High-Grade Glioma

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Introduction

Gliomas are primary brain tumors derived from the glial cell (astrocytic and/or oligodendroglial) lineage. These tumours are historically separated into low- or high-grade categories according to the World Health Organization (WHO) classification system. Low-grade astrocytomas (WHO grades I and II) constitute approximately 50 % of primary supratentorial tumors of childhood and are more common than high-grade astrocytomas (WHO grades III and IV) [1, 2]. High-grade gliomas (HGGs) are less common in the pediatric age group when compared to adults [1] constituting 3–7 % of all childhood brain tumors [2, 3], are a histologically heterogeneous group of tumors, and are classified, according to the putative cell of origin, as: astrocytic tumors (anaplastic astrocytoma (AA), glioblastoma (GBM), giant cell GBM, and gliosarcoma), oligodendroglial tumors (anaplastic oligodendroglioma), or oligoastrocytic (mixed) tumors (anaplastic oligoastrocytoma). Other rare HGG varieties include anaplastic ganglioglioma, which appears to have a more favorable prognosis than other HGGs and anaplastic pleiomorphic xanthoastrocytoma [1]. Special categories of HGG include diffuse intrinsic pontine gliomas [DIPG, WHO grade IV; discussed in a separate chapter] and gliomatosis cerebri (grade III). All of these HGG tumors are characterized by their highly invasive nature leading to difficulty in treatment and they are poorly responsive to even the most aggressive therapies. Surgery and Radiation therapy (RT) are the usual modes of therapy, especially for AAs and GBM and prognosis is better in children than adults [2]. The optimal use and selection of chemotherapy, given concurrently with RT and/or in the adjuvant setting, remain to be determined.

Epidemiology

Gliomas are the most common childhood tumors of the central nervous system (CNS), accounting for 53 % of tumors in children ages 0–14 years and 37 % in adolescents aged 15–19 years [2]. HGGs comprise ~17 % of childhood and ~8 % of adolescent brain tumors when including DIPG [2]. HGGs are at least 20 times more common in adults than in children, particularly GBM, which

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is the most common primary malignant brain tumor in adults. GBM comprises approximately 3 % of all brain and CNS tumors reported among 0–19 year olds [2]. In the pediatric population HGGs seem to affect boys and girls equally [2].

Etiology and Associations

The causes of gliomas remain largely unknown, although certain familial cancer predisposition syndromes are associated with an increased risk of HGG. Li–Fraumeni syndrome (LFS), a dominantly inherited syndrome involving the p53 tumor suppressor gene, is characterized by one or more cancer occurrences in children including HGGs. *p53* mutations are rare in sporadic pediatric CNS tumors lacking a typical family history. In addition to LFS, neurofibromatosis type I (NF-I, with mutations in the neurofibromin gene, which is also a tumor suppressor gene) and familial cancer syndromes involving the DNA mismatch repair (MMR) genes can predispose to HGG [4]. These disorders include: (i) Turcot syndrome, type I (HNPCC, hereditary non-polyposis colorectal cancer) with MSH6 gene mutations; (ii) Turcot syndrome, type II with APC gene mutations; and (iii) BRCA syndrome with BRCA1 or BRCA2 gene mutations. As well, patients with multiple enchondromatosis are at increased risk of HGG. However, to date, the most robust association linked to the development of malignant gliomas is prior exposure to therapeutic ionizing radiation.

Clinical Features

The presentation of HGG varies and depends largely on the age of the patient, the anatomic location of the tumor, and the associated effects on the structures surrounding the tumor. Compared with low-grade gliomas (LGG), HGGs tend to have a shorter interval of symptoms. The signs and symptoms can be broadly divided into three categories:

(a) *General and Non-localizing Features:* Constitutional symptoms such as developmental delay, failure to thrive, behavioral or mood changes, declining school performance, changes in handwriting, and loss or regression of previously attained milestones.
(b) *Increased Intracranial Pressure* (ICP): Children with HGG frequently present with symptoms related to raised ICP, including headache, nausea, and vomiting, which are all classically worse in the morning attributed to increased cerebrovenous pooling during sleep. Clinical signs include papilledema, Parinaud's syndrome ("setting sun" sign), anisocoria (pupillary size inequality), ataxia, and head tilt. In the infantile period when the sutures are still open, the signs may include delayed closure of the fontanelles, or a bulging anterior fontanelle with separation of sutures and increased head circumference usually due to concurrent hydrocephalus.
(c) *Localizing Signs*: Localizing neurological deficits depend on the site of the tumor. HGGs that originate supratentorially often present with hemiparesis or progressively worsening seizures, although seizures are a less common presenting sign in HGG than in LGG. Cortical gliomas can present with dysphasia, hemisensory loss, early handedness, or change in handedness apart from the nonspecific signs described above. Midline gliomas can present with cranial neuropathies (visual loss, diplopia, facial palsy, etc.). Dissemination of malignant gliomas into the cerebrospinal fluid is less common than for medulloblastoma and other neural tumors but is being recognized more frequently, particularly as patients survive longer. In a large German series approximately 3 % of patients with HGGs had metastatic disease at presentation [5]. Though a delay in diagnosis is a frequent occurrence, the impact on overall survival may not be significant although the quality of survival may be affected by inordinate delays [6].

Diagnostic Evaluation

Imaging Studies

Neuroimaging examinations in HGG are used to determine the size and site of origin of the lesion, establishing a primary diagnosis (DIPG),

and planning treatment. Various neuroimaging modalities are being used for selecting a site for stereotactic biopsy, guiding resection, radiation therapy planning, application of experimental therapeutics (such as convection-enhanced delivery or CED), and delineation of tumor from functionally important brain parenchyma.

CT Scans

Computed tomographic (CT) scans are usually the first imaging procedure done in patients with raised ICP or seizures in the emergency room. HGG can be identified on computed tomographic (CT) scans as irregular isodense or hypodense white matter lesions. There is overlap in anatomical localization of pediatric supratentorial HGG and LGG (grade II). Both grade II and grade III lesions tend to be ill-defined, being hypodense masses on CT studies. Calcification or cystic changes may be seen. Anaplastic astrocytoma often shows enhancement, at least focally. GBM characteristically presents as a ring-enhancing lesion in post-contrast-enhanced CT images. CT scans are used rarely for routine surveillance and follow-up of pediatric patients due to poor anatomic delineation of tumor to adjacent brain and to potential radiation exposure and long-term cancer risk. However, CT scan is very helpful for rapid assessment of ventricular status and to determine whether intracranial or intra-tumoral bleeding has occurred in the inpatient or emergency room setting.

MRI

Magnetic resonance imaging (MRI) is currently the modality of choice for localization and assessment of HGG. MRI provides valuable information about secondary phenomena such as mass effect, edema (pseudoresponse vs. progression during therapy), hemorrhage, necrosis (radiologic), and signs of increased ICP. In addition, MRI provides excellent tissue contrast and high spatial resolution. Standard (conventional) MRI sequences obtained during routine imaging include T1-weighted (pre- and post-contrast images, usually with gadolinium), T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images. Examples of two patients with HGG are shown (Fig. 10.1).

