or combined modality therapies. Pediatric low-grade gliomas share a unique association with several inherited genetic conditions, including neurofibromatosis type 1 and tuberous sclerosis. Children with these genetic disorders have a markedly increased risk of developing low-grade gliomas during childhood, and the prognosis and treatment choices may differ substantially from children with identical tumors who do not carry these genetic mutations. Long-term overall survival of all children with low-grade gliomas is very good; therefore, the potential late effects of treatment must be considered carefully in making treatment decisions. As our understanding of the genetic aberrations in low-grade gliomas evolves, novel molecular targets are being identified that may allow for more precise, tumor-directed drug delivery.

A.J. Waanders • J.E. Minturn • M.J. Fisher (✉)
Division of Oncology, The Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, 10th Floor, 3501 Civic Center Blvd., Philadelphia, PA, USA, 19104
e-mail: fisherm@email.chop.edu

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 14*,
DOI 10.1007/978-94-017-7224-2_2

Introduction

Low-grade gliomas are the most common type of brain tumor in children. They can occur anywhere within the central nervous system (CNS) including the cerebellum (15–25% of all pediatric CNS tumors), cerebral hemisphere (10–15%), deep midline structures (10–15%), optic pathway (5%), spinal cord (<5%), and brain stem (2–4%) (Sievert and Fisher 2009; Scheinemann et al. 2009). They comprise a heterogeneous group of tumor histologies. Classification is based on which normal cell they most closely resemble and includes astrocytomas, oligodendrogliomas, and mixed glial-neuronal tumors. Grading is determined by a number of factors including presence of necrosis, giant cells, mitosis, endothelial proliferation, hyperchromatic nuclei, and pleomorphic cells. Low-grade gliomas encompass World Health Organization (WHO) grade I and grade II tumors.

As a group, low-grade gliomas in children tend to be indolent. Unlike their adult counterparts, malignant transformation is rare. Dissemination is also uncommon, occurring at diagnosis in approximately 5% and at the time of progression in up to 10% of patients (Perilongo et al. 2003). Pilocytic astrocytomas (WHO grade I) and diffuse fibrillary astrocytomas (WHO grade II) account for the majority of pediatric low-grade gliomas. Pilocytic astrocytomas (WHO grade I) are considered the classic pediatric low-grade glioma and most commonly occur in the 0–14 year age range. Although they can arise anywhere in the central nervous system, they are more frequently located in the cerebellum, hypothalamus/optic pathway, dorsally exophytic brain stem, and spinal cord. In contrast, only 10% of diffuse fibrillary astrocytomas occur before the age of 20 years (Dolecek et al. 2012). These tumors are more often located in the supratentorial region, deep midline structures, and the cervicomedullary region of the brain stem. Although dissemination has been reported with primary tumors in all CNS locations and most low grade glioma histologies, it appears to occur more commonly with pilocytic astrocytomas and primary tumors of the hypothalamic-chiasmatic region (Perilongo et al. 2003).

Other low-grade glioma histologies are less common in children. Pilomyxoid astrocytoma (WHO grade II) describes a subset of pilocytic tumors with more aggressive clinical behavior. These tumors tend to occur in the hypothalamus and more often arise in very young children with mean age of 21 months (Johnson et al. 2010). Although they are also WHO grade II, pleomorphic xanthoastrocytomas are less aggressive than diffuse fibrillary astrocytomas, with a clinical phenotype similar to pilocytic astrocytomas. Gangliogliomas (WHO grade II) are often discovered as an incidental finding in children with seizures and localize to the temporal lobes. Subependymal giant cell astrocytomas (WHO grade I) occur in the ventricles and are almost exclusively seen in children with tuberous sclerosis syndrome. Oligodendrogliomas (WHO grade II) are uncommon, accounting for only 2% of brain tumors in children less than 14 years of age.

