Low-Grade Gliomas

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10.1 Introduction

Tumors of the central nervous system (CNS) are the most common solid tumors in childhood and the second most common overall malignancy in children. The majority of pediatric CNS tumors are gliomas and they are most frequently low-grade. Of the pediatric low-grade gliomas (PLGG), astrocytomas are the predominating histopathologic diagnosis, and include the more prevalent pilocytic astrocytoma and diffuse astrocytoma as well as less common tumors, such as pleomorphic xanthoastrocytoma (PXA), subependymal giant cell astrocytoma (SEGA), and pilomyxoid astrocytoma. Other PLGGs include oligodendroglioma, angiocentric glioma, astroblastoma, and mixed glioneuronal tumors, such as ganglioglioma and dysembryoplastic neuroepithelial tumor (DNT).

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Evaluation and treatment of PLGG is complex due to the wide variety of tumor types and tumor locations. Surgical removal is often complicated and chemotherapy and radiation treatment have long-term significant side effects and sequelae. Overall prognosis, however, is very good and recent advances in molecular profiling of the tumors have presented an increasing armamentarium of targeted agents with the potential to improve outcomes for young patients.

10.2 Epidemiology

Overall, CNS malignancies account for 20–25% of childhood malignancies, with the highest incidence in children 1–4 years of age and the lowest among children 10–14 years of age. In the United States the annual incidence of PLGG is 2.1 per 100,000, accounting for 1600 new diagnoses every year (Bergthold et al. 2014).

The etiology of PLGG is unknown for the majority of patients. However, 2–5% of CNS tumors are attributed to genetic syndromes (Halperin et al. 2013) (discussed further in Sect. 11.3). Ionizing radiation is a known and established environmental risk and is associated with a 2.6-fold increase in risk of developing a glioma (Ron et al. 1988). Other potential risk factors that have been studied, but that are less clear-cut, include parental exposure to pesticides, dietary exposure to nitrosamines, parental exposure to

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excessive heat in the 3 months prior to conception, increased birth weight, mother having a prior abortion, and exposure to antiretroviral medication during pregnancy. However, these risk factors have not been reproducible, and the relative risk is rarely greater than 2 (Dulac et al. 2013).

Low-grade astrocytomas (LGAs) can occur anywhere within the cerebral hemispheres, cerebellum, brainstem, or spinal cord. Most commonly, they are found in the posterior fossa (15–20%), followed by the cerebral hemispheres, midline structures such as the ventricles, hypothalamus, thalamus, and brainstem (10–15% for each sub-site), and finally 3–6% are found in the spinal cord (Gupta et al. 2004).

Pilocytic astrocytomas (WHO grade I) are the most common type of PLGG. They account for approximately 35% of pediatric posterior fossa and optic pathway lesions, though they can be found in the deep midline structures and cerebral hemispheres as well (Gupta et al. 2004). Pilomyxoid astrocytoma is a histologic variant of pilocytic astrocytoma with a more aggressive clinical course that has been described in infants and young children. This tumor is often centered within the optic chiasm or hypothalamus. Another PLGG histological subtype is subependymal giant cell astrocytoma (SEGA, WHO grade I), which arises almost exclusively in patients with tuberous sclerosis (TS) and invariably is centered within the lateral ventricles (Gupta et al. 2004).

Among the infiltrative PLGG, diffuse astrocytomas (WHO grade II) most often arise in the cerebral hemispheres and make up a relatively higher proportion of lesions seen in infants and adolescents (Gupta et al. 2004). Oligodendrogliomas are a rare subtype of PLGG. The relative incidence ranges from 4 to 33% depending on the study series; however, they represent only 2% of brain tumors in patients under the age of 14 (Sievert and Fisher 2009).

Approximately 20–30% of PLGG arise within the optic pathway; these are most frequently pilocytic astrocytomas, or less commonly diffuse astrocytomas (Dulac et al. 2013). The peak incidence for gliomas involving the optic pathway is during the first decade of life, and there is no gender predilection. Neurofibromatosis type 1 (NF-1, also referred to as peripheral neurofibromatosis or von Recklinghausen's disease) is present in about one-third to one-half of patients with optic pathway gliomas. Ten percent of gliomas arising within the optic pathway are confined to a single optic nerve, and 30% have bilateral nerve involvement, which is pathognomonic of NF-1 (Gupta et al. 2004; Ris and Beebe 2008). However, the majority involve the posterior optic chiasm or the hypothalamus.

Glioneuronal tumors are uncommon tumors composed of a mixture of both neoplastic ganglion cells and glial cells. Subtypes include gangliglioma, desmoplastic infantile ganglioglioma (DIG), and dysembryoplastic neuroepithelial tumor (DNT). They most commonly arise within the cerebral hemispheres, most often within the temporal lobes, and are WHO grade I tumors, although rare glioneuronal tumors with anaplastic features (WHO grade III) have been described (Dulac et al. 2013).

Additional information on Epidemiology can be found in Chap. 1.

10.3 Molecular Biology and Genetics of Pediatric Low-Grade Gliomas (PLGG)

Although morphological classification of PLGG has been the mainstay of determining diagnosis and management, morphology alone has limitations in characterizing this heterogeneous tumor group, as there is considerable overlap in histology and clinical behavior. A better approach for guiding management and predicting prognosis may be to integrate histopathology with emerging molecular biology and genomic data (Bergthold et al. 2014). Early insights into the molecular underpinnings of PLGG came from genetic syndromes, namely NF-1 and TS. Recent advances in high-throughput genetic sequencing and gene expression profiling have furthered our understanding of the specific signaling pathway disturbances involved in the pathogenesis of PLGG (Bergthold et al. 2014; Meyerson et al. 2010; Nakamura et al. 2007). Notably, PLGG are genetically distinct from low-grade gliomas in adult patients, particularly the infiltrative

gliomas. Some of the most important genetic alterations and signaling pathway alterations in PLGG are discussed here.

10.3.1 Neurofibromatosis Type 1

Up to 15% of patients with NF-1 develop a cerebral neoplasm before adulthood, with the most common tumors being pilocytic astrocytomas and diffuse astrocytomas (Hernaiz Driever et al. 2010). NF-1-associated PLGG appear to have clinical patterns that are distinct from their sporadic counterparts. NF-1-associated pilocytic astrocytomas more commonly occur in the optic pathway, present at a later age, and tend to have better clinical outcomes (Arun and Gutmann 2004; Rodriguez et al. 2008; Parsa et al. 2001; Perilongo et al. 1999; Piccirilli et al. 2006), with some reports of spontaneous regression.

NF-1 is due to a constitutional mutation in the tumor suppressor gene *neurofibromin 1* (*NF1*) located on chromosome 17q. The functional domain of NF1, RasGAP-related domain (Ras-GRD), accelerates the conversion of the active GTP-bound Ras into its inactive GDP form, thus downregulating the Raf and PI3K transduction pathways (Le and Parada 2007) (Fig. 10.1). The majority of *NF1* mutations cause premature truncation of the protein. Disturbances in the Ras-GRD hinder the ability of NF1 to deactivate Ras-GTP and result in the dysregulation of the Raf and PI3K transduction pathways, thereby promoting cellular proliferation (Le and Parada 2007; Costa et al. 2002).

NF-1 is inherited as an autosomal-dominant trait, and the development of neurofibromas and pilocytic astrocytomas results from loss of heterozygosity (Cichowski et al. 1999), consistent with the Knudson "two-hit" model of tumorigenesis (Le and Parada 2007). However, the development of malignant gliomas in NF-1 patients, either from anaplastic transformation of a pre-existing pilocytic astrocytoma or de novo high-grade infiltrative astrocytomas, requires additional genetic aberrations, such as inactivation of PTEN, ATRX, TP53, CDKN2A, or amplification of EGFR or PDGFRA (Rodriguez et al. 2016) (Le and Parada 2007). This suggests that multiple alterations in cellular proliferation signaling pathways must be disturbed for tumorigenesis.

10.3.2 Tuberous Sclerosis (TS)

Up to 15% of patients with TS develop a SEGA (Hargrave 2009). TS results from germline mutations in one of the two tumor suppressor genes, *TSC1* (*hamartin* on chromosome 9q34) and *TSC2* (*tuberin* on 16p13.3) (Hargrave 2009; van Slegtenhorst et al. 1997; Reuss and von

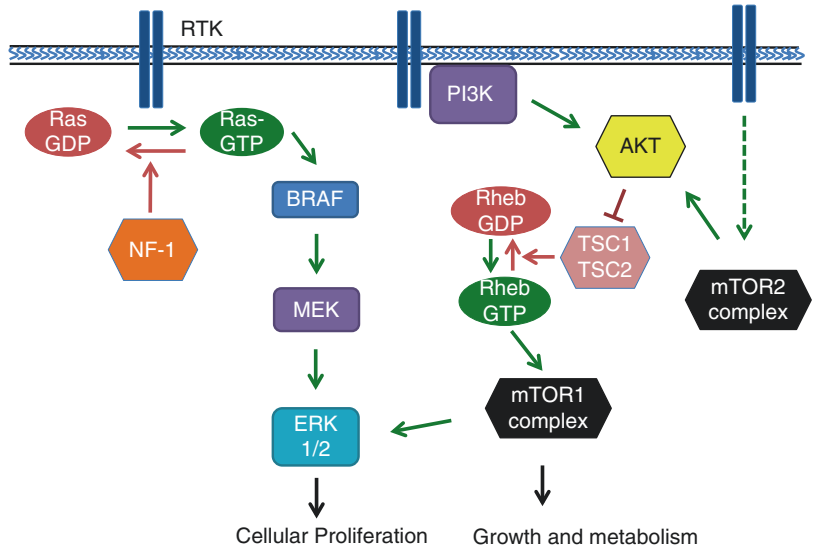


Fig. 10.1 BRAF and mTOR signaling pathways

Deimling 2009). *TSC1* and *TSC2* function together as part of a tumor suppressor complex within the mTOR signaling pathway (Hargrave 2009) (Fig. 10.1). The tuberin–hamartin complex inactivates the GTP-bound Ras-homolog-enhanced-in-the-brain (Rheb) into an inactive GDP-bound state (Hargrave 2009; Rosner et al. 2008). Specific mutations in either tuberin or hamartin can hinder deactivation of Rheb-GTP. Unopposed Rheb-GTP activates mTOR in an unregulated fashion, thus promoting the development of hamartomatous lesions (i.e., tubers) as well tumorigenesis of SEGA (Hargrave 2009; Reuss and von Deimling 2009).