Conventional MRI features of HGG are varied and can resemble LGG. These tumors are usually solitary or rarely can be multifocal. Cortical tumors usually have an irregularly enhancing rim surrounding a necrotic core or can be poorly marginated with diffuse infiltration into white matter tracts such as the corpus callosum and anterior and posterior commissures. On pre-contrast T1-weighted sequences, these tumors are iso- or hypointense. Post-contrast T1-weighted sequences typically show an irregular enhancing rim surrounding a non-enhancing area of central necrosis. Intratumoral hemorrhage may be present in grade IV tumors. The enhancing rim typically represents highly proliferative, invasive, and radio-resistant tumor cells. T2-weighted and FLAIR sequences usually show a heterogeneous mass with variable signal intensity surrounded by bright areas representing a zone of vasogenic edema. It is important to note that infiltrating malignant tumor cells extend far beyond the area of enhancement. Giant cell glioblastoma and gliosarcoma tend to be more demarcated than other glioblastomas. In gliomatosis cerebri at least three cerebral lobes are typically involved, and these tumors are usually bilateral and extend into deep gray matter structures. Gliomatosis may extend to involve the posterior fossa or even the spinal cord. Lesions are characteristically hyperintense on T2 and FLAIR MR imaging. Imaging of the neuraxis is indicated when there is concern for disseminated disease throughout the brain and spinal cord.

Functional Neuroimaging

Conventional MRI which gives information based largely on tumor structure and anatomic location is increasingly being supplemented by methods commonly referred to by the collective term "functional imaging" [7]. A range of functional imaging techniques for brain tumors that provide information on cellularity, tissue ultrastructure, metabolism, and vascularity are available and best acquired as part of a multimodal protocol. There has been an increased interest in using functional

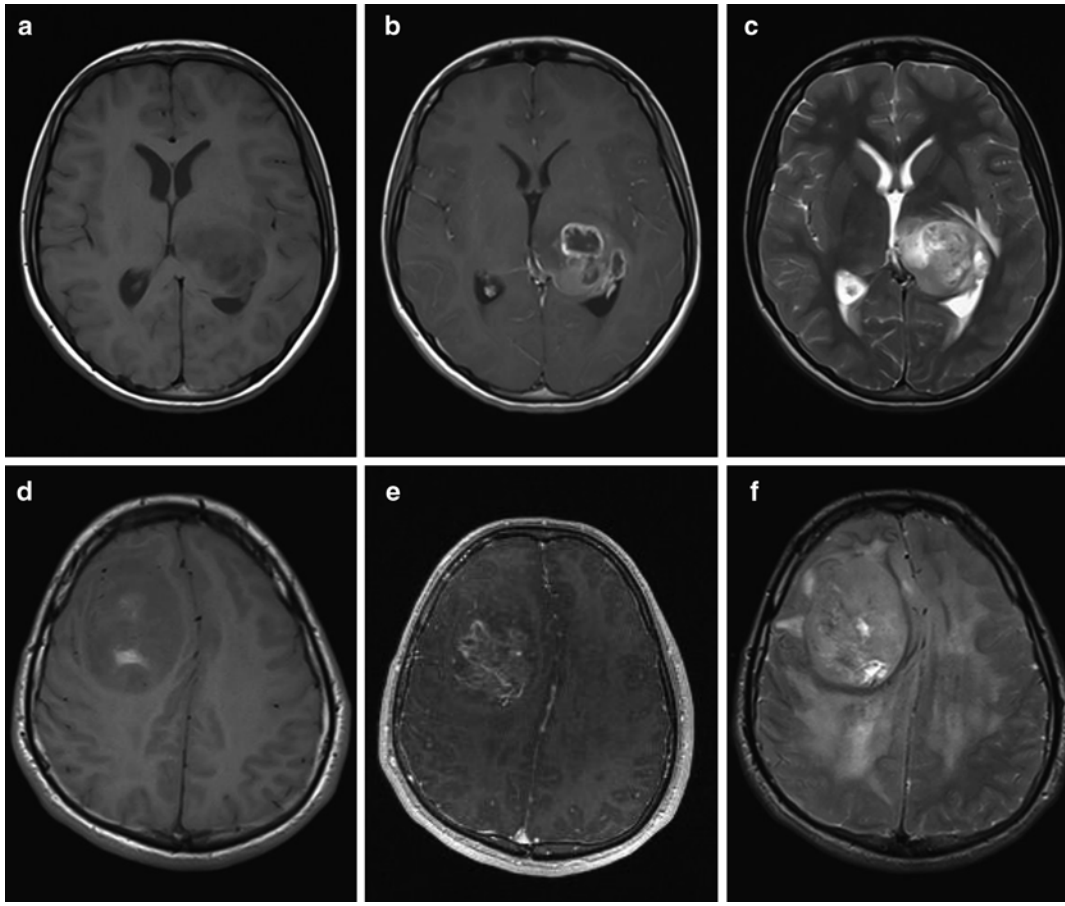

Fig. 10.1 (**a–c**) **A** 12-year-old female with GBM. (**a**) Axial T1, (**b**) axial T1 with gadolinium, (**c**) axial T2. (**d–f**) **A** 15-year-old male with malignant glioma. (**d**) Axial T1, (**e**) axial T1 with gadolinium, and (**f**) axial T2. Both tumors demonstrate minimal contrast enhancement

imaging to assist in the diagnosis, management, and determination of treatment response of HGG. Some of the commonly used functional imaging techniques and their clinical uses are:

(a) *Diffusion MRI* with two different techniques: diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI). DWI uses apparent diffusion coefficient (ADC) histograms and has been valuable in the grading of gliomas (especially LGG). Low ADC values correlate with high cellularity and proliferation, most often seen in aggressive tumors. DTI has been shown to be useful in discriminating LGG from HGG and also in presurgical evaluation and radiosurgical planning of white matter tracts surrounding the tumor (DT tractography). Fractional anisotropy (FA) using DTI may prove helpful for the assessment of treatment-induced white matter changes in children during follow-up.

(b) *Perfusion MRI* (pMRI) provides a surrogate for neo-angiogenesis, which is a key feature of many malignant gliomas. An indirect measurement of pMRI, the relative cerebral blood volume (rCBV), has been shown to correlate with tumor vascularity and HGGs tend to have higher rCBV values than low-grade tumors.

(c) *Functional MRI* (fMRI) is a commonly used technique for identifying the eloquent gray matter in cortical HGGs prior to surgery. This approach may be limited to older children and adolescents.