Low-grade gliomas present in a similar manner as other brain tumors, although often with a prolonged duration of symptoms prior to diagnosis. Symptoms are either due to obstruction of the ventricles resulting in increased intracranial pressure or dependent on the location of the tumor. With the former, symptoms include headaches (particularly in the morning), nausea, vomiting, and lethargy with findings of decreased upward gaze, sixth cranial nerve palsies, and papilledema on neurological examination. In addition to symptoms of increased intracranial pressure, low-grade gliomas of the cerebellum often present with ataxia and dysmetria. Symptoms of cortical tumors are dependent on which lobe is involved; for example, temporal lobe tumors present with seizures while frontal lobe tumors are often associated with behavioral changes. Hypothalamic gliomas can present with failure to thrive, diabetes insipidus, precocious puberty, delayed growth, or other endocrine abnormalities. In addition, because of the proximity of the hypothalamus to the optic chiasm, visual field deficits can occur. Children with optic pathway gliomas, frequently present with visual acuity loss, nystagmus, strabismus, head-tilt, proptosis,

and optic nerve pallor on examination. Of note, multifocal involvement of the optic pathway is found almost exclusively in children with neurofibromatosis type 1 (NF1). These patients account for up to 70% of all optic pathway gliomas in children. The presentation of low-grade gliomas of the brain stem is dependent on tumor location but often includes lower cranial nerve deficits (dysphagia, dysarthria, abnormal breathing) and long tract signs (hemiparesis, spasticity, hyperreflexia, extensor plantar response). Children with low-grade gliomas in the spinal cord typically present with back or neck pain, extremity weakness, gait disturbance, and/or kyphoscoliosis.

This chapter will focus on diagnosis, current treatment strategies, outcomes, and future treatment directions in the most common pediatric low-grade gliomas.

Diagnosis

Despite their clinical heterogeneity, pediatric low-grade gliomas demonstrate common features on magnetic resonance imaging (MRI), including hypointensity on T1-weighted images and hyperintensity on T2-weighted or fluid attenuation inversion recovery (FLAIR) sequences (Figs. 2.1 and 2.2). Enhancement patterns on post-gadolinium sequences are variable. Pilocytic astrocytomas tend to be well-circumscribed, with a brightly contrast-enhancing mural nodule and often a large cystic component (Fig. 2.1). In contrast, diffuse fibrillary astrocytomas are less circumscribed and typically exhibit minimal enhancement. It is important to distinguish low-grade brain stem gliomas (e.g. dorsally exophytic, cervicomedullary, and focal) (Fig. 2.2) from the highly aggressive diffuse intrinsic pontine brain stem gliomas. The latter expand the brain stem, have non-discrete borders and do not enhance to a large extent. Low-grade gliomas of the spinal cord tend to be focal, well-circumscribed lesions (Fig. 2.2), often associated with a syrinx.

In most cases, surgical biopsy is performed to obtain tumor tissue for histological diagnosis, and more recently for characterization of genetic alterations. On rare occasions, diagnosis can be made without obtaining tissue because of characteristic appearance of the tumor on MRI; examples include optic pathway gliomas in the setting of NF1 and most tectal gliomas. Extent of resection is determined with postoperative MRI, which should be performed within 24–48 h after surgery in order to better distinguish residual tumor from post-operative changes. Although uncommon, if leptomeningeal dissemination is suspected, MRI of the entire spine (Fig. 2.2) and lumbar puncture for CSF cytology should be performed.

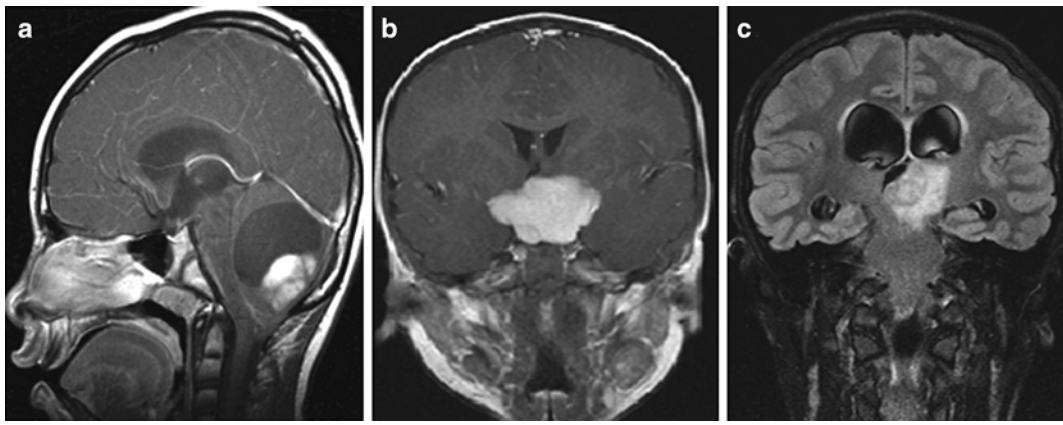

Fig. 2.1 Magnetic resonance images of three different pediatric low-grade gliomas. (**a**) Cerebellar pilocytic astrocytoma (sagittal post-gadolinium sequence) with mural nodule and large cystic component. (**b**) Hypothalamic/optic chiasm glioma (coronal post-gadolinium sequence). (**c**) Thalamic pilocytic astrocytoma (coronal fluid attenuation inversion recovery sequence)