10.3.3 Ras-Raf-MAP Kinase Pathway

As initially implicated by early studies of the NF-1 syndrome, dysregulation of the Ras-Raf-MAP kinase pathway has a pivotal role in the pathobiology of PLGG (Dasgupta and Haas-Kogan 2013). Within this pathway, Raf regulates the MEK/MAP kinase cascade, a regulator of cellular differentiation and proliferation (Dasgupta and Haas-Kogan 2013; Gilheeney and Kieran 2012) (Fig. 10.1). There has been considerable attention over the last decade focused on a specific member of the Raf family, BRAF, one of the most commonly mutated genes in human cancer (Bergthold et al. 2014; Dasgupta and Haas-Kogan 2013; Lawrence et al. 2014). Two major genomic alterations of BRAF have been observed in PLGG: V600E mutation and kinase domain duplication/fusion.

A mutation at codon 600 of the BRAF gene occurs in up to 40% of sporadic PLGG tumors (Dougherty et al. 2010), most commonly in pleomorphic xanthoastrocytoma, ganglioglioma, pilocytic astrocytoma, and pilomyxoid astrocytoma (Bergthold et al. 2014; Schindler et al. 2011). The BRAF V600E mutation involves the replacement of valine by glutamic acid within the activation loop of the enzyme, which mimics phosphorylation of the activation site (Dasgupta and Haas-Kogan 2013) and results in constitutive activation of BRAF serine/threonine kinase domain (Bergthold et al. 2014), leading to disinhibition of the MEK/MAP kinase cascade (Fig. 10.1). The V600E mutation is sufficient to transform NIH3T3 fibroblasts in vitro and also results in proliferative transformation of human neural stem cells followed by senescence (Raabe et al. 2011). Intriguingly, it has been hypothesized that this "oncogene-induced senescence" may partly account for the low-grade pathobiology of pilocytic astrocytomas (Raabe et al. 2011; Jacob et al. 2011).

In addition to the V600E missense mutation, genetic rearrangements and duplications of the kinase domain of BRAF are common in PLGG, including pilocytic astrocytoma, pilomyxoid astrocytoma, and ganglioglioma, and lead to dysregulated kinase activity. Comparative genomic hybridization studies have shown that the gain of chromosomal region 7q34, which contains the *BRAF* locus, is the most common copy number alteration in sporadic PLGG, with frequent tandem insertion into the *KIAA1549* gene (Bergthold et al. 2014; Hemmati et al. 2003; Jacob et al. 2009). Greater than 90% of pilocytic astrocytomas arising in the cerebellum in patients without NF-1 have KIAA1549-BRAF gene fusions, while pilocytic astrocytomas outside the cerebellum (e.g., hypothalamus) have a lower frequency of KIAA1549-BRAF gene fusions, reportedly around 50% (Zhang et al. 2013; Jones et al. 2013). Pilomyxoid astrocytomas also have been reported to harbor KIAA1549-BRAF gene fusions (Lin et al. 2012; Gierke et al. 2016), demonstrating that this entity has similar genetics to pilocytic astrocytoma and providing support that pilomyxoid astrocytoma represents a more aggressive histologic variant of pilocytic astrocytoma rather than a distinct entity. Other *BRAF* fusion transcripts have been found to involve *GNA11, MKRN1, CLCN6, SRGAP3, FAM131B, MACF1*, and *RNF130*, and all known *BRAF* fusion transcripts are characterized by the loss of the N-terminal inhibitory domain of BRAF, resulting in constitutive activation of the kinase domain and dysregulation of the downstream MAP kinase signaling pathway (Bergthold et al. 2014).

10.3.4 PI3-Kinase-AKT-mTOR Pathway

As suggested by early studies of TS, genetic aberrations in the PI3K-Akt-mTOR signaling pathway predispose to PLGG. This pathway normally integrates intracellular and extracellular signals to regulate cellular metabolism, proliferation, and survival (Hassan et al. 2013). mTOR is a multi-protein serine-threonine kinase, composed of two protein complexes (mTORC1 and mTORC2), that is a master regulator of protein translation (Laplante and Sabatini 2012). In high nutritional states, conformational changes allow mTORC1 to interact with Rheb, stimulating mTORC1, which itself activates p70S6 kinase. This results in formation of phospho-S6 and phospho-4EBP1, leading to protein translation and cellular proliferation (Dasgupta and Haas-Kogan 2013) (Fig. 10.1).

The importance of the mTORC1 pathway in PLGG pathogenesis is highlighted by the fact that approximately half of these tumors show enhanced expression of phospho-S6 and phospho-4EBP1 (Dasgupta and Haas-Kogan 2013). Furthermore, overexpression of these two proteins is associated with significantly worse progression-free survival (Populo et al. 2012), with a trend toward shorter overall survival as well (McBride et al. 2010).

The mTORC2 component is also an important regulator of cellular proliferation in response to cell nutritional status and redox states. A critical function of mTORC2 is phosphorylative activation of Akt. Akt has a role in multiple cellular processes, including metabolism, cell cycle regulation, and apoptosis. Abnormal activation of Akt is implicated in many human cancers (Schindler et al. 2011) and may be important in both management and prognosis. In a series of 92 pilocytic astrocytomas, Akt phosphorylation was associated with more aggressive histology and worse clinical outcomes (Rodriguez et al. 2011). Like Akt, other members of the PI3K-AKT-mTOR and Ras-Raf-MAPK pathways are being targeted by novel agents that are currently being developed and used in the treatment of PLGG. These and other new agents will be discussed in Sect. 11.6.4.

10.3.5 Genetic Alterations in Pediatric Infiltrative Gliomas

The genetic alterations that drive infiltrative gliomas are highly specific, depending on patient age and site of origin within the CNS. Infiltrative gliomas arising sporadically within the cerebral hemispheres in older pediatric patients in their late teenage years (i.e., 15–20 years of age) often have genetic alterations similar to those found in adult patients. In diffuse astrocytomas, these include mutations in TP53, ATRX, and either IDH1 or IDH2 in the majority of tumors (Cancer Genome Atlas Research Network 2015; Eckel-Passow et al. 2015; Suzuki et al. 2015). In oligodendrogliomas, these include co-deletion of chromosomes 1p and 19q, TERT promoter mutation, and mutation of either IDH1 or IDH2 in the majority of tumors (Suzuki et al. 2015; Eckel-Passow et al. 2015; Cancer Genome Atlas Research Network 2015). Further discussion of the genetic alterations that drive these adult-type infiltrative gliomas is beyond the scope of this review, and interested readers should refer to the three references above and other references therein for more information on the molecular mechanisms by which IDH, TP53, ATRX, and TERT promoter mutations drive gliomagenesis.

In contrast, diffuse astrocytomas arising in the cerebral hemispheres in younger pediatric patients lack these adult-type molecular alterations and instead harbor rearrangements involving MYB or MYBL1 genes or, less commonly, BRAF-V600E mutation (Ramkissoon et al. 2013; Zhang et al. 2013). MYB and MYBL1 are proto-oncogenes that encode transcriptional activator proteins, and the rearrangements in pediatric gliomas involving these genes typically lead to truncation of their C-terminal negative regulatory domains causing constitutive activation and altered gene transcription (Zhang et al. 2013; Ramkissoon et al. 2013). The rearrangements present in MYB and MYBL1 genes have only been found in PLGGs within the cerebral hemispheres and have not been found in pediatric high-grade

gliomas (Zhang et al. 2013). Recent studies have shown that angiocentric glioma, an epilepsy-associated cortical neoplasm of childhood, also is genetically characterized by MYB rearrangement, most commonly as MYB-QKI gene fusion (Bandopadhayay et al. 2016).

As opposed to those infiltrative gliomas arising in the cerebral hemispheres, infiltrative astrocytomas arising within midline structures, including the thalamus, pons, and spinal cord, from both pediatric patients and young adults often harbor a missense mutation at codon 27 in either of the H3F3A or HIST1H3B genes, which encode the histone H3 variants, H3.3 and H3.1, respectively (Schwartzentruber et al. 2012; Khuong-Quang et al. 2012; Sturm et al. 2012; Gielen et al. 2013; Wu et al. 2014; Aihara et al. 2014). These missense mutations cause a lysine to methionine substitution (K27M) that alters an important site of posttranslational modification in these histone H3 variants and leads to altered gene expression profiles thought to drive gliomagenesis (Bender et al. 2013; Chan et al. 2013). These diffuse midline gliomas with histone H3 K27M mutations are associated with a poor prognosis irrespective of the histologic grade seen at the time of biopsy or resection (Aihara et al. 2014; Khuong-Quang et al. 2012; Schwartzentruber et al. 2012; Sturm et al. 2012; Wu et al. 2014; Gielen et al. 2013). As such, "Diffuse midline glioma, H3 K27M-mutant" was included as a grade IV entity in the 2016 WHO Classification of Tumors of the Central Nervous System, which is the recommended designation for all diffuse midline gliomas with H3 K27M mutation regardless of the presence or absence of high grade histologic features (e.g. increased mitotic activity, necrosis, and microvascular proliferation). A mutant-specific antibody for the detection of histone H3-K27M mutant protein has now been developed and is routinely being using in the practice of surgical neuropathology and has been highly effective in the identification of diffuse midline gliomas with this important molecular alteration (Bechet et al. 2014; Venneti et al. 2014).