(d) *Magnetic resonance spectroscopy* (MRS) measures the chemical composition of tissue and provides semiquantitative information about major cellular metabolites. A common pattern in brain tumors is a decrease in *N*-acetylaspartate (NAA), a neuron-specific marker, a decrease in creatine (Cr), and an increase in choline (Cho), lactate (Lac), and lipids (L). The concentration of Cho is a reflection of the turnover of cell membranes (due to accelerated synthesis and destruction) and is more elevated in regions with a high neoplastic activity. Lactate is the end product of nonoxidative glycolysis and a marker of hypoxia and possibly necrosis in tumor tissue. Tumor hypoxia is now recognized as a major promoter of tumor angiogenesis and invasion. MRS may be used in distinguishing tumor from non-tumor masses (abscess, infections, and metabolic disorders) or from radiation necrosis and in characterizing tumor grade (high grade vs. low grade). Multivoxel MRS imaging (MRSI) has the advantage of improved characterization of heterogeneous tumors but is technically more demanding, may be less reproducible, and is not widely available except in tertiary or quaternary treatment centers.

(e) *Positron emission tomography* using fluorodeoxyglucose or F^{18} (FDG-PET) is another noninvasive molecular imaging modality that aids in the diagnosis of malignant tumors and may distinguish active tumor from radionecrosis. Besides F^{18}, other radioisotopes, such as C^{11}, are under the increasing use in adults and children.

Functional imaging techniques are becoming more widely available in clinical practice and have an important role in aiding the clinical management of children with HGG. They are increasingly used preoperatively to differentiate between tumor and non-tumor pathology (MRS, pMRI), high- and low-grade tumors (MRS, DWI), and primary HGG and metastatic lesions to the brain (MRS). These adjunct studies may also improve diagnostic accuracy of a biopsy by determining the most abnormal region of the tumor (MRS, DWI) and to define tumor margins for both surgical resection and radiation fields (fMRI, DTI). In the intraoperative and postoperative periods, functional imaging is most commonly used to identify eloquent areas of the brain especially in cortical tumors (fMRI, DTI) and for treatment planning for surgery, stereotactic radiosurgery, and radiation therapy (DT tractography). Monitoring for therapy-induced white matter changes and related toxicities (DTI), radiation necrosis versus residual/recurrent tumor, (MRS, DWI), and especially treatment response monitoring, including pseudoresponse (PsR) and pseudoprogression (PsP), is enhanced by these MRI- or PET-related imaging modalities [7]. The Response Assessment in Neuro-Oncology (RANO) criteria uses conventional MRI to assess treatment response of patients with gliomas (Table 10.1) [8]. Pediatric RANO (RAPNO) criteria are under development [9].

Pathology

Pediatric HGGs are less common than many other brain tumors occurring in infancy, childhood, and adolescence. Based upon the CCG-945 study and others, central neuropathology review can often result in a reclassification of HGG to an LGG or other histopathological entity [10–12].

Morphology

Macroscopically HGGs, particularly GBM, tend to have a heterogeneous appearance, forming obvious masses, often containing areas of hemorrhage and/or necrosis. They typically have a mottled tan, red, and brown coloration with alternating firm and softened zones. Gliosarcomas may be quite firm in consistency, due to the presence of sarcomatous components.

Histology

Microscopically, HGGs are distinguished from LGG by the presence of four important histologic criteria: nuclear atypia, mitotic activity (WHO

Table 10.1 Response Assessment in Neuro-Oncology (RANO)

First progression	Definition
Progressive disease <12 weeks after completion of chemoRT	• Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80 % isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (e.g., solid tumor areas [i.e., > 70 % tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor)
	• Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoRT
Progressive disease >or equal to 12 weeks after completion of chemoRT	• New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids
	• Increase by >or equal to 25 % in the sum of the products of perpendicular diameters between the first post-radiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids
	• Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence
	• For patients receiving antiangiogenic therapy, a significant increase in T2/FLAIR non-enhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not been a result of comorbid events (e.g., effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects)

Based on data from Ref. [8]

grades III and IV), necrosis (grade IV), and/or microvascular proliferation (grade IV). Tumor grade is established based on the area of the greatest anaplasia. AAs (grade III) are hypercellular astrocytomas that in addition to nuclear atypia have increased mitotic activity. Vascular proliferation and necrosis are absent. Cells with large pleiomorphic or multiple nuclei may be present. GBM (grade IV), in addition to findings listed for AA, display necrosis (typically pseudopalisading necrosis) or microvascular proliferation. Atypical mitotic figures may be present. Gliosarcoma (grade IV) is a biphasic high-grade glioma with both malignant astrocytic (GBM) and sarcomatous components. The sarcomatous portion is frequently fibrosarcoma, though it may include malignant fibrous histiocytoma, chondrosarcoma, osteosarcoma, leiomyosarcoma, rhabdomyosarcoma, or even liposarcoma. Trichrome and reticulin stains are frequently helpful. Gliomatosis cerebri (GC, grade III) is most frequently astrocytic tumors, though infrequently may contain oligodendroglial elements. Nuclei tend to be elongated and hyperchromatic, and pleiomorphic forms are not uncommon. Secondary structures are frequently present. Mitotic activity is variable. Areas resembling GBM may be present in some cases.

Immunohistochemistry

Expression of the intermediate filament *glial fibrillary acidic protein* (GFAP) reflects the glial origin of these tumors and sometimes the extent of cytoplasmic development and is present in the intervening fibrillary matrix of these lesions. *S100* often shows diffuse nuclear and cytoplasmic positivity, and another intermediate filament *vimentin* is similarly positive. The proliferation marker *Ki-67* (or *MIB-1*) is variably positive, reflecting the low (grade II) to brisk (grades III and IV) proliferative activity of these lesions, respectively. *Neurofilament* staining of intratumoral neuritic processes provides evidence of the infiltrative pattern of these neoplasms.

Pancytokeratin is often positive at least focally in higher grade lesions, showing cross-reactivity with glial intermediate filaments. More specific cytokeratin antibodies are usually negative. Sarcomatous portions of gliosarcoma, though not positive for GFAP, are consistently vimentin positive and tend to take on the staining properties of the particular sarcoma element present (muscle, fat, cartilage, etc.). Gliomatosis is variably positive for GFAP and S100 expression [1]. It may sometimes be a challenge for the neuropathologist to distinguish pediatric HGG from supratentorial primitive neuroectodermal tumors (sPNET), mandating central review for patients entered on a clinical trial.

Molecular Biology

In adults, GBM is typically classified as either primary or secondary based on clinical and biological features. The vast majority of GBM (approximately 90 %) develop rapidly de novo in middle-aged or elderly patients, without clinical or histological evidence of a less malignant precursor lesion (primary glioblastomas). Secondary GBM progress stepwise from low-grade diffuse astrocytoma (grade II) or anaplastic astrocytoma (grade III). Histologically, primary and secondary glioblastomas may be indistinguishable, but they differ in their genetic and epigenetic profiles. Isocitrate dehydrogenase IDH1 mutations are classically seen only in secondary glioblastoma [13] and associated with a hypermethylation phenotype [14].