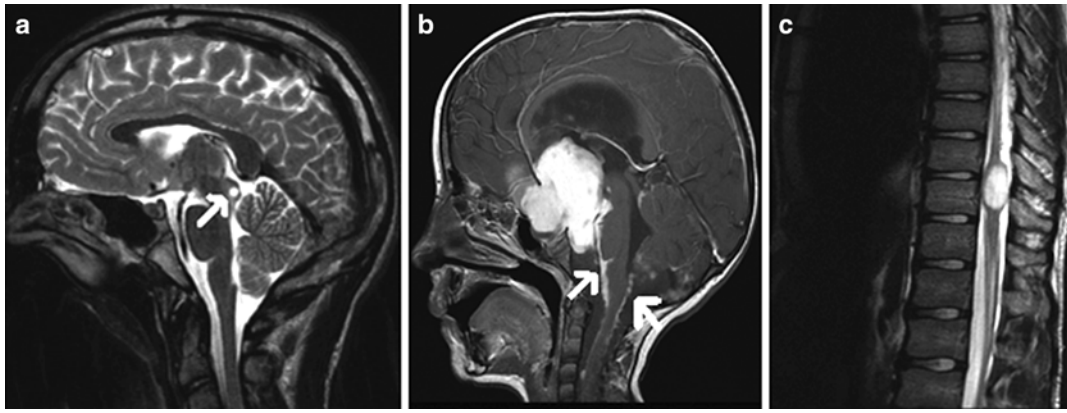

Fig. 2.2 Magnetic resonance images of three different pediatric low-grade gliomas. (**a**) Tectal glioma (sagittal T2 sequence, marked by *arrow*). (**b**) Disseminated pilocytic astrocytoma (sagittal post-gadolinium sequence) with large hypothalamic primary and leptomingeal seeding (*arrows*). (**c**) Thoracic spinal cord diffuse fibrillary astrocytoma (sagittal T2 sequence)

Despite WHO criteria, histopathological classification of gliomas can be difficult. Although partly due to intra-tumoral heterogeneity, more often, the difficulty lies with the experience of the individual neuropathologist and lack of molecular markers for accurate classification. Post-hoc neuropathology review of specimens from a large pediatric high-grade glioma trial resulted in 70 of the 250 cases being reclassified from high-grade to low-grade (Gilles et al. 2008). Although this study was conducted before the current WHO criteria, it highlights the subjective nature and risk for error in classification.

Treatment and Outcomes

Complete surgical resection is the most consistent prognostic factor for prolonged progression-free (PFS) and overall survival (OS) for pediatric low-grade gliomas, and is associated with 10-year overall survival rates of 90% or greater and rare tumor recurrences (Sievert and Fisher 2009). A significantly higher rate of tumor progression is reported in children with subtotal resections. In one report, the 10-year PFS after subtotal resection was only 55% (Fisher et al. 2001). Similarly, a large (660 children), prospective, cooperative intergroup trial, performed by the Children's Cancer Group and Pediatric Oncology Group, reported a 5-year progression-free survival of 45–65% in subjects with residual tumor of any size (Shaw and Wisoff 2003). A recent single institution review of spinal cord low-grade glioma outcomes also supports extent of surgical resection as the most important prognostic factor for PFS; 5-year PFS was 88% in children with complete resection, but only 34% after subtotal resection (Scheinemann et al. 2009). Although diffuse infiltrating histology is associated with an increased risk of progression and/or recurrence compared to pilocytic astrocytomas, treatment decisions are still primarily driven by tumor location, as this is the best indicator of expected extent of resection.