Pediatric oligodendrogliomas are a rare entity, and the largest case series reported to date has found that they do not harbor IDH mutations and deletion of chromosomes 1p and 19q typical of oligodendrogliomas in adult patients (Rodriguez et al. 2014). Genome-wide analysis of pediatric oligodendrogliomas has revealed alterations in the FGFR1 oncogene in the majority of cases, either through tandem duplication of the kinase domain, gene fusions such as FGFR1-TACC1, or hotspot missense mutations that localize within the kinase domain, typically either N546K or K656E (Zhang et al. 2013). Dysembryoplastic neuroepithelial tumors also frequently harbor FGFR1 alterations through either kinase domain mutation or tandem duplication (Rivera et al. 2016). A recent study integrating histologic features with underlying genetic alterations in PLGG demonstrated that tumors with astrocytic morphology most commonly harbor alterations in BRAF or MYB/MYBL1, whereas those tumors with oligodendroglial morphology most commonly harbor FGFR1 alterations (Qaddoumi et al. 2016).

Additional information regarding predisposition syndromes and molecular classification can be found in Chaps. 5 and 6, respectively.

10.4 Clinical Features

Presenting symptoms of low-grade gliomas in the pediatric population are highly variable and are dependent on location of the lesion, age at presentation, and tumor biology. Symptoms can be divided into generalized and localized symptoms.

Seizures are the most common general symptom and occur in more than 50% of children at any age who have hemispheric tumors (Gupta et al. 2004). Generalized seizures are more common with slowly progressive disease, whereas rapidly growing tumors are more likely

to produce complex partial motor or sensory seizures. Gangliogliomas, due to their location, often present with seizures, which are often refractory until the lesion is surgically removed (Dulac et al. 2013). Other general signs and symptoms include increased intracranial pressure that can manifest as headache, hydrocephalus, or nausea and vomiting in a more acute setting. This constellation of symptoms is common in posterior fossa tumors where an enlarging lesion can cause blockage of the fourth ventricle (Dulac et al. 2013).

In infants with open cranial sutures, enlarging head circumference can be a sign of a CNS lesion. As children age, failure to meet developmental milestones can warrant further neurologic evaluation (Gupta et al. 2004). Finally, in school-age children, gradual changes such as developmental delay, personality changes, irritability, altered psychomotor function, apathy, and declining school performance can be seen as well (Gupta et al. 2004).

Focal neurologic deficits, including hemiparesis, monoparesis, aphasia, dysphasia, and other cranial nerve or long tract signs, can represent localizing signs of an intracranial tumor. Optic pathway lesions in the nerves or chiasm can lead to decreased visual acuity, strabismus, proptosis, hemianopsia, and quadrantanopsia (Sievert and Fisher 2009). Cortical blindness can be noted when the lesion involves bilateral occipital lobes. Ataxia or dysmetria can present as difficulty with balance and is associated with patients who have cerebellar tumors (Sievert and Fisher 2009). Hypothalamic lesions or pituitary lesions can result in endocrine disturbances leading to precocious puberty, growth retardation, diabetes insipidus, or visual field deficits due to compression of the optic chiasm.

Since many of these symptoms are nonspecific for pediatric gliomas, thorough neurologic evaluation is paramount in children who present with deficits to aid in early diagnosis and treatment.

10.5 Imaging and Workup

At the time of presentation with concerning neurologic symptoms, MRI should be obtained in all cases. Important sequences to obtain include T1 axial and coronal images, both pre- and post-gadolinium contrast (Fig. 10.2), and T2 axial and coronal fluid-attenuated inversion recovery (FLAIR) sequences (Fig. 10.3a, b). Sagittal sequences are often helpful to define the anatomy of supra-sellar and midline tumors (Fig. 10.2a, b). Newer sequences, such as diffusion weighted imaging (DWI), MR spectroscopy, and functional MRI, are noninvasive modalities used to glean biochemical and functional information that may contribute to obtaining a pathologic diagnosis in the future and could be of prognostic importance. Of note, many children may need conscious sedation or anesthesia to obtain an MRI.

PLGGs tend to be T1 iso- to hypointense, T2 hyperintense and non-enhancing post-gadolinium administration. The lack of contrast enhancement makes FLAIR sequences ideal for delineating tumor extent (Gupta et al. 2004; Alkonyi et al. 2015).

Gliomas involving the optic pathway have a fusiform appearance and are typified by enlargement of the optic nerve(s) and chiasm (Avery et al. 2011). FLAIR sequences demonstrate an infiltrative component extending along the optic tracts. For all gliomas involving the optic pathways, detailed fine cuts of the sella should be obtained (Gupta et al. 2004). In patients with NF-1, there is often extensive streaking along the optic pathway and/or involvement of the optic nerve at the time of diagnosis, in addition to nonspecific T2 white matter abnormalities. Tumor can spread into the perivascular space along the circle of Willis, as well as posteriorly toward the brainstem with rostral invasion into the third ventricle. Chiasmatic and hypothalamic lesions have an increased risk for neuraxis dissemination (Gupta et al. 2004). In children without NF-1, tumors tend to be more globular and restricted to a single anatomic location without significant

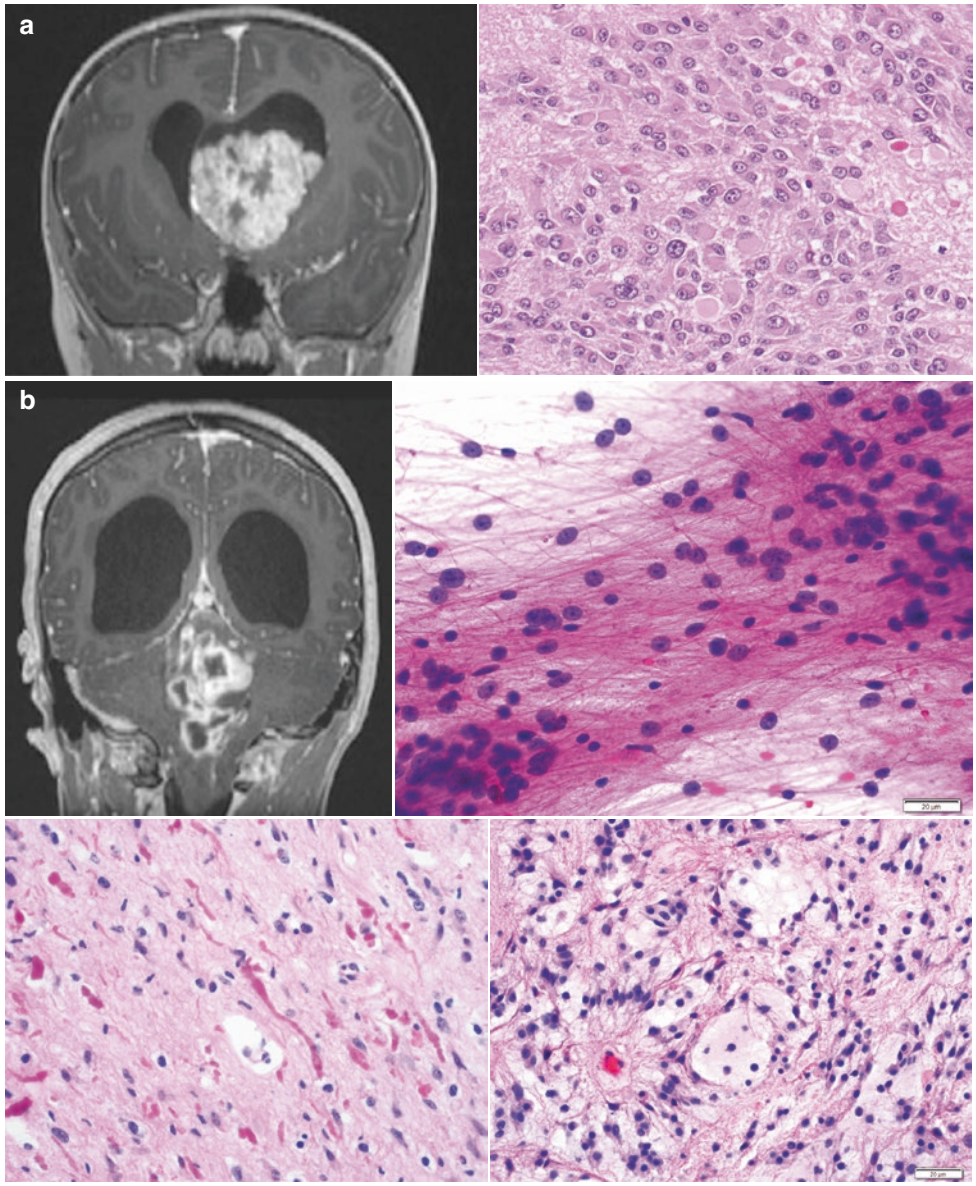


Fig. 10.2 Representative examples of circumscribed gliomas. (**a**) Subependymal giant cell astrocytoma (SEGA), WHO grade I. Coronal T1-weighted MR image post-gadolinium administration (left) demonstrating a solidly enhancing intraventricular mass lesion without invasion of the adjacent brain parenchyma. H&E stained section (right) demonstrating a solid neoplasm composed of large epithelioid astrocytes with abundant eosinophilic cytoplasm within a densely fibrillar background. (**b**) Pilocytic astrocytoma, WHO grade I. Coronal T1-weighted MR image post-gadolinium administration (top left) demonstrating a complex solid and cystic lesion with peripheral enhancement centered in the midline of the posterior fossa. Intraoperative cytologic preparation (top right) demonstrating a proliferation of bipolar astrocytes with elongate ("piloid") cytoplasmic processes. H&E stained section (bottom left) demonstrating a compact area of the neoplasm of piloid astrocytes containing numerous Rosenthal fibers. H&E stained section (bottom right) demonstrating a loose area of the neoplasm with microcysts and oligodendroglioma-like cells with round nuclei. (**c**) Pleomorphic xanthoastrocytoma (PXA), WHO grade II. Sagittal T1-weighted MR image post-gadolinium administration (top left) demonstrating a solid and cystic lesion in the parieto-occipital lobes. H&E stained section (top right) demonstrating a solid neoplasm of markedly pleomorphic astrocytes including occasional cells with lipidized cytoplasm and scattered eosinophilic granular bodies in the background. Laidlaw reticulin stain (bottom left) demonstrating abundant pericellular reticulin deposition among the tumor cells. Immunohistochemical stain using a mutant-specific antibody against BRAF-V600E mutant protein (bottom right) demonstrating cytoplasmic staining within the neoplastic astrocytes, indicative of *BRAF* gene mutation