Based on the histological similarity and recurrent genomic aberrations, pediatric GBM (pGBM) were historically thought to more closely resemble the secondary adult GBM (aGBM). PDGFRA mutations and focal amplifications are often present. Paugh et al. discovered somatic activating mutations in 14.3 % of pediatric non-brainstem HGG [15]. In another study using FISH, PDGFRA amplification was noted in 29.3 % pediatric and 20.9 % adult HGG, but amplification was not prognostic in children [16]. EGFR amplification and EGFRvIII and PTEN mutations are less common in pGBM than aGBM [17, 18]. MGMT methylation as assessed by MGMT overexpression [19, 20] or methylation-specific PCR assays [21] has been correlated with improved EFS but has not yet been validated as either an independent predictive or prognostic marker for pediatric HGG when compared to adult GBM [22].

Rapid advances in the field of genomics (exome and whole genome sequencing studies) and international collaborative efforts (providing access to a large number of pediatric tumors) have led to greater understanding of HGG in children and adults. It is now clear that in the majority of cases described to date, pGBM is biologically distinct from aGBM [23, 24]. The majority of pediatric GBM arise de novo and have characteristic clinical, genetic, and epigenetic features. Recurrent somatic driver mutations in the H3F3A gene, which encodes the replication-independent histone 3 variant (H3.3), lead to amino acid substitutions at key residues, namely lysine (K) 27 (K27M) and glycine 34 (G34R/V), identify distinct subgroups of pediatric GBM, and are seen in 30–45 % of cases [23–25]. H3.3 K27M mutations are more frequent in subcortical regions such as the thalamus and brainstem, whereas the H3.3 G34R/V lesions tend to be in hemispheric locations [26]. IDH1/2 mutations are very rare in childhood GBM (<10 %) [27]. Moreover mutations in H3F3A and IDH1 are mutually exclusive anatomically and across specific age groups: in children (K27M mutations), adolescents (G34R/V mutations), and young adult patients (IDH1 mutations) locations [26].

Whole exome sequencing studies of pediatric GBM identified mutations in α-thalassemia/mental retardation syndrome X-linked (ATRX) and death domain-associated protein (DAXX) genes in 45 % of cases [6]. These genes encode two subunits of a chromatin-remodeling complex required for H3.3 incorporation in pericentric heterochromatin and telomeres. ATRX and/or DAXX mutations have a strong association with TP53 mutations and alternative lengthening of telomeres (ALT) [23, 24]. IDH1/2 mutations lead to overproduction of 2-hydroxyglutarate (2-HG) which inhibits demethylases required for modification of histones and DNA and may

thereby block differentiation and tumorigenesis. The H3F3A mutations (K27M leading to transcriptional derepression and G34R leading to altered gene expression, such as of MYCN; [28] are hypothesized to induce epigenetic reprogramming leading to tumorigenesis [29], although the exact mechanisms remain to be fully elucidated. Very recently, mutations were identified in SETD2, a H3K36 trimethyltransferase, in pediatric HGGs localized to the cerebral hemispheres. SETD2 mutations are specific to HGG in children (15 %) and adults (8 %). In HGG these mutations are mutually exclusive with H3F3A mutations but sometimes overlap with IDH1 mutations [30].

Of interest, activating BRAF mutations such as BRAF V600E are also present in 15–20 % of pediatric HGG (reviewed in [31]). The genetic differences of HGGs across the age spectrum are summarized in Table 10.2 [32].

Therapy

Treatment of HGGs requires a multidisciplinary approach and involves surgery, radiation therapy (RT), and chemotherapy.

Surgery

Patients presenting with signs of increased ICP may require emergent neurosurgical intervention to relieve obstructive hydrocephalus with several alternatives in addition to tumor debulking: placement of external ventricular drain (EVD) or a ventriculoperitoneal shunt (VP shunt) or by means of a third ventriculostomy, and the latter via the use of a neurosurgical endoscope. The use of preoperative corticosteroids, usually dexamethasone, can significantly decrease peritumoral edema, thus decreasing focal symptoms and often eliminating the need for emergency surgery. Tumor resection is safer when performed 1–2 days following reduction in edema and ICP by these means. Seizures are treated with anticonvulsants. Prophylactic anticonvulsants in patients who do not present with seizures are not recommended, and antiseizure medications are usually tapered and discontinued in the postoperative period.

The main goals of tumor surgery include obtaining tissue for histopathologic diagnosis and whenever possible, to achieve a gross total resection (GTR). The *extent of resection* (EOR) in HGGs has two important limitations. First, these highly infiltrative tumors invade the surrounding brain tissue, beyond the margins of the visible tumor in neuroimaging. Hence, even in the case of a GTR of all visible tumors, microscopic disease is present beyond the surgical margins, and surgery alone is not considered curative. The second limitation derives from the growth pattern and the anatomic location of the tumor. Multifocal or diffusely infiltrative tumors, deep-seated tumors, and tumors adjacent to or within eloquent areas of the brain may limit the possible extent of resection or even preclude any attempt of surgery beyond a biopsy. Preoperative functional imaging techniques (fMRI, DTI) and intraoperative MRI scans help in achieving the maximum resection possible with minimal impact on postoperative neurologic ability. The diagnostic yield of stereotactic biopsy in deep-seated lesions is greatly improved by functional imaging (MRS, DWI) to localize the tumor tissue.

The extent of resection (EOR) along with age at diagnosis and the grade of the tumor are considered to be the most important prognostic factors in pediatric HGG. If a GTR cannot be achieved, surgical debulking to achieve a maximum possible resection with preservation of neurologic function should be attempted. Aggressive cytoreduction will not only relieve the signs and symptoms due to mass effect but will also reduce the residual tumor volume to be treated by adjuvant therapies (RT, chemotherapy) and may also improve tolerance to RT. In the CCG945 study overall, children with HGGs who underwent GTRs (defined as >90 % resection) had a 5-year progression-free survival (PFS) of 35 % in comparison with 17 % in the group that underwent subtotal resection (STR) ($p = 0.006$). Patients with GBM (grade IV) who underwent GTR had a 5-year PFS of 26 % in comparison