Low-grade gliomas in the cerebellum and superficial cerebral hemispheres are most amenable to definitive surgical therapy. If a gross total resection is achieved, adjuvant treatment is not indicated. Post-operative management consists of observation with close clinical and radiographic follow-up. The treatment decision for children with subtotal resection is less straightforward. If the child tolerated the initial surgery with minimal morbidity, a second surgery in the immediate post-operative period to attempt a more definitive resection can be considered. Alternatively, given the generally indolent nature of these tumors, serial follow-up with brain MRI at regular intervals, and deferring the decision for

repeat resection or adjuvant therapy until there is evidence of tumor progression, is an accepted approach. If further therapy is indicated and repeat surgery is not feasible or would result in unacceptable morbidity, adjuvant chemotherapy should be considered for young children, with radiation therapy reserved for older children. The role of adjuvant therapy along with specific treatment regimens will be discussed below. Overall survival outcomes are excellent for children with low-grade gliomas in these locations (greater than 90% at 10 years). Ten year PFS is 82% in cerebellar tumors and 79% in cerebral hemisphere tumors, and this rises to virtually 100% if total resection was achieved on initial surgery (reviewed in Sievert and Fisher 2009).

Low-grade gliomas located in the supratentorial midline structures are more difficult to manage because extent of resection is often limited. Biopsy of these tumors is essential, to guide treatment and inform prognosis. This is particularly important in unilateral and bilateral tumors of the thalamus, in which a significant proportion are high-grade in histology (Puget et al. 2007). As these tumors may have mixed histology with both low-grade and high-grade areas, it is important to sample the part of the tumor that has the most malignant characteristics. A single institution retrospective review of 54 children with unilateral thalamic tumors demonstrated a mean overall survival of greater than 60 months (low-grade glioma) versus 21 months (high-grade glioma) (Puget et al. 2007). Positron emission tomography (PET) can be used to help guide stereotactic biopsy. Imaging with amino acid tracers may have an advantage over fluorodeoxyglucose (FDG), because of the high FDG uptake in pilocytic astrocytomas (Fisher and Phillips 2006). Although aggressive resection has historically been deferred because of the risk of significant neurological compromise, recent data suggests that greater than 90% resection can be achieved in almost half of unilateral thalamic gliomas, and that extent of resection is a significant prognostic factor (Puget et al. 2007). However, almost one third of patients were neurologically worse following aggressive surgical resection. Following biopsy or attempted resection, if symptoms are minimal, observation until radiographic progression is a reasonable approach. Thalamic low-grade gliomas are usually associated with a worse progression free and overall survival in comparison to tumors in the cerebellar region, likely related to extent of surgical resection as well as anatomical location. Moreover, children with bithalamic low-grade gliomas have a reported worse overall survival compared to those with unilateral thalamic tumors (Puget et al. 2007).

Historically, following biopsy, focal radiation therapy (45–54 Gy) was considered as front-line therapy for supratentorial midline low-grade gliomas. Data looking at the impact of radiotherapy on overall survival is conflicting. Reported 10-year progression-free survival rates for children receiving radiation therapy have typically been as high as 65–90% (Sievert and Fisher 2009). More recent studies suggest that immediate postoperative irradiation, when compared to cytotoxic chemotherapy or observation alone, does not result in improved progression free survival in children with residual low-grade gliomas (Kortmann et al. 2010). In this context, the role of radiotherapy needs to be carefully considered, particularly weighing possible benefit against the known neurocognitive effects. Multiple studies confirm the adverse effect of whole brain irradiation on IQ in survivors of pediatric brain tumors (reviewed in Sievert and Fisher 2009). Other neurocognitive effects of radiotherapy to the brain include memory impairment and attentional difficulties, and are not limited to young children. In addition, radiation is associated with hormone deficits, secondary malignant neoplasms, vasculopathy and stoke.

Given the risks of radiotherapy, there is an increasingly prominent role for adjuvant chemotherapy in children with progressive low-grade gliomas, particularly those less than 12 years of age, who are at highest risk for radiation-related neurocognitive impairment. A summary of clinical trials using multi-agent chemotherapy for low-grade glioma is listed in Table 2.1.