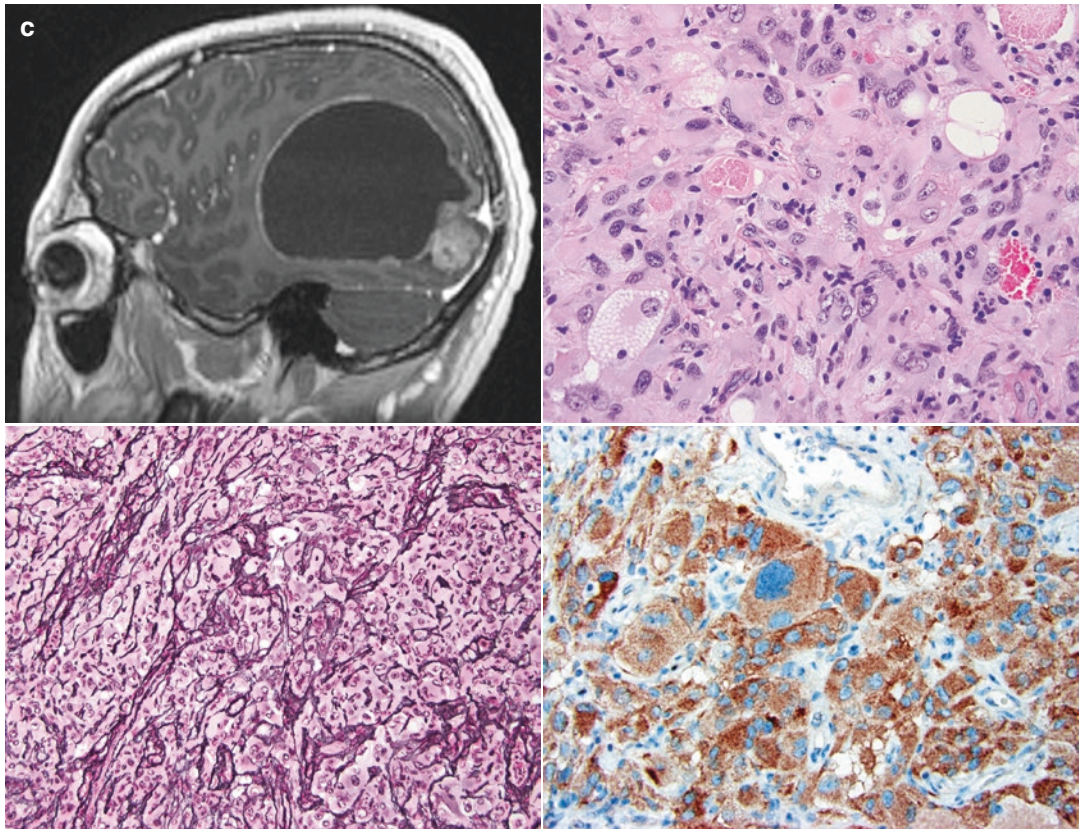


Fig. 10.2 (continued)

involvement of the meninges. Gadolinium enhancement and cyst formation is also more common in sporadic gliomas involving the optic pathway (Avery et al. 2011).

Oligodendrogliomas are lesions with involvement of the superficial cortex and are typically non-enhancing on MR-based imaging. 60–90% of these lesions have characteristic intrinsic calcification (Gupta et al. 2004). Pilocytic astrocytomas are well-circumscribed lesions (Fig. 10.2b) that have characteristic cystic changes and an enhancing mural nodule (Alkonyi et al. 2015). Diffuse astrocytomas (Fig. 10.4a) by definition are infiltrative lesions that appear less circumscribed and typically do not enhance unless a higher-grade component of the tumor is present (Sievert and Fisher 2009).

If unable to obtain an MRI, CT imaging of the brain with and without contrast can detect an intracranial abnormality. Low-grade gliomas typically appear as non-enhancing iso- or hypodense masses on CT. Mild to moderate nonhomogeneous contrast enhancement may be seen in up to 40% of cases. Calcifications are seen in 15–20% of cases and CT imaging represents the best modality with which to visualize calcified lesions (Gupta et al. 2004).

Obtaining serial imaging over time is paramount since many lesions can progress or recur. It is important to obtain a postoperative baseline MRI 24–48 h after surgery to distinguish residual tumor from postoperative changes. Quality imaging scans should subsequently be obtained every 3–6 months or as neurologic symptoms dictate (Gupta et al. 2004). Differentiating between treatment changes, radiation necrosis, and tumor recurrence can present a radiologic challenge. Notable findings concerning for progression or recurrence include increase in volume of T2-weighted abnormality on MRI or new enhancement on the post-contrast images (Gupta et al. 2004).

Example MRI sequences with corresponding histopathologic images from select pediatric low-grade gliomas are demonstrated in Figs. 10.2, 10.3, and 10.4.

10.6 Treatment and Outcomes

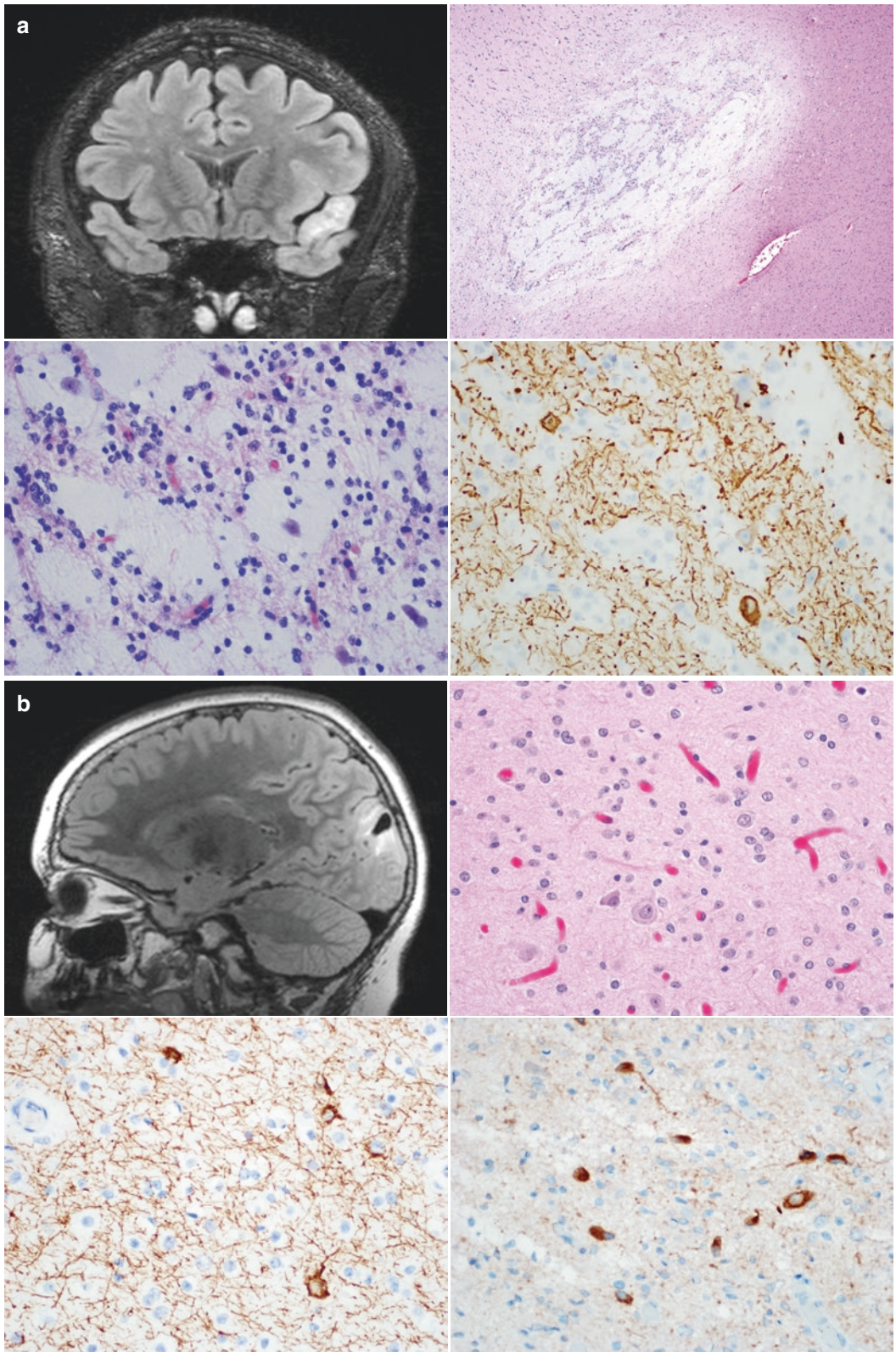
Overall survival is generally excellent for the majority of PLGG (Wisoff et al. 2011), with 20-year overall survival rates up to 87% (Bandopadhayay et al. 2014). Therefore, the treatment goals should not only include long-term tumor control, but also minimization of treatment-related morbidity. Management options include surgery, radiation, and chemotherapy. In addition, our growing understanding of the pathobiology of PLGG is leading to the establishment of novel targeted molecular agents (Dasgupta and Haas-Kogan 2013; Nageswara Rao and Packer 2014).