Table 10.2 Integrated genomic classification of GBM

Subgroup	K27	G34	RTKI	IDH	Mesenchymal	RTKII (classic)
Clinical features						
Age distribution in years (median, range)	10.5 (5–23) child/ adolescent	18 (9–42) adolescent/young adult	36 (8–74) adolescent/ young adult, with another peak in adult/elderly	40 (13–71) young adult/ adult	47 (2–85) adult, with a smaller peak in childhood	58 (36–81) adult/elderly
Tumor location	Midline/deep	Cortical	Cortical	Cortical	Cortical	Cortical
	- ST 70–80 % (thalamus, basal ganglia)	T>P>O	F>P>T	F>>>T>P	F=P>T	F=T>P
	- IT 60 % (brainstem, spinal cord)					
Gender ratio (M/F)	~ 1:1	~ 1:1	~ 1:1	1:1.7	~ 1:1	1.46:1
Histology	GBM	GBM	GBM	GBM	GBM	GBM
Survival	Very poor	Poor	Poor/fair	<10 % long-term survivors	<10 % long-term survivors	<10 % long-term survivors
Genomic features						
Mutations/cytogenetics	H3F3A (K27M)	H3F3A (G34R/V)	PDGFRA (ampl/mut)	IDH1(R132H)	–	EGFR(ampl)
			CDKN2A/B (del)		Copy number variations (low)	Chr 7 (gain)
						Chr 10q (loss)
						CDKN2A(del)
TP53	+++	+++	–	+++	+	++
ATRX	++	+++	–	++	–	–
DAXX	+	+++	–	–	–	–
ALT	NR	+++	NR	NR	NR	NR
SETD2	–	–	+	+		
Gene expression signature	Proneural	Mixed	Proneural	Proneural	Mesenchymal	Classical
Immunohistochemistry (FOXG1/OLIG2)	*FOXG1*$^{-}$/OLIG2^{+}	FOXG1^{+}/*OLIG2*$^{-}$	FOXG1^{+}/OLIG2^{+}	*IDH1*^{R132H}	FOXG1^{+}/OLIG2^{+}	FOXG1^{+}/ OLIG2^{+}
Epigenetic features						
DNA methylation		CHOP^{+}		G-CIMP^{+}		

ALT alternative lengthening of telomeres, *CHOP* *C*pG island *h*ypo*m*ethylator *p*henotype, *F* frontal lobe, *G-CIMP GBM* *C*pG *i*sland *m*ethylator *p*henotype, *IT* infratentorial, *O* occipital lobe, *P* parietal lobe, *ST* supratentorial, *T* temporal lobe
Adapted from Refs. [24, 32, 57]

with 4 % in those who underwent subtotal resections (STRs) ($p=0.046$). In the same study, patients with AA (grade III) who underwent GTRs had a 5-year PFS of 44 % in comparison with 22 % in those who underwent STRs ($p=0.055$) [33].

Radiation Therapy

Most patients (especially children >3 years old) with HGG require external radiotherapy to achieve local control of microscopic or macroscopic residual disease. Adjuvant RT has been shown to be a very effective treatment modality with rapid symptomatic improvement and increased EFS and overall survival (OS) when offered at doses greater than or equal to 5,400 cGy as delivered in ~30 fractions over 6 weeks. Three-dimensional conformal treatment planning techniques including intensity-modulated radiation therapy (IMRT) are well tolerated and may have decreased side effects by decreasing the exposure of adjacent brain. Adaptation of these techniques has resulted in reduction of the margins used by radiation oncologists, including the gross target volume (GTV), the clinical target volume (CTV) to treat microscopic disease extending beyond the GTV, and the planning target volume (PTV). The CTV is anatomically confined and is usually limited to 2 cm. The PTV compensates for movement and uncertainties regarding daily positioning of the patient and setup of equipment and software; usually the PTV ranges from 0.3 to 0.5 cm. The use of palliative re-irradiation in relapsed cases can help by improving symptom control, but its impact regarding extending survival has yet to be established. Concern regarding long-term toxicities of radiation to the developing CNS (cognition, growth, endocrinopathies, and second malignancies) has led to the implementation of chemotherapeutic strategies to delay or obviate the need for RT and radiosensitization to decrease the dose of RT. *Proton beam* RT (protons) may be less effective than conventional RT (photons) due to the highly invasive nature of HGG and proton RT is currently not recommended for the adjuvant treatment of pediatric HGG. Brachytherapy, stereotactic radiosurgery, and fractionated stereotactic radiosurgery as alternatives to conventional RT are presently under study and may prove useful in selected relapsed patients.

Chemotherapy

In children, multi-agent adjuvant chemotherapy added to postoperative radiation results in a significant but modest improvement in event-free survival (EFS) compared with postoperative radiation alone. Historically, HGGs in children have been treated by using traditional cytotoxic drugs either as single agents or in various combinations, schedules, and doses. However, no particular chemotherapeutic regimen has clearly demonstrated superiority, and thus, the most effective agent(s) remains to be determined. To date, the Children's Cancer Group (CCG) study CCG-943 is the only study to show a clear survival advantage associated with adjuvant chemotherapy in pediatric HGG. In this study following surgical resection patients were randomized to RT alone (standard arm) or RT plus prednisone, CCNU/lomustine, and vincristine chemotherapy. Children in the chemotherapy arm showed a significant survival advantage (33 % 5-year EFS) when compared to RT alone [34]. These results have never been improved over the subsequent two decades. The follow-up CCG study CCG-945 enrolled 172 children in a phase III RCT comparing the nitrosourea-containing chemotherapy arm of CCG-943 to a new regimen known as "8-in-1" (eight drugs in one day) given pre- and post-RT; neither arm of the study was superior [35]. Subsequent to CCG-945, commonly used adjuvant chemotherapy regimens using lomustine included PCV (procarbazine, CCNU, and vincristine) and TPCH (6-thioguanine, procarbazine, lomustine, and hydroxyurea). The Children's Oncology Group phase II trial ACNS0126 offered concomitant oral temozolomide (TMZ) with RT followed by post-RT adjuvant TMZ (using the 5-day regimen) [36] to newly diagnosed children with HGG [20]. Temozolomide crosses the blood–brain barrier

(BBB) and has good oral bioavailability. Results of this study showed an overall 3-year EFS of 11 % and OS of 22 % (3-year EFS of 13 % for AA and 7 % for GBM) [20].

Unfortunately, the use of temozolomide in children has not improved outcomes for pediatric HGG, especially when accounting for improvements in neuroimaging, surgical technique, and delivery of RT. Apart from considering the fact that children who were enrolled in ACNS0126 were given TMZ the evening before daily RT when compared to 2 h or less on the day of RT (as administered on the adult EORTC/NCIC CTG trial), the most likely reason for the lack of a favorable impact of TMZ on survival in pHGG is due to the innate biological differences between pediatric and adult HGG. However, due to the favorable toxicity profile and the ability to add to this chemotherapy backbone in current and future studies, temozolomide-containing regimens are in common use at diagnosis. The completed phase II study ACNS0423 added adjuvant lomustine (CCNU) to TMZ following chemoradiation with TMZ; results are pending publication.

Other current clinical trials for newly diagnosed patients are incorporating *antiangiogenesis* strategies concurrent with and/or adjuvant to RT, such as bevacizumab, a recombinant humanized monoclonal antibody to the vascular endothelial growth factor A (VEGF-A). The current COG randomized phase II/III study ACNS0822 assigns patients to receive either temozolomide (TMZ), bevacizumab, or the HDAC inhibitor vorinostat (SAHA) as radiosensitizers with RT followed by TMZ and bevacizumab. A multicooperative group (ITCC/SIOP-E, Australian CCTG) randomized phase II study is comparing bevacizumab concurrent with TMZ and RT followed by TMZ and bevacizumab to chemoradiation with TMZ followed by adjuvant TMZ.