The most widely used combination therapy is carboplatin and vincristine. In a large multi-institutional trial enrolling 78 children, reduction

Table 2.1 Multi-agent chemotherapy for pediatric low grade glioma

Drugs	N	Objective response[a]	PFS
Vincristine/Actinomycin D (Packer et al. 1988)	24[b]	37.5%	~48% (4 years)
Carboplatin/Vincristine (Packer et al. 1997)	78	56%	68% (3 years)
Carboplatin/Vincristine (Ater et al. 2012)	137	50%	39% (5 years EFS)
Carboplatin/Vincristine (Ater et al. 2008)	127[b, c]	61%	69% (5 years EFS)
TPCDV (Prados et al. 1997; Mishra et al. 2010[b])	42	36%	45% (3 years)
	33[b]	n/a[b]	30% (5 years)[b]
			23% (15 years)[b]
TPCV (Ater et al. 2012)	137	52%	52% (5 years EFS)
Cisplatin/Etoposide (Massimino et al. 2002)	34	70%	78% (3 years)
Cisplatin/Etoposide (lower-dose regimen) (Massimino et al. 2010)	37	65%	65% (3 years EFS)
Procarbazine/Carboplatin, Etoposide/Cisplatin, Vincristine/Cyclophosphamide (Laithier et al. 2003)	85[b]	60%	34% (5 years)

Abbreviations: *PFS* progression-free survival, *EFS* event-free survival, *T* thioguanine, *P* procarbazine, *C* CCNU (Lomustine), *D* dibromodulcitol, *V* vincristine

[a]Complete, partial, and minor response

[b]Hypothalamic/optic pathway glioma only

[c]Neurofibromatosis type 1 only

in tumor size or disease stabilization occurred in the majority of patients with a 3-year PFS rate of 68% (Packer et al. 1997). The primary limitation to this drug combination is that many children, up to 40% in some reports, develop an anaphylactoid hypersensitivity reaction to carboplatin with increased exposure to the drug (Sievert and Fisher 2009). An alternative regimen using the combination of thioguanine, procarbazine, lomustine (CCNU), dibromodulcitol, and vincristine (TPCDV) is also effective against progressive low-grade gliomas, with a reported 3-year PFS of 45% (Prados et al. 1997). However, the 15-year PFS rate of the same TPCDV regimen in children with hypothalamic/optic pathway low-grade gliomas is only 23% (Mishra et al. 2010). A modification of this regimen (eliminating dibromodulcitol, now "TPCV") was directly compared to carboplatin/vincristine in a randomized clinical trial within the Children's Oncology Group. Results from this trial demonstrate a non-statistically significant trend toward improved event-free survival with the TPCV regimen over carboplatin/vincristine, though both regimens had equal response rates and both allowed delay in radiotherapy (Ater et al. 2012).

Chemotherapy options are limited for children with tumors that do not respond to either of these two, commonly used, front-line chemotherapy regimens. Cisplatin plus etoposide has been evaluated in a small group of children with unresectable low-grade gliomas with a reported 3-year progression free survival of 78 and 65% using a lower dose regimen (Massimino et al. 2010). Cisplatin is not associated with the same rate of allergic reactions as carboplatin; however, there is a risk of hearing loss with cisplatin, which is a particular issue in children with optic pathway or hypothalamic tumors, who are already at risk for visual impairment.

Single agent, low-dose weekly vinblastine, has demonstrated disease stabilization in 42% of patients who were started on it for recurrent or refractory disease (Bouffet et al. 2012). Several chemotherapy regimens used for adult and pediatric high-grade glioma have been studied in recurrent/refractory low-grade glioma with varying success. Single agent temozolomide demonstrated activity in a subset of pediatric low-grade gliomas, but provides only limited disease stabilization with a 4 year PFS rate of 17% (Gururangan et al. 2007). Bevacuzimab-based therapy, commonly used in adult high-grade gliomas, demonstrates activity in limited early trials of multiply recurrent childhood low-grade glioma and warrants further study and attention (Hwang et al. 2012).