10.6.1 Surgery

Historically, surgery has been the cornerstone of PLGG management (Bergthold et al. 2014). The goal of surgery is maximal safe removal of tumor and decompression of adjacent normal tissue structures (Sutton et al. 1995). Deep lesions in the brain, such as those located in the hypothalamus, optic pathways, or brainstem, are many times not amenable to surgical resection; therefore, alternate therapeutic options such as radiation and chemotherapy come into play as primary treatment.

In a prospective natural history trial of patients treated with primary surgery and subsequent observation by Wisoff and colleagues, the 5-year overall survival (OS) rate was 97%, and progression-free survival (PFS) rate was 80%. Gross total resection (GTR) without residual disease was a strong and independent predictor of PFS. The ability to obtain a GTR varied significantly by location. About 75% of patients with cerebral and cerebellar hemisphere tumors had a GTR, while less than a quarter of children with chiasmic-hypothalamic and midline tumors had a complete resection. For subtotal resections (STR), the volume of residual tumor was predictive of disease progression (Fig. 10.5). However, the degree of surgical resection (including GTR) was not predictive of OS when tumor location, histology, and age were taken into account. This is thought to be due to the indolent nature of PLGG (Wisoff et al. 2011). In this series, only histology and tumor location were independently associated with OS.

Fig. 10.3 Representative examples of glioneuronal tumors. (**a**) Dysembryoplastic neuroepithelial tumor (DNT), WHO grade I. Coronal T2-weighted fluid-attenuated inversion recovery MR image (top left) demonstrating a well-circumscribed, cortically based mass lesion in the temporal lobe with internal nodularity. H&E stained section at low power (top right) demonstrating a sharply demarcated mucin-rich nodule within the cortex. H&E stained section at high power (bottom left) demonstrating a neoplasm of round oligodendrocyte-like cells arranged in linear columns along capillaries and neuronal processes within a mucin-rich stroma containing "floating" neurons. Immunohistochemical stain for neurofilament protein (bottom right) highlighting a background of neuronal processes within the nodules and showing cytoplasmic staining with the neurons floating in the mucin-rich stroma. (**b**) Ganglioglioma, WHO grade I. Sagittal T2-weighted fluid-attenuated inversion recovery MR image (top left) demonstrating a well-circumscribed, cortically based solid and cystic mass lesion in the occipital lobe. H&E stained section (top right) demonstrating a biphasic tumor composed of large dysmorphic ganglion cells admixed with neoplastic astrocytes. Immunohistochemical stain for neurofilament protein (bottom left) highlighting the delicate neuronal processes in the background and showing staining in the cells bodies of the neoplastic ganglion cells. Immunohistochemical stain using a mutant-specific antibody against BRAF-V600E mutant protein (bottom right) demonstrating cytoplasmic staining within the tumor with accentuated staining in the neoplastic ganglion cells, indicative of *BRAF* gene mutation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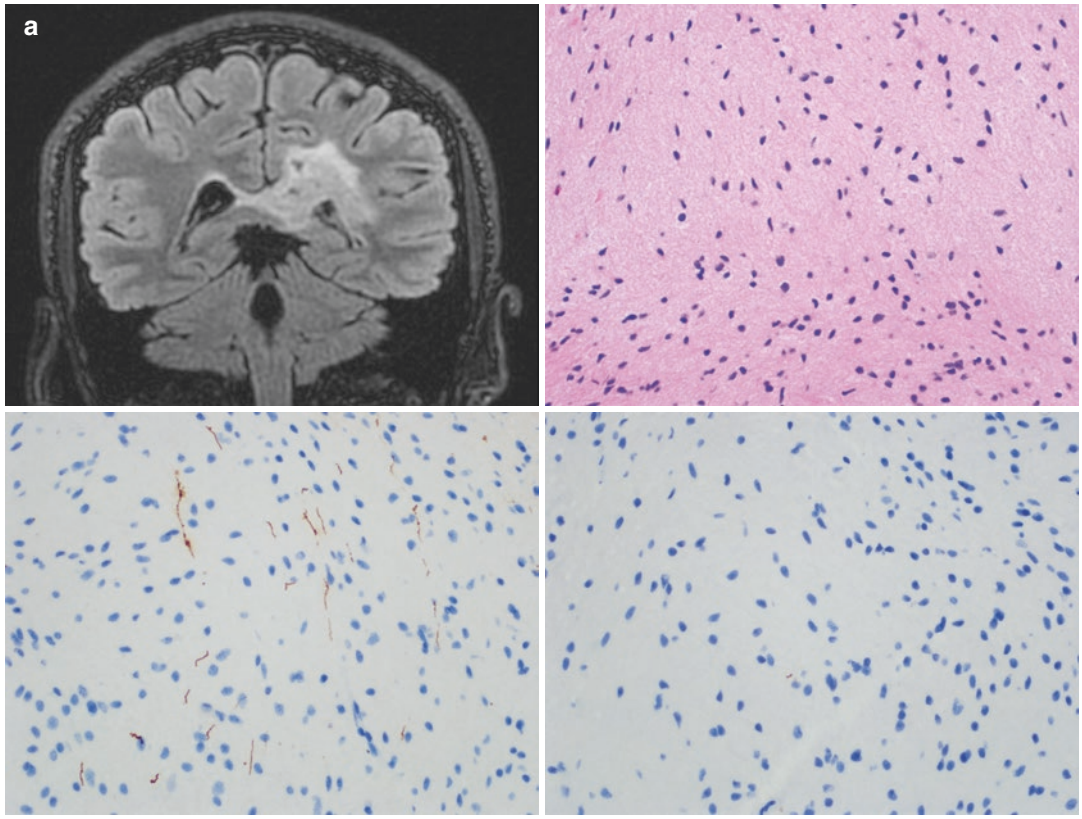

Fig. 10.4 Representative examples of infiltrative gliomas. (**a**), Diffuse astrocytoma with *MYB* gene rearrangement, WHO grade II. Coronal T2-weighted fluid-attenuated inversion recovery MR image (top left) demonstrating an infiltrative hyperintense lesion within the deep white matter of the parietal lobe and crossing over the splenium of the corpus callosum into the contralateral cerebral hemisphere. H&E stained section (top right) demonstrating infiltrating neoplastic astrocytes with elongate nuclei in a background of densely fibrillar glial processes. Immunohistochemical stain for neurofilament protein (bottom left) highlighting the presence of infiltrated axons among the tumor cells. Immunohistochemical stain using a mutant-specific antibody against IDH1-R132H mutant protein (bottom right) demonstrating absence of staining in the neoplastic astrocytes. Fluorescence in situ hybridization (not shown) demonstrated rearrangement of the *MYB* gene in this diffuse astrocytoma. (**b**) Diffuse astrocytoma, IDH-mutant, WHO grade II. Sagittal T2-weighted fluid-attenuated inversion recovery MR image (top left) demonstrating an irregular mass-like area of hyperintensity expanding the gyri of the frontal lobe. H&E stained section (top right) demonstrating neoplastic astrocytes with ovoid nuclei containing coarse chromatin infiltrating through the cortex with satellitosis of preexisting neurons. Immunohistochemical stain using a mutant-specific antibody against IDH1-R132H mutant protein (bottom left) demonstrating cytoplasmic staining within the neoplastic astrocytes, indicative of *IDH1* gene mutation. Immunohistochemical stain for ATRX protein (bottom right) demonstrating loss of staining in the tumor cells with retained expression in the entrapped, preexisting neurons suggestive of *ATRX* gene mutation. (**c**) Diffuse midline glioma, H3 K27M-mutant, WHO grade IV. Coronal (top left) and sagittal (top right) T2-weighted fluid-attenuated inversion recovery MR image demonstrating a hyperintense mass lesion expanding the pons. H&E stained section (bottom left) demonstrating neoplastic astrocytes with elongate nuclei and coarse chromatin infiltrating through the parenchyma of the pons, with a couple of entrapped neurons seen. Immunohistochemical stain using a mutant-specific antibody against histone H3-K27M mutant protein (bottom right) demonstrating nuclear staining in the neoplastic astrocytes, indicative of *H3F3A* gene mutation. Despite lacking significant mitotic activity, necrosis, or microvascular proliferation, this tumor should be classified as grade IV per the 2016 WHO Classification of Tumors of the Central Nervous System