High-dose myeloablative chemotherapy with autologous hematopoietic stem cell rescue (ASCR) has resulted in survival for selected groups of patients (those with minimal or no residual disease prior to consolidation with myeloablative chemotherapy). The majority of reports are limited to small numbers of patients either newly diagnosed [37] or with recurrent disease [38]. However, overall long-term survival rates remain poor with significant long-term morbidity and mortality from the treatment regimen, and this therapeutic approach is not currently recommended for newly diagnosed patients.

Treatment of Infants with HGG

Although HGG is rare in this age group, infants (children younger than 3 years) have a better outcome than older children. In order to avoid the long-term devastating side effects of RT to the developing brain, clinical trials have been designed to either delay or totally avoid RT. There is a subset of patients younger than 3 years of age who have improved outcomes with chemotherapy alone [39–41]. Whenever possible, RT should be omitted or delayed in the treatment of children <3 years with HGG.

Local Therapies

One of the major limitations of HGG treatment is the successful and efficient delivery of effective therapies. The blood–brain barrier (BBB), although disrupted in some types of tumors (AA, cortical GBM), is largely intact (midline HGGs: thalamic GBM, DIPG) and plays an active role in restricting the delivery of systemically administered conventional and biological therapies. This leads to decreased effective concentration of the therapeutic agents in the tumor. In order to overcome this limitation, several alternative drug delivery strategies have been tried including: osmotic disruption of the BBB, use of lipophilic drugs, inhibition of membrane pumps such as p-glycoprotein, and intra-arterial and intrathecal chemotherapy; however, these treatment approaches have met with limited success. Novel controlled release systems which circumvent the BBB include direct intra-tumoral injection through an indwelling catheter or implantable chemotherapy-impregnated biodegradable wafers for which the best studied (in adults) includes BCNU. Convection-enhanced delivery

Table 10.3 Molecular targets in pediatric high-grade glioma

Target	Agent	Recurrent/relapsed	Median PFS (mo.)	PFS-6 (%)	Reference
VEGF	Bevacizumab (with irinotecan)	Recurrent/relapsed	4.5	42	[44]
EGFR	Erlotinib	Recurrent/relapsed	1.5	34	[45, 46]
	Gefitinib	Recurrent/relapsed	NR	15 (1-year PFS)	[47]
	Nimotuzumab	Recurrent/relapsed	1.8	NR	[48, 49]
PDGFR	Imatinib	Recurrent/relapsed	NR	18	[50, 51]
mTOR	Temsirolimus	Recurrent/relapsed	1.9	NR	[52]
αV-integrin	Cilengitide	Recurrent/relapsed	1.0	NR	[43]

EGFR epidermal growth factor receptor, *mTOR* mammalian target of rapamycin, *NR* not reported, *PDGFR* platelet-derived growth factor, *VEGF* vascular endothelial growth factor

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(CED) using external or implantable subcutaneous pumps allows intra-tumoral injection of novel therapeutic agents (chemotherapy, cytotoxic cytokines, and radio-immunotherapeutic agents) and is in early stages of clinical development in adults and children.

Novel Therapeutic Approaches: Targeted Therapies and Immunotherapy

The increased understanding of the biology and the pathways involved in HGGs has led to development of novel targeted therapies [32]. Broadly, these can be divided into small molecule receptor tyrosine kinase inhibitors (RTKI) versus EGFR, VEGFR, IGF1R, etc.; specific signaling pathway inhibitors (PI3K/AKT/mTOR, Ras/Raf/MEK, and CDK pathways); chromatin-remodeling/post-translational histone modification pathway inhibitors; antiangiogenic therapies; radiosensitizers; and immunotherapies [42]. Recent encouraging results in glioma immunotherapy in adults and children including EGFRvIII and dendritic cell-based tumor vaccines have led to a number of clinical trials in various stages of clinical trial development [42].

Recurrent HGGs

Relapse or progression of disease is very common in pediatric HGG and mortality approaches 100 % in these cases. The tumor recurrence can be local (at or adjacent to the site of the primary tumor) or disseminated (especially in nonresponsive tumors). Treatment options for relapsed HGG are limited and depend on factors such as the patient's age, performance status, response to initial therapy, time since original diagnosis, and whether tumor recurrence is local or diffuse. Limited therapeutic options include repeat resection, re-irradiation, and systemic chemotherapy. A large number of single-agent phase I/II trials have been conducted in children with recurrent HGG, but the majority of agents tested have revealed minimal or no activity (range of response rates: 0–23 %) (Table 10.3). The Pediatric Preclinical Testing Program, along with the Pediatric Brain Tumor Consortium (PBTC, USA), COG, and other cooperative groups, is developing a preclinical pipeline prior to testing these new agents in early phase clinical trials in children. Targeted therapies such as bevacizumab as single agents or in combination with cytotoxic chemotherapy have been used with some success in adults but have been disappointing in children. Recently completed phase II studies combining O^6-benzylguanine O^6BG with temozolomide [53] and the anti-integrin agent cilengitide (ACNS0621) [43] for recurrent disease have not provided sufficient response data to proceed to phase III studies. Patients with no or minimal residual disease following re-resection of a recurrent tumor may benefit from myeloablative chemotherapy with ASCR; however, this approach remains experimental.

Outcome

The overall clinical outcome for children with HGG is poor, with only ~30 % of the patients surviving within 3 years of diagnosis. Yet, children have a more favorable prognosis than adults where a 5-year OS using chemoradiation strategies is approaching 10 % [54]. Age at diagnosis, histologic grade, and extent of surgical resection all have an important bearing on the survival outcomes. Children younger than 3 years of age have improved outcomes when compared to older children. Patients with AA (grade III) have a more favorable prognosis than those with GBM (grade IV) emphasizing the importance of central neuropathological review. Children who undergo a GTR have a better 5-year PFS when compared to children who have an STR or a biopsy. Biological characteristics including the absence of TP53, lack of MGMT expression, and the presence of IDH1 mutations and wild-type H3.3 have all been identified as good prognostic factors with improved overall survival. Postsurgical adjuvant therapy (chemotherapy, RT) increases survival rate when compared to surgery alone.

Long-term survivors of children with HGG usually have profound therapy-induced

sequelae [55]. Functional neurological deficits are usually seen in patients with large cortical tumors in the eloquent areas of the brain. Some of the devastating therapy (chemotherapy and cranio-spinal RT) induced side effects include severe neurocognitive deficits, endocrinopathies, sterility, growth failure, and the risk of second malignancies (including meningioma) [55, 56].