Hypothalamic/optic tract low-grade gliomas represent a unique category of low-grade glioma in pediatrics. Up to 70% of these tumors occur in the setting of neurofibromatosis type 1 (NF1). Most are pilocytic astrocytomas, although other low-grade glioma histologies can occur. Fortunately, most of these tumors are indolent; in fact, less than half of those associated with NF1 will become symptomatic and require treatment (Fisher et al. 2012). Favorable prognostic factors include a concurrent diagnosis of NF-1 and tumor location, with tumors of the optic nerves and chiasm associated with a better visual outcome than tumors involving the hypothalamus and optic tracts/radiations (Fisher et al. 2012; Sievert and Fisher 2009). Management of these patients is focused primarily on the goal of preserving vision. In most cases, newly diagnosed patients are observed with short-interval MRI and ophthalmologic follow-up. Indications for treatment include a documented decline in visual acuity or significant tumor progression on MRI scan with associated symptoms and signs. Treatment may be considered at diagnosis for patients with severe visual impairment, extensive tumor, and/or tumor involving the hypothalamus and optic tracts/radiations. Surgical resection is usually contraindicated due to the risk of worsening vision loss, compromise of the hypothalamic-pituitary axis, and risk of stroke. However, resection of unilateral optic nerve tumors is considered when there is absent or severe impairment of vision and painful or disfiguring proptosis. In addition, large chiasmal/hypothalamic tumors that exert mass effect on surrounding structures and obstruct the third ventricle with resultant hydrocephalus may benefit from surgical debulking. When treatment is indicated, chemotherapy is usually pursued initially. Carboplatin/vincristine is the preferred front line regimen, as TPCV is avoided in children with NF1 due to the increased risk of secondary malignancies in this patient population with exposure to the alkylating agents procarbazine and CCNU. Focal radiation to the optic pathway/hypothalamus may result in worsening of vision and permanent endocrine dysfunction. In addition, the risks of cerebrovascular disease, secondary malignant neoplasms, and neurocognitive deficits are particularly high for those with NF1 (Sievert and Fisher 2009). Therefore, radiotherapy is reserved for older children without NF1 or those with refractory progressive tumors that have failed multiple chemotherapy regimens.

Low-grade gliomas of the brainstem include dorsally exophytic, cervicomedullary, and tectal gliomas. Diffuse intrinsic pontine gliomas, even if low-grade in histology, are not included in this category as they have an especially aggressive clinical course and poor overall survival. Surgical resection is the primary treatment for children with dorsally exophytic brainstem gliomas. As these tumors arise from the floor of the fourth ventricle, a thin layer of tumor often remains. However, the majority of patients remain progression-free after resection (Rutka and Kuo 2004). Cervicomedullary low-grade gliomas tend to grow slowly. As such, they are usually managed conservatively with close observation. Surgical resection should be considered with radiographic or clinical progression. However, gross total resection often cannot be achieved without unacceptable risk (Rutka and Kuo 2004). Adjuvant therapy is recommended for tumors that progress following surgery. Tectal gliomas are indolent tumors and rarely cause functional impairment. They typically present with hydrocephalus, and therefore are managed with endoscopic third ventriculostomy or placement of a ventriculoperitoneal shunt. Biopsy and further therapy is pursued only for radiographic or clinical progression (Rutka and Kuo 2004).

There are few reports on spinal cord low-grade glioma in children, and a consistent approach to treatment does not exist. The majority of low-grade gliomas of the spinal cord are located in the cervical or thoracic cord and are WHO grade I histology. Progression free and overall survival rates are reportedly comparable to intracranial tumors; however, controversy remains regarding the role of adjuvant therapy for residual spinal cord tumors after surgery. Extent of resection has the greatest impact on PFS; unfortunately, orthopedic and neurologic surgical morbidity can be unacceptably high (Scheinemann et al. 2009). Carboplatin/vincristine, TPCV, and vinblastine

have been used at initial presentation and/or at recurrence with reported activity. Chemotherapy appears to warrant further study as an approach to improve PFS, minimize the need for aggressive surgical attempts, and delay or eliminate the use of radiation therapy (Scheinemann et al. 2009).

There is no standard management for disseminated low-grade glioma. Although biopsy is indicated to confirm diagnosis, aggressive resection is rarely pursued, as gross total resection of the primary tumor is not curative in and of itself. The selection of radiation or chemotherapy is made based on similar factors (age and tumor location) as for non-metastatic tumors. Objective tumor responses and prolonged stable disease can be achieved; however both PFS and OS are worse compared with isolated tumors (Perilongo et al. 2003).

Future Directions

Newer treatments are needed for the many children each year who suffer considerable morbidity and premature death from progressive low-grade gliomas. Treatment options are limited for children with tumors that cannot be completely surgically resected. Studies of adjuvant chemotherapy and radiation therapy reveal significant rates of early and late progression. Very young children and infants present an even more difficult treatment challenge as they are at higher risk for significant, neurocognitive treatment-related deficits. Newer radiation treatment strategies are being assessed for their ability to minimize long-term toxicity while maintaining efficacy. Stereotactic fractionated radiotherapy appears to have similar efficacy compared with traditional radiotherapy approaches, however, whether it minimizes the neurocognitive risks is not yet clear (Sievert and Fisher 2009). Proton radiotherapy is currently under evaluation for this population (Brower et al. 2013).