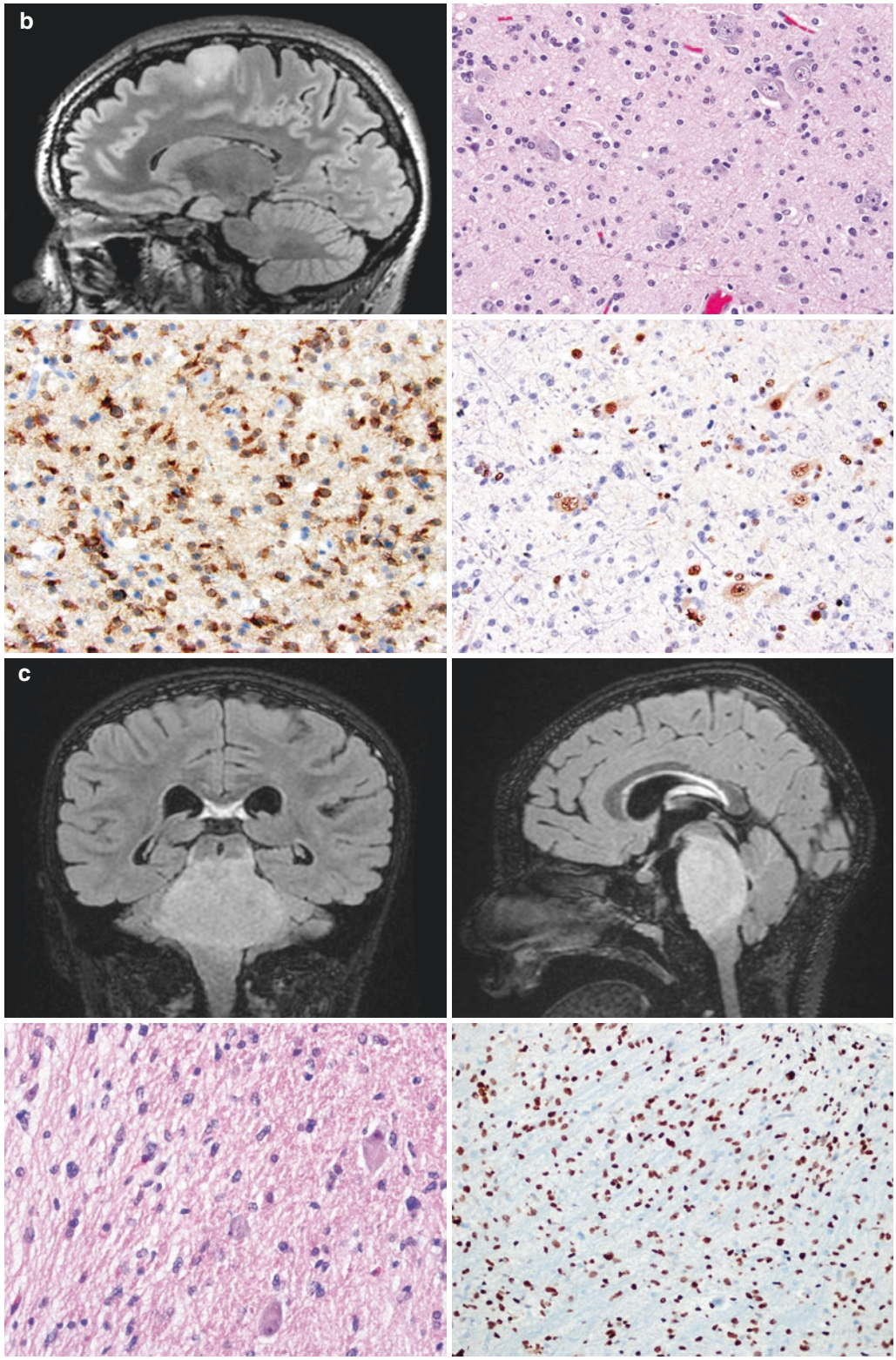

Fig. 10.4 (continued)

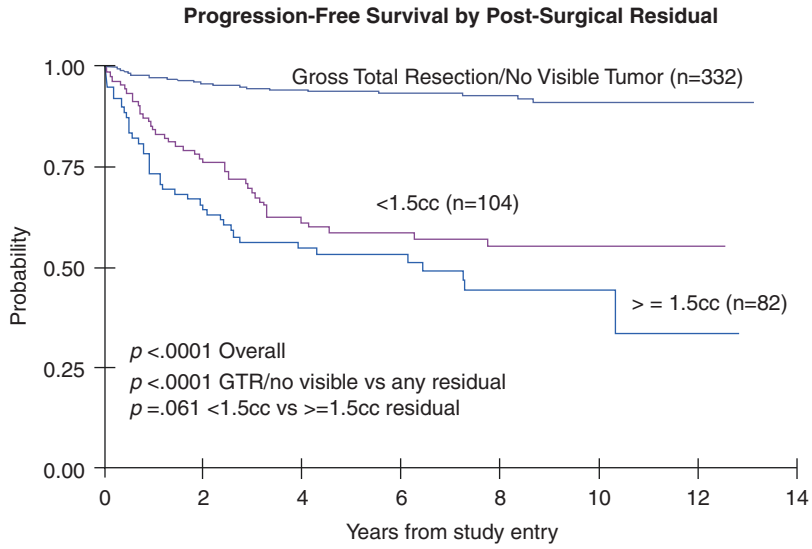

Fig. 10.5 Progression-free survival by postsurgical residual disease. In this prospective natural history trial, Wisoff and colleagues followed postsurgical patients with any pediatric low-grade glial neoplasm. Tumors with anaplastic features were excluded. All intracranial sites were included except for intrinsic brainstem tumors and tumors limited to the optic nerves. Wisoff et al. Neurosurgery. 2011;68(6):1548–1555

Notably, over 50% of children with residual tumor volume after resection have no disease progression at 5 years (Wisoff et al. 2011), 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. In addition, because not all patients will progress after resection most are observed expectantly (Benesch et al. 2006), reserving chemotherapy, radiation, and re-resection for salvage therapies.

10.6.2 Radiation

Radiation therapy has been used as up-front treatment and as salvage therapy in PLGG. However, the observance of cognitive effects, endocrine deficiencies, secondary malignancies, vascular damage, and growth abnormalities associated with older radiation techniques have largely led to the avoidance of radiation therapy in the up-front management setting of PLGG. In addition, old retrospective studies that evaluated more historic radiation delivery techniques showed poor 5-year PFS (less than 50%) (Fisher et al. 2008). However, advancements in three-dimensional treatment planning have allowed for highly conformal radiation delivery with the sparing of normal adjacent tissue structures. The role and safety of these radiation therapy techniques for PLGG is being re-evaluated.

A prospective study by Marcus and colleagues at Dana Farber Cancer Institute evaluated the efficacy of highly conformal radiotherapy for small (less than 5 cm) tumors either as up-front treatment or as salvage therapy. The mean radiation dose delivered to the gross tumor volume with a 2 mm planning treatment margin was 52.2 Gy in 1.8 Gy fractions. PFS was 82.5% at 5 years, and OS was 97.8% at 5 years. At a median follow-up of 6.9 years, 7 of 81 patients had local progression. There were no marginal failures observed. Other than rare temporary hair thinning, no acute radiation-related toxicities occurred. One child developed a primitive neuroectodermal tumor 6 years after radiation, and four children developed moyamoya syndrome during follow-up. The authors concluded that stereotactic radiotherapy provides excellent local control for children with small, localized PLGG, and limiting the treatment margins may protect against radiation-related toxicity while not compromising local control (Marcus et al. 2005).

A phase II trial at St. Jude Children's Research Hospital also evaluated the efficacy of conformal radiation therapy. In this study, 54 Gy was delivered to the tumor with a 10 mm margin. This trial demonstrated a 5-year PFS of 87% and OS of 96%. During the 89-month follow-up, the cumulative vasculopathy rate was less than 6% (Merchant et al. 2009). Cognitive function was largely preserved with the use of conformal radiotherapy. However, cognitive decline did appear to be strongly associated with age, with the steepest decline in IQ among the youngest children. At 5 years of follow-up, a 5-year-old child would be predicted to have an IQ drop of 10 points, and each year of increasing age decreased the decline in IQ by 0.03 points per month (Merchant et al. 2009). There is a more detailed discussion of radiation toxicity below.

These two studies highlight the ability to achieve excellent local control using highly conformal radiation techniques that spare normal tissues and decrease the risk of radiation-related toxicities. Figure 10.6 demonstrates an example of the ability of highly conformal radiation therapy to spare the optic chiasm. Of note, the patient population in these two prospective studies was somewhat heterogeneous and included both children who were treated in the up-front and the salvage settings.

Mishra and colleagues at the University of California, San Francisco, retrospectively evaluated the role of radiation therapy in the up-front setting for children with incompletely resected WHO grade II PLGG. After subtotal resection, PFS and OS did not differ between children who received adjuvant radiation therapy (median dose 54 Gy) and those who did not (Mishra et al. 2006). The series reproduced previous observations that extent of resection affects PFS.

Overall, highly conformal radiation therapy appears to be a safe and effective way to achieve local control, likely best reserved for the salvage setting. At this time there does not appear to be clear benefit in the immediate postoperative setting since many children may not go on to have disease progression. When radiation therapy is employed for PLGG, doses of 52–54 Gy appear to be effective, and planning setup margin can safely be limited to 1 cm or less to protect adjacent normal tissues.