Summary and Future Directions

Pediatric HGGs are not the same as adult malignant gliomas. Recent integrated genomic studies have identified six different biological subgroups of GBM across all ages. The clinical and biological data clearly show that GBM in adults and children have significant differences in their underlying biology (Table 10.2) [57]. Even within a given tumor type, there is a distinct molecular heterogeneity that occurs between different ages and brain location. Chromatin remodeling defects are central to the pathogenesis of pediatric and young adult HGG. Historically, treatment protocols for pediatric HGG have been derived from adult therapies and have had poor outcomes. Future molecularly driven classifications and treatment strategies should take into account distinct biological differences including genetic drivers and, in the pediatric setting, identify relevant therapeutic targets and design appropriate preclinical model systems to test these targets. Positive findings from such model systems when incorporated into biology-based trials will hopefully facilitate rapid translation of therapeutic breakthroughs into the clinic.

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References

1. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007;114(2):97–109.
2. Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS Statistical Report: primary brain and central nervous system tumors diagnosed in the United States in 2005–2009. Neuro Oncol. 2012;14:v1–49.
3. Kaderali Z, Lamberti-Pasculli M, Rutka JT. The changing epidemiology of paediatric brain tumours: a review from the hospital for sick children. Childs Nerv Syst. 2009;25(7):787–93.
4. Kyritsis AP, Bondy ML, Rao JS, Sioka C. Inherited predisposition to glioma. Neuro Oncol. 2010;12(1):104–13.
5. Benesch M, Wagner S, Berthold F, Wolff JE. Primary dissemination of high-grade gliomas in children: experiences from four studies of the Pediatric Oncology and Hematology Society of the German Language Group (GPOH). J Neurooncol. 2005;72(2):179–83.
6. Wilne SH, Dineen RA, Dommett RM, Chu TP, Walker DA. Identifying brain tumours in children and young adults. BMJ. 2013;347:f5844.
7. Peet AC, Arvanitis TN, Leach MO, Waldman AD. Functional imaging in adult and paediatric brain tumors. Nat Rev Clin Oncol. 2012;9(12):700–11.

8. Wen PY, MacDonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria for high-grade gliomas: response assessment in Neuro-Oncology Working Group. J Clin Oncol. 2010;28:1963–72.
9. Warren KE, Poussaint TY, Vezina G, Hargrave D, Packer RJ, Goldman S, et al. Challenges with defining response to antitumor agents in pediatric neuro-oncology: a report from the response assessment in pediatric neuro-oncology (RAPNO) working group. Pediatr Blood Cancer. 2013;60(9):1397–401.
10. Fouladi M, Hunt DL, Pollack IF, Dueckers G, Burger PC, Becker LE, et al. Outcome of children with centrally reviewed low-grade gliomas treated with chemotherapy with or without radiotherapy on Children's Cancer Group high-grade glioma study CCG-945. Cancer. 2003;98(6):1243–52.
11. Pollack IF, Boyett JM, Yates AJ, Burger PC, Gilles FH, Davis RL, Finlay JL, Children's Cancer Group. The influence of central review on outcome associations in childhood malignant gliomas: results from the CCG-945 experience. Neuro Oncol. 2003;5(3):197–207.
12. Gilles FH, Tavaré CJ, Becker LE, Burger PC, Yates AJ, Pollack IF, Finlay JL. Pathologist interobserver variability of histologic features in childhood brain tumors: results from the CCG-945 study. Pediatr Dev Pathol. 2008;11(2):108–17.
13. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008;321(5897):1807–12.
14. Noushmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, Berman BP, et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. Cancer Cell. 2010;17(5):510–22.
15. Paugh BS, Zhu X, Qu C, Endersby R, Diaz AK, Zhang J, et al. Novel oncogenic PDGFRA mutations in pediatric high-grade gliomas. Cancer Res. 2013;73(20):6219–29.
16. Phillips JJ, Aranda D, Ellison DW, Judkins AR, Croul SE, Brat DJ, et al. PDGFRA amplification is common in pediatric and adult high-grade astrocytomas and identifies a poor prognostic group in IDH1 mutant glioblastoma. Brain Pathol. 2013;23(5):565–73.
17. Pollack IF, Hamilton RL, James CD, Finkelstein SD, Burnham J, Yates AJ, Children's Oncology Group, et al. Rarity of PTEN deletions and EGFR amplification in malignant gliomas of childhood: results from the Children's Cancer Group 945 cohort. J Neurosurg. 2006;105(5 Suppl):418–24.
18. Bax DA, Gaspar N, Little SE, Marshall L, Perryman L, Regairaz M, et al. EGFRvIII deletion mutations in pediatric high-grade glioma and response to targeted therapy in pediatric glioma cell lines. Clin Cancer Res. 2009;15(18):5753–61.
19. Pollack IF, Hamilton RL, Sobol RW, Burnham J, Yates AJ, Holmes EJ, et al. O6-methylguanine-DNA methyltransferase expression strongly correlates with outcome in childhood malignant gliomas: results from the CCG-945 Cohort. J Clin Oncol. 2006;24(21):3431–7.
20. Cohen KJ, Pollack IF, Zhou T, Buxton A, Holmes EJ, Burger PC, et al. Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. Neuro Oncol. 2011; 13(3):317–23.
21. Schlosser S, Wagner S, Mühlisch J, Hasselblatt M, Gerss J, Wolff JE, Frühwald MC. MGMT as a potential stratification marker in relapsed high-grade glioma of children: the HIT-GBM experience. Pediatr Blood Cancer. 2010;54(2):228–37.
22. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005;352(10):997–1003.
23. Schwartzentruber J, Korshunov A, Liu XY, Jones DT, Pfaff E, Jacob K, et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature. 2012;482(7384):226–31.
24. Sturm D, Witt H, Hovestadt H, Khuong-Quang DA, Jones DTW, Konermann C, et al. Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. Cancer Cell. 2012;22:425–37.
25. Chan KM, Fang D, Gan H, Hashizume R, Yu C, Schroeder M, et al. The histone H3.3K27M mutation in pediatric glioma reprograms H3K27 methylation and gene expression. Genes Dev. 2013;27(9):985–90.
26. Fontebasso AM, Liu XY, Sturm D, Jabado N. Chromatin remodeling defects in pediatric and young adult glioblastoma: a tale of a variant histone 3 tail. Brain Pathol. 2013;23(2):210–6.
27. Paugh BS, Qu C, Jones C, Liu Z, Adamowicz-Brice M, Zhang J, et al. Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. J Clin Oncol. 2010; 28(18):3061–8.
28. Bjerke L, Mackay A, Nandhabalan M, Burford A, Jury A, Popov S, et al. Histone H3.3 mutations drive pediatric glioblastoma through upregulation of MYCN. Cancer Discov 2013; Epub ahead of print.
29. Rheinbay E, Louis DN, Bernstein BE, Suvà ML. A tell-tail sign of chromatin: histone mutations drive pediatric glioblastoma. Cancer Cell. 2012;21(3):329–31.
30. Fontebasso AM, Schwartzentruber J, Khuong-Quang DA, Liu XY, Sturm D, Korshunov A, et al. Mutations in SETD2 and genes affecting histone H3K36 methylation target hemispheric high-grade gliomas. Acta Neuropathol. 2013;125(5):659–69.
31. Dasgupta T, Haas-Kogan DA. The combination of novel targeted molecular agents and radiation in the treatment of pediatric gliomas. Front Oncol. 2013;3:110.
32. Jones C, Perryman L, Hargrave D. Paediatric and adult malignant glioma: close relatives or distant cousins? Nat Rev Clin Oncol. 2012;9:400–13.
33. Wisoff JH, Boyett JM, Berger MS, Brant C, Li H, Yates AJ, et al. Current neurosurgical management