Intensification of treatment with traditional chemotherapy agents does not improve survival (Fouladi et al. 2003), likely secondary to biological reasons. Cytotoxic chemotherapy targets rapidly dividing cancer cells. Conversely, pediatric low-grade gliomas often display indolent growth patterns. Despite this, their location can make even sub-centimeter growth potentially devastating with neurological sequela such as loss of vision or disruption of hypothalamic function. Moreover, for long-term survivors, there is significant risk of adverse neurocognitive and neuroendocrine outcomes. Survivors who had tumors located in the cerebral hemisphere, were younger at diagnosis, and/or had hydrocephalus requiring a shunt are more likely to have lower cognitive performance on IQ scales (Reimers et al. 2007). Even survivors of pediatric low-grade glioma of the cerebellum, treated with surgery alone, have long-term cognitive and adaptive-behavioral impairment (Ris et al. 2008).

Improvements in pediatric low-grade glioma therapy have previously been slow to advance, and only recently, has the biology underlying these tumors begun to be molecularly characterized, and potential therapeutic targets identified. Historically, glioma classification has relied on histological characterization. As, large-scale sequencing efforts utilizing whole-genome, transcriptome, and targeted high-throughput sequencing of tumors have become available, recurrent genetic alterations driving aberrant cell signaling pathways have been identified. In 2008/2009, the identification of an oncogenic *KIAA1549-BRAF* fusion gene, resulting in constitutive BRAF activation was described in the majority of pilocytic astrocytomas and first implicated BRAF in pediatric low-grade glioma development (Pfister et al. 2008; Sievert et al. 2009). Additional activating mutations of BRAF, including $BRAF^{V600E}$ in WHO grade II pleiomorphic xanthoastrocytomas and diffuse astrocytomas (Zhang et al. 2013), new *KIAA1549-BRAF* fusion variants, and novel *BRAF* fusions and mutations in non-cerebellar pilocytic astrocytomas (Jones et al. 2013) further validate BRAF as an oncogenic driver in low-grade gliomas. More recently, recurrent mutations, fusions, and duplications affecting the tyrosine kinase domain in the fibroblast growth factor receptor (*FGFR1*) were identified in diffuse grade II (Zhang et al. 2013) and non-cerebellar pilocytic (Jones et al. 2013)

astrocytomas, which, like mutated *BRAF*, result in dysregulation of the mitogen-activated protein kinase (MAPK) and PI3K pathways (Fig. 2.3). The convergence of multiple, mutually exclusive genomic alterations in multiple pediatric low-grade glioma subtypes on a single, common signaling pathway (MAPK), confirm the importance of this signaling pathway in low-grade glioma development. Inhibitors of BRAF and of the MAPK pathway are currently in early phase clinical trials in pediatrics. Although these new targeted agents may be promising, they will likely need to be combined with traditional chemotherapy regimens or with other pathway inhibitors, as adult clinical trials reveal that drug resistance may develop rapidly with selective targeted inhibitors (Salama and Flaherty 2013). In addition, it has been demonstrated that some RAF-specific inhibitors paradoxically activate (instead of inhibit) the MAPK pathway (Sievert et al. 2013; Heidorn et al. 2010; Hatzivassiliou et al. 2010); defining mechanisms of resistance is under investigation. Regardless, this creates an additional safety concern when conducting clinical trials in children with slow-growing tumors who may require treatment with these medications for a prolonged period (months to years).

Neurofibromatosis type 1 (NF-1) is caused by a germline, inherited or sporadic, inactivating mutation of the NF1 gene on chromosome 17, whose protein product neurofibromin negatively regulates RAS, functioning as a tumor suppressor. Therefore, inactivation of neurofibromin causes increased activation of the RAS/RAF/MEK/MAPK and the PI3K/AKT pathways (Fig. 2.3). There are a number of different