10.6.3 Chemotherapy

Given the generally favorable outcomes after surgery, chemotherapy is not routinely employed in the adjuvant setting but rather reserved for unresectable or symptomatic progression (Bergthold et al. 2014), especially in younger patients, to

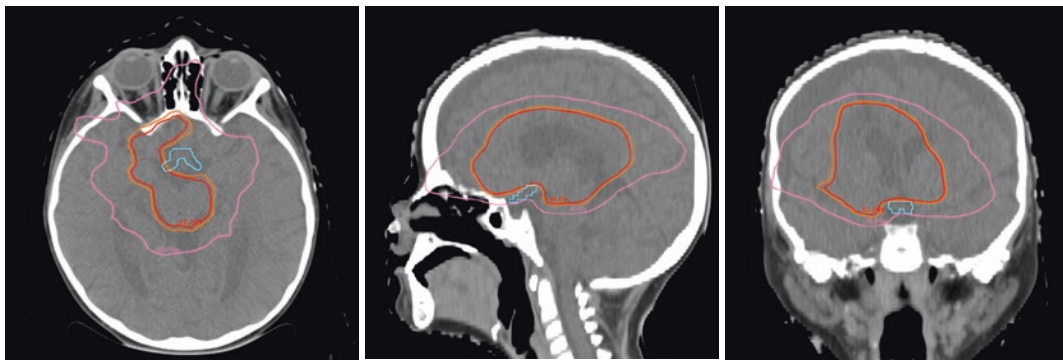

Fig. 10.6 Pediatric patient undergoing radiation treatment for PLGG. The optic chiasm is outlined in light blue. The red line represents the prescription dose, 5220 cGy, the orange line represents the volume receiving 5000 cGy, and the pink line represents the volume receiving 3000 cGy. Using highly conformal radiation treatment (Intensity Modulated Radiation Treatment-IMRT), sparing normal tissue structures such as the optic chiasm can greatly decrease the risk of radiation-related toxicity

Table 10.1 Chemotherapy regimens for PLGG

Study	Chemotherapy regimen	Number of patients	Event-free survival (%)		
			2 years	3 years	5 years
Ater et al. J Clin Oncol. 30:2641–2647, 2012	CV TPCV	137 137			39 52 (ns)
Mishra et al. J Neurooncol.100:121–7, 2010	TPD(CCNU)V	33			30
Gnekow et al. Klin Padiatr 216:331–342, 2004	CV	198			61
Massimino et al. J Clin Oncol 20:4209–4216, 2002	CisVP	31		78	
Prados et al. J Neurooncol 32:235–241, 1997	TPCV	42	50		
Packer et al. J Neurosurg 86:747–754, 1997	CV	78		68	

C carboplatin, *V* vincristine, *T* thioguanine, *P* procarbazine, *Cis* cisplatin, *VP* etoposide, *D* dibromodulcitol, *(CCNU)* Lomustine, *ns* not statistically significant. Adapted from: Merchant et al. J Clin Oncol. 2009;27(22):3598–3604

delay or obviate the need for radiation therapy (Merchant et al. 2009). A number of poly-chemotherapy regimens have been used in PLGG, detailed in Table 10.1 (Merchant et al. 2009). With these regimens, 2–3-year PFS rates range from 50 to 78%.

The Children's Oncology Group (COG) published the results of Protocol A9952, which randomized children with progressive or residual PLGG to carboplatin and vincristine (CV) versus thioguanine, procarbazine, lomustine, and vincristine (TPCV) (Table 10.1). The 5-year event-free survival was not significantly different (39% for CV and 52% for TPCV). Toxicity was slightly worse with TPCV (Ater et al. 2012). Because of the potential for long-term morbidity associated with alkylating agents, such as infertility and secondary malignancies, most oncologists favor CV as first line chemotherapy over TPCV (Bergthold et al. 2014).

Monotherapy with temozolomide, vinblastine, or cyclophosphamide has been evaluated in phase II studies, although with mixed results (Bergthold et al. 2014). A COG study of temozolomide for recurrent brain tumors found one partial response in 21 children with PLGG and 41% of these children had stable disease through 12 months of treatment (Nicholson et al. 2007). Another COG phase II trial of cyclophosphamide for progressive low-grade astrocytoma in 14 patients demonstrated a complete response in one patient and disease stability in 8 patients. The excessive number of children (5) with progressive disease prompted the study to close (Kadota et al. 1999). Single agent vinblastine was evaluated in 51 patients with recurrent or refractory PLGG, among whom 36% had a complete, partial, or minor response and 5-year PFS was 42%. Thirty-eight patients had grade 3 or 4 hematologic toxicity (Bouffet et al. 2012).

Chemotherapy has also been combined with noncytotoxic agents. A recent phase II study evaluating irinotecan with the anti-VEGF monoclonal antibody bevacizumab for progressive PLGG demonstrated a 47.8% PFS at 2 years (Gururangan et al. 2014). Bevacizumab is well tolerated, although children need to be monitored closely for hypertension and proteinuria (Bergthold et al. 2014).

10.6.4 Targeted Systemic Agents

The prevalence of mutations within the Ras-Raf-MAP kinase and PI3-kinase-AKT-mTOR pathways (see Fig. 10.1) has led to the development of antitumor agents that specifically target the oncogenic protein within these pathways (Dasgupta and Haas-Kogan 2013). As described in Sect. 11.3, the BRAF V600E mutation occurs in up to 40% of PLGG. Vemurafenib specifically inhibits BRAF V600E from activating MEK. Vemurafenib has remarkable clinical activity against BRAF V600E mutated melanoma and prolongs OS (Chapman et al. 2011). This has led to great interest in using vemurafenib in other BRAF V600E positive cancers.

A multicenter phase I trial under the auspices of the Pacific Pediatric Neuro-Oncology Consortium (PNOC) is currently enrolling

patients with recurrent or refractory gliomas to evaluate the safety and pharmacokinetic characteristics of vemurafenib (http://www.pnoc.us). It is important to note that in addition to the V600E mutation, a significant proportion of BRAF alterations in PLGG involve duplication/gene fusions, and the efficacy of various RAF inhibitors against fusion molecules is unknown, but may be associated with paradoxical activation in some cases (Dasgupta and Haas-Kogan 2013).

BRAF-mutated tumors appear to have sensitivity to MEK inhibition (Flaherty et al. 2012, b). The MEK inhibitor trametinib is now FDA approved for the treatment of melanoma and has demonstrated efficacy against colorectal, hepatocellular, and non-small cell lung cancers in ongoing clinical trials. Another small molecule MEK inhibitor, selumetinib, was shown to have activity against a pilocytic astrocytoma xenograft harboring the BRAF V600E mutation (Kolb et al. 2010). The Pediatric Brain Tumor Consortium (PBTC) protocol PBTC 029 is an open phase I trial evaluating the maximal safe dose of selumetinib in patients with histologically confirmed recurrent or refractory PLGG. In addition, the National Cancer Institute is currently sponsoring a phase II trial of selumetinib for patients with recurrent or refractory PLGGs.

Targeting the mTOR pathway also appears promising. Approximately half of PLGGs have activation of the PI3-kinase-AKT-mTOR pathway. Rapamycin (sirolimus), an allosteric inhibitor of mTORC1, blocks the ability of mTORC1 to activate S6 kinase (a regulator of translation and a critical downstream target) but not 4E-BP1. It has been documented to cause regression of SEGAs in patients with TS harboring TSC1/2 gene mutation (Northrup et al. 1993). Everolimus, a derivative of rapamycin, has been used clinically for cancer therapy (Motzer et al. 2008), and is approved for multiple indications in adults. Among children with TS and progressive SEGA, 75% of tumors exhibited responses to everolimus (Krueger et al. 2010). Indeed, everolimus was recently approved for the treatment of SEGA in patients with TS.

Clinical trials have demonstrated promising results for mTOR inhibition in PLGGs more generally. Yalon et al. examined the activity of sirolimus and erlotinib in recurrent PLGGs (Yalon et al. 2013). Responses in 19 patients included 1 partial response, 5 stable, and 10 progressive disease (3 discontinued therapy). Six patients had tumor stabilization for ≥12 months, and two experienced tumor control for >1 year after therapy completion. Kieran et al. reported 23 patients with PLGGs who were treated with everolimus after progression following carboplatin-containing chemotherapy regimens. Observed responses included 13 stable, 6 progressive disease, and 4 partial responses (Kieran, M. personal communication). This study met its goal of greater than 25% response rate defined a priori in order to consider everolimus a promising regimen for further study in PLGGs. Copious evidence indicates that molecular markers will define subgroups of PLGGs that are likely to respond to everolimus, but answers to this critical question remain elusive as of yet. A notable manuscript provides a persuasive mechanism for these promising results of mTOR inhibition in sporadic PLGGs. Kaul et al. documented that KIAA1549:BRAF is sufficient to induce glioma-like lesions in vivo in a cell type-specific and mTOR-dependent manner. Rapamycin-mediated mTOR inhibition blocks KIAA1549:BRAF-induced S6 activation and proliferation in neural stem cells. These data provide preclinical evidence for the use of mTOR inhibitors for sporadic PLGGs (Kaul et al. 2012). A PNOC phase II study of everolimus is enrolling children with recurrent or progressive PLGGs with the aim of seeking a molecular signature that will predict responses to mTOR inhibition.

10.7 Late Effects and Follow-Up

Current estimates indicate that approximately one adult in 2500 is a survivor of a childhood brain tumor (Dulac et al. 2013). Due to the combined treatment modalities and the location of the tumors, CNS lesions in children are frequently associated with high morbidity and long-term side effects. Survival, however, ranges from 87 to 99% at 5 years, so while many of these patients are cured of their disease, cure often comes at the price of late sequelae of treatment (Wisoff et al. 2011 and Shaw

and Wisoff 2003). The burden of long-term disability is not inconsequential, as reports have shown up to half of patients treated for pediatric brain tumors have mild to severe disabilities, including cognitive and social impairment (Aarsen et al. 2006).