and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group trial no. CCG-945. J Neurosurg. 1998;89(1):52–9.
34. Sposto R, Ertel IJ, Jenkin RD, Boesel CP, Venes JL, Ortega JA, et al. The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial. A report from the Childrens Cancer Study Group. J Neurooncol. 1989;7(2):165–77.
35. Finlay JL, Boyett JM, Yates AJ, Wisoff JH, Milstein JM, Geyer JR, et al. Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen. Childrens Cancer Group. J Clin Oncol. 1995;13(1):112–23.
36. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups, National Cancer Institute of Canada Clinical Trials Group, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–96.
37. Massimino M, Gandola L, Luksch R, Spreafico F, Riva D, Solero C, et al. Sequential chemotherapy, high-dose thiotepa, circulating progenitor cell rescue, and radiotherapy for childhood high-grade glioma. Neuro Oncol. 2005;7(1):41–8.
38. Finlay JL, Dhall G, Boyett JM, Dunkel IJ, Gardner SL, Goldman S, Children's Cancer Group, et al. Myeloablative chemotherapy with autologous bone marrow rescue in children and adolescents with recurrent malignant astrocytoma: outcome compared with conventional chemotherapy: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2008;51(6):806–11.
39. Geyer JR, Finlay JL, Boyett JM, Wisoff J, Yates A, Mao L, Packer RJ. Survival of infants with malignant astrocytomas. A Report from the Childrens Cancer Group. Cancer. 1995;75(4):1045–50.
40. Duffner PK, Krischer JP, Burger PC, Cohen ME, Backstrom JW, Horowitz ME, et al. Treatment of infants with malignant gliomas: the Pediatric Oncology Group experience. J Neurooncol. 1996;28(2–3):245–56.
41. Dufour C, Grill J, Lellouch-Tubiana A, Puget S, Chastagner P, Frappaz D, et al. High-grade glioma in children under 5 years of age: a chemotherapy only approach with the BBSFOP protocol. Eur J Cancer. 2006;42(17):2939–45.
42. Tanaka S, Louis DN, Curry TW, Batchelor TT, Dietrich J. Diagnostic and therapeutic avenues for glioblastoma: no longer a dead end? Nat Rev Clin Oncol. 2013;10(1):14–26.
43. MacDonald TJ, Vezina G, Stewart CF, Turner D, Pierson CR, Chen L, et al. Phase II study of cilengitide in the treatment of refractory or relapsed high-grade gliomas in children: a report from the Children's Oncology Group. Neuro Oncol. 2013;15(10):1438–44.
44. Gururangan S, Chi SN, Young Poussaint T, Onar-Thomas A, Gilbertson RJ, Vajapeyam S, et al. Lack of efficacy of bevacizumab plus irinotecan in children with recurrent malignant glioma and diffuse brainstem glioma: a Pediatric Brain Tumor Consortium study. J Clin Oncol. 2010;28(18):3069–75.
45. Geoerger B, Hargrave D, Thomas F, Ndiaye A, Frappaz D, Andreiuolo F, et al. ITCC (Innovative Therapies for Children with Cancer) European Consortium Innovative Therapies for Children with Cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors. Neuro Oncol. 2011;13(1):109–18.
46. Broniscer A, Baker SJ, Stewart CF, Merchant TE, Laningham FH, Schaiquevich P, et al. Phase I and pharmacokinetic studies of erlotinib administered concurrently with radiotherapy for children, adolescents, and young adults with high-grade glioma. Clin Cancer Res. 2009;15(2):701–7.
47. Geyer JR, Stewart CF, Kocak M, Broniscer A, Phillips P, Douglas JG, et al. A phase I and biology study of gefitinib and radiation in children with newly diagnosed brain stem gliomas or supratentorial malignant gliomas. Eur J Cancer. 2010;46(18):3287–93.
48. Massimino M, Bode U, Biassoni V, Fleischhack G. Nimotuzumab for pediatric diffuse intrinsic pontine gliomas. Expert Opin Biol Ther. 2011;11(2):247–56.
49. Lam C, Bouffet E, Bartels U. Nimotuzumab in pediatric glioma. Future Oncol. 2009;5(9):1349–61.
50. Pollack IF, Jakacki RI, Blaney SM, Hancock ML, Kieran MW, Phillips P, et al. Phase I trial of imatinib in children with newly diagnosed brainstem and recurrent malignant gliomas: a Pediatric Brain Tumor Consortium report. Neuro Oncol. 2007;9(2):145–60.
51. Baruchel S, Sharp JR, Bartels U, Hukin J, Odame I, Portwine C, et al. A Canadian paediatric brain tumour consortium (CPBTC) phase II molecularly targeted study of imatinib in recurrent and refractory paediatric central nervous system tumours. Eur J Cancer. 2009;45(13):2352–9.
52. Geoerger B, Kieran MW, Grupp S, Perek D, Clancy J, Krygowski M, et al. Phase II trial of temsirolimus in children with high-grade glioma, neuroblastoma and rhabdomyosarcoma. Eur J Cancer. 2012; 48(2):253–62.
53. Warren KE, Gururangan S, Geyer JR, McLendon RE, Poussaint TY, Wallace D, et al. A phase II study of O6-benzylguanine and temozolomide in pediatric patients with recurrent or progressive high-grade gliomas and brainstem gliomas: a Pediatric Brain Tumor Consortium study. J Neurooncol. 2012;106(3):643–9.
54. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups, National Cancer Institute

of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009;10(5):459–66.
55. Merchant TE, Pollack IF, Loeffler JS. Brain tumors across the age spectrum: biology, therapy and late effects. Semin Radiat Oncol. 2010;20(1):58–66.
56. Sands SA, Zhou T, O'Neil SH, Patel SK, Allen J, McGuire Cullen P, et al. Long-term follow-up of children treated for high-grade gliomas: children's oncology group L991 final study report. J Clin Oncol. 2012;30(9):943–9.
57. Fontebasso AM, Bechet D, Jabado N. Molecular biomarkers in pediatric glial tumors: a needed wind of change. Curr Opin Oncol. 2013;25(6):665–73.