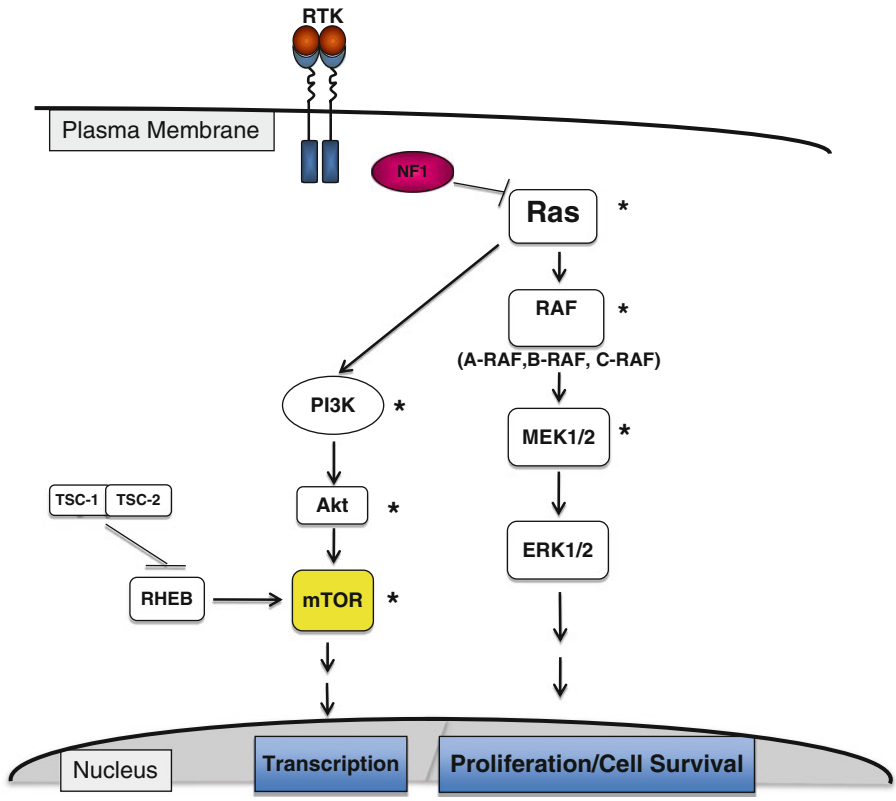

Fig. 2.3 Schematic diagram of the Ras-mediated signal transduction pathways (RAS/RAF/MEK/MAPK and RAS/PI3K/AKT) commonly dysregulated in low-grade gliomas. Distinct mutations of different effector molecules along the pathway (see text for detail) provide unique targets for therapeutic intervention. (*asterisks* identify targets for which drug inhibitors are currently in clinical trial)

neurofibromin mutations described, most resulting in truncation of the protein. SNP-microarray analysis of pediatric low-grade gliomas demonstrates that loss of NF1 and activating BRAF mutations are mutually exclusive (Pfister et al. 2008; Sievert et al. 2009; Jones et al. 2013), which further supports the importance of the MAPK pathway in glioma biology. The mTOR pathway, downstream of the PI3K pathway, also appears to play a role in low-grade glioma, especially in the context of inherited predisposition syndromes. Children with Tuberous Sclerosis (TS) can have biallelic inactivation in either of the TS tumor suppressor genes (TSC1 or TSC2) that result in direct activation of mTOR pathway, and mTOR inhibition has demonstrated efficacy in treating TS-associated astrocytomas (Franz et al. 2013). In addition, up-regulation of mTOR has been noted in NF1-associated glioma mouse models (Banerjee et al. 2011). Inhibitors of mTOR are currently in clinical trials for children with TS and subependymal giant cell astrocytoma and for children (with or without NF1) with recurrent or refractory low-grade glioma (Franz and Weiss 2012).

Future therapies for pediatric low-grade gliomas are currently under development with biologic rationale. Collaborative basic and translational research efforts are identifying the molecular characteristics and biochemical signatures for this diverse set of tumors. Targeted agents carry the potential of improved tumor control with limited toxicity; however, the burden of proving their effectiveness in a low-grade tumor will be much higher as the overall survival for these children is more favorable than those with high-grade tumors. Goals of therapy should focus not only on improving progression free survival but on minimizing the morbidity to long-term survivors.

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http://www.springer.com/978-94-017-7223-5

Tumors of the Central Nervous System, Volume 14
Glioma, Meningioma, Neuroblastoma, and Spinal Tumors
Hayat, M.A. (Ed.)
2015, XXXVIII, 98 p., Hardcover
ISBN: 978-94-017-7223-5