10.7.1 Surgical Toxicity

In children who undergo surgery alone for cerebellar and cerebral lesions, there is an elevated rate of below-average IQ, lower achievement, and difficulties with adaptive behavior. Behavioral and emotional adjustment measures appear to remain intact (Pollack 2011). It is unclear if location of the lesion correlates with the magnitude of poor cognitive performance, though patients with cerebral lesions may perform better than those with posterior fossa lesions (Aarsen et al. 2006; Beebe et al. 2005; Ris et al. 2008; Ris and Noll 1994). This finding implicates the importance of the cerebellum in cognitive and emotional regulatory circuits (Sancak et al. 2016). Patients with left hemispheric lesions tend to have inferior performance, likely due to the impact of a left-sided lesion on language functions (Beebe et al. 2005; Roncadin et al. 2008).

10.7.2 Toxicity Due to Chemotherapy and Other Medical Therapy

Multiple chemotherapeutic options exist for treatment of PLGG, and many have associated long-term morbidity. There is well-known ototoxicity and peripheral neuropathy that result from treatment with platinum analogs and vincristine, respectively. Procarbazine and lomustine have a higher risk of secondary leukemia and are typically avoided in children with NF-1, due to their increased underlying risk of hematologic malignancy (Shannon et al. 1994; Matsui et al. 1993; Leone et al. 1999). Cisplatin and etoposide-based regimens have a risk of secondary leukemia as well (Le Deley et al. 2005).

The risk of neurotoxicity associated with chemotherapy, however, remains an unanswered question. Anti-folates such as methotrexate have been shown to impart delayed neurotoxicity (Cole and Kamen 2006); however, other studies have shown no neuropsychological differences between patients treated with chemotherapy and healthy controls (Anderson et al. 2000; Reddick et al. 1998).

A significant proportion of PLGG patients require anti-epileptic medications that have been implicated in long-term neurocognitive deficits. Patients who were prescribed seizure medication performed worse on delayed list memory tasks (King et al. 2004). However, this finding may be confounded by tumor location as well.

10.7.3 Radiation Associated Toxicity

In a series of studies performed in the last 20 years, chemotherapy has been notable in its ability to delay or obviate the need for radiation therapy in children with subtotal resections or progressive disease (Pollack 2011). When radiation is indicated, though, it is important to note that the late side effects of radiation therapy are pronounced in the pediatric population. In general, children who undergo radiation at a young age are at increased risk for development of in-field cranial and spinal meningiomas, gliomas, and sarcomas. Usually these lesions are benign; however, malignant meningiomas can occur as a result as well.

Cranial irradiation also increases the risk of neurovascular disease due to vascular injury, endothelial proliferation, collagen synthesis, and loss of intercellular junctions (Siffert and Allen 2000). These effects in both small and large vessels increase the risk for both hemorrhagic and ischemic strokes, as well as moyamoya disease. Moyamoya disease is radiation-induced vascular injury characterized by progressive bilateral occlusion of the internal carotid arteries and development of anomalous collateral circulation. Highest risk patients are those of Japanese ancestry and those affected by NF-1 treated with radiation to the circle of Willis (Siffert and Allen 2000). In a large 2014 Surveillance, Epidemiology, and End Results (SEER) retrospective study of PLGG, radiation treatment was found to be the greatest

predictor of worst survival (Bandopadhayay et al. 2014). However, it is extremely likely this finding is strongly influenced by selection bias since the patients who are treated with radiation have a worse prognosis, regardless of the addition of radiation.

Long-term neurocognitive deficits are notable and are clearly associated with radiation dose and volume (Fuss et al. 2000). Toxicity includes, but is not limited to, a lower average IQ, difficulty with visuospatial skills, and expressive language and verbal memory deficits (Ris and Beebe 2008). Again, tumor location is a confounding factor for interpreting the magnitude with which radiation contributes to long-term disability (Fouladi et al. 2003). Although focal radiation treatment has reduced this risk, over time patients who are treated with radiation remain at an increased risk for social adjustment disorders and withdrawal as well as many other neurocognitive deficits (Aarsen et al. 2006).

A recent phase II study from St. Jude Children's Research Hospital assessed long-term neurocognitive outcomes following focal radiation therapy (Merchant et al. 2009). Cognitive effects, such as internalizing and behavioral problem scores, visual auditory learning, communication and reading and spelling, were followed through 5 years after the completion of radiotherapy using psychological testing. At the 5-year time point, only the decline in ability to spell was clinically significant. Patients with NF-1, on average, had significantly lower baseline performance scores. Those who were treated at a younger age, with higher radiation doses (between 30 and 60 Gy), and those who had larger volumes of brain irradiated experienced more dramatic declines in IQ 5 years after the completion of treatment. Older patients, however, were more likely to have preserved IQ scores over time after the completion of treatment. Extent of surgery impacted psychology scores. Initially, patients who had a biopsy performed better than patients with a subtotal resection, but eventually the patients who had a more complete resection demonstrated superior performance. Overall, conclusions from this study indicate that age at the time of treatment is the most important factor to consider when weighing the risk of long-term side effects. Delaying adjuvant treatment, such as radiation or chemotherapy, if clinically indicated, can positively impact long-term functional outcome.

10.7.4 Chiasmatic, Hypothalamic, and Diencephalic Toxicity

Endocrine abnormalities and hypothalamic dysfunction are common for tumors that arise in the midline and diencephalic region. In order of decreasing incidence, deficits include growth hormone deficiency, hypothyroidism, glucocorticoid deficiency, and gonadotropin deficiency (Merchant et al. 2010). It is often unclear if the deficit results from the treatment itself or from the structural stress placed on intracranial tissues by the tumor, but the deficits are likely to be multifactorial in nature and are strongly influenced by the extent of surgical resection and dose of radiation (Ris and Beebe 2008; Ris and Noll 1994; Ris et al. 2008; Siffert and Allen 2000; Fouladi et al. 2003).

When the lesion involves the optic nerve or chiasm, visual impairment can occur as a result of tumor infiltration or treatment. These lesions are usually subtotally resected due to their location, and therefore adjuvant chemotherapy or radiation is necessary to stabilize residual disease. Patients with anterior chiasmatic lesions have been noted to have IQ impairment at diagnosis but it is unclear if subsequent chemotherapy or radiation treatment further impair intellectual performance (Lacaze et al. 2003; Fouladi et al. 2003), as these studies include NF-1 patients who many times have baseline neurocognitive deficits.

Diencephalic syndrome (DS) is a rare, but potentially fatal, metabolic syndrome that can be associated with low-grade gliomas that arise from the hypothalamus or chiasm in young children. DS is characterized by profound emaciation and failure to thrive despite adequate caloric intake (Kilday et al. 2014). Long-term care for children with DS frequently includes nutritional support with both nasogastric and subsequent

gastrostomy tube to aid in weight gain and recovery and there has been data to suggest that aggressive nutritional support during treatment yields better outcomes. Post-treatment sequelae include significant visual impairment, partial- or panhypopituitarism and learning difficulties, excessive weight gain, motor deficits, psychiatric disturbances, and seizures (Kilday 2014).

10.7.5 Delayed Toxicity

Since PLGGs are associated with very good overall survival, there is a growing population of adult survivors that have been studied. When surveyed, adult patients who were treated with various combinations of treatment (chemotherapy, radiation, and surgery) reported higher incidences of global distress and depression compared to their control siblings (Kilday 2014). Furthermore, some patients were found to have "grown into" a deficit, meaning they experienced normal functioning for a period of time, then developed behavioral and cognitive disabilities years after diagnosis and treatment (Aarsen et al. 2006).

Adult survivors were also less likely to be fully employed, married, to have graduated from college, or to have an annual income over $20,000. Additionally, those affected with pediatric malignancies were also more likely to have reported a major medical condition and to describe their current health as "fair" or "poor" (Zebrack et al. 2004). This effect is likely multifactorial in etiology, related to both tumor and treatment effects.

10.7.6 Approaches to Management of Long-Term Toxicity

Because the pediatric population affected by CNS tumors is at high risk for long-term sequelae from tumor effect and treatment toxicity, it is important to implement a multidisciplinary approach to optimize health and function of survivors. Several studies have documented survivors' knowledge of their diagnosis, prior treatment, and future oncologic screening guidelines (Byrne et al. 1989; Hudson et al. 2002, 2003; Kadan-Lottick et al. 2002; Nathan et al. 2007). At the completion of treatment, providing patients, their families and their primary care providers with a comprehensive treatment summary and recommendations for follow-up is paramount. Oncologists provide an essential role in counseling patients to engage in prevention strategies, risk-stratified medical monitoring, and healthy behavior.

Since many of the survivors of pediatric CNS tumors experience long-term neuropsychological and cognitive difficulties, complete neuropsychological testing prior to treatment and involvement in a follow-up clinic is essential. Communicating the special needs of the child to day-care and school officials helps to ensure adequate resources, aiding the child's ability to adapt and succeed. Involvement of a school psychologist as a liaison between physicians and school administrators can often be helpful.

Multidisciplinary follow-up through adulthood provides these patients with resources and care to optimize their functional outcome. The COG, which consists of over 240 institutions, provides "Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent and Young-Adult Cancer," available at www.survivorshipguidelines.org.

Conclusion

In conclusion, PLGG are a heterogeneous group of childhood tumors with generally favorable prognosis. Our understanding of the underlying molecular pathobiology of these tumors is allowing us to better define prognosis and guide management. Surgical resection is the hallmark of management, although there is also a role for chemotherapy, radiation, and targeted systemic agents in unresectable or recurrent tumors. Given the young age of PLGG patients, there has been concern regarding long-term side effects of treatment. However, an evolving theory suggests that younger age confers greater resilience to treatment, rather than vulnerability, and that children have a greater potential for recovery due to neuronal

plasticity (Kolb and Gibb 2007). Improving outcomes and long-term follow-up of children treated for brain tumors will provide insight into that hypothesis. Furthermore, as therapies are becoming more targeted, both on the anatomic and molecular levels, short- and long-term toxicities may likely be mitigated.

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