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Brainstem Glioma: A Review

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Abstract Brainstem gliomas (BGs) are a heterogenous group of gliomas that occur predominately in children. They can be separated into groups on the basis of anatomy and clinical behavior: diffuse intrinsic pontine glioma (DIPG), exophytic medullary glioma, and tectal glioma. DIPG is the commonest BG. Median age at onset is 6.5 years and median survival is less than 1 year. Adults with DIPG survive longer, suggesting a less aggressive and biologically different tumor from that in children. Patients present with cranial nerve dysfunction, long tract signs, or ataxia, either in isolation or in combination. Magnetic resonance imaging shows an infiltrative lesion occupying most of the pons and contrast enhancement is usually not prominent. Standard treatment is fractionated radiotherapy. Platelet-derived growth factor receptor alpha and epidermal growth factor receptor mutations have been identified. Inhibitors of these growth factor receptors are being evaluated in clinical trials. Exophytic medullary and tectal gliomas are relatively indolent tumors that can often be followed closely without treatment.

Keywords Brainstem glioma · Pontine glioma · Diffuse intrinsic pontine glioma

Introduction

Brainstem glioma (BG) is a primary glial tumor that arises within the brainstem. In most instances the term refers to a highly aggressive tumor of the pons, but it can be used for tumors arising elsewhere in the brainstem. According to the most recent Central Brain Tumor Registry of the United States (CBTRUS) report, 4.2 % of all gliomas are localized to the brainstem [1]. In children, BGs account for up to 20 % or more of primary brain tumors [2]. Because tumor behavior and patient clinical course differ depending on the brainstem localization, it is customary to classify BG anatomically as diffuse intrinsic pontine glioma (DIPG), exophytic medullary glioma, and midbrain or tectal glioma [3]. Table 1 displays the topographic localization, survival based on location, and imaging characteristics from a series of 76 patients with BG [3]. This review focuses on DIPG, the most aggressive and frequently encountered BG.

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Diffuse Intrinsic Pontine Glioma

Epidemiology and Diagnosis

DIPG occurs in all age groups but predominates in children. The median age at diagnosis in children is 6–7 years [4]. The tumor is aggressive as reflected in survival of less than 1 year in most children [5–7]. Because of their infiltrative nature and brainstem localization, DIPGs are not amendable to surgical resection. Patients usually present with brainstem syndromes comprising cranial nerve dysfunction, long tract signs, and ataxia, either in isolation or in combination. Symptoms are usually of rapid onset with short duration (1–2 months) prior to diagnosis [8]. Magnetic resonance imaging (MRI) with and without intravenous contrast medium is the diagnostic procedure of choice. The classic appearance on MRI is an infiltrative T2/fluid-attenuated inversion recovery high-signal lesion occupying two thirds or more of the pons that frequently extends laterally into the cerebellar peduncles and cerebellar hemispheres and often extends vertically into the midbrain and medulla [9••].

Table 1 Topographic localization and magnetic resonance (*MR*) features of brainstem gliomas [3]

	Percentage of patients	5-year survival (%)
Location		
Medulla	18	83
Pons	59	29
Midbrain	14	100
Tectum	9	83
MR characteristics		
Dorsal exophytic component	45	
Hydrocephalus	41	
Cystic	51	
Contrast enhancement	60	
Engulfment of basilar artery	25	

Contrast enhancement is not usually a prominent feature, involving only 0–25 % of the tumor volume on average [9••]. Necrosis can be present; however, cysts are rare. Restricted diffusion of water as imaged by diffusion-weighted MRI is typically not present. With advanced neuroimaging, DIPGs have hypoperfusion (low cerebral blood volume), and magnetic resonance spectroscopy shows a modest increase in choline levels and a decrease in *N*-acetylaspartate levels. The magnetic resonance appearance of DIPG is so characteristic on imaging that a tissue biopsy is not warranted in most cases because of the attendant risk of morbidity and lack of therapeutic value. However, because of the lack of tumor tissue, molecular characterization of DIPG is only now being done (as discussed in the subsequent text).

Pathology and Molecular Characterization

Because of the paucity of biopsies, most of the knowledge regarding the pathologic characteristics of DIPG comes from autopsy studies. In a clinicopathological study of 38 DIPGs, the tumor type was glioblastoma (GB) in 32 cases (84 %), anaplastic astrocytoma in five cases (13 %), and astrocytoma in one case (3 %) [7]. The proliferating cell indices of Ki-67 and proliferating cell nuclear antigen were 8.0–45.4 % (mean 20.4 %) and 14.7–83 % (mean 37 %), respectively [7].

A single-nucleotide polymorphism (SNP)-based DNA microarray analysis of a series of DIPGs showed that 36 % of DIPGs had gains in platelet-derived growth factor receptor alpha (PDGFR-α; four to 18 copies) and all showed PDGFR-α expression. Low-level gains in poly (ADP-ribose) polymerase 1 were identified in three cases. [10••] Another SNP-based DNA microarray study of 43 DIPGs showed focal amplifications of genes within the receptor tyrosine kinase–Ras–phosphoinositide 3-kinase signaling pathway in 47 % of the DIPGs [11••]. The commonest mutations involved PDGFR-α and MET. Thirty percent contained focal amplifications of cell-cycle regulatory genes controlling retinoblastoma protein phosphorylation, and 21 % had concurrent amplification of genes from both pathways. In another seminal study, Sturm et al. [12••] described a high frequency of H3F3A mutations (a regulatory histone) affecting the amino acid K27 of histone H3.3 in pediatric thalamic GB and DIPG, suggesting that these tumor types share a closely related origin. This pediatric glioma subgroup, termed K27, displayed a markedly lower expression of the ventral telencephalic marker FOXG1 than other subgroups. The K27 cluster showed an enrichment of tumors with a "proneural" gene expression signature.

Another molecular abnormality present in most DIPGs is amplification and overexpression of the epidermal growth factor receptor (EGFR) [13]. The EGFR variant III (EFGRvIII) mutation, present in 24-67 % of adult GBs, was identified in six of 11 DIPGs (55 %) in one series [14].

On the basis of these genetic abnormalities, current clinical trials are investigating targeted therapy against PDGFR-α and EGFR. Similarly, mutations in the H3F3A/ATRX-DAAX/ALT complex that are observed in nearly 50 % of DIPGs may also represent a new molecular target for pediatric DIPG.

Initial Treatment

Standard treatment of DIPG consists of external beam radiation therapy (RT) administered in fractions over approximately 6 weeks to a total tumor dose of 60 Gy. A prior study demonstrated no benefit from a hyperfractionated RT schedule that escalated the tumor-delivered dose to 72 Gy [15]. A hypofractionated RT schedule (over 3–4 weeks) can be used to lessen treatment burden without compromising overall survival [16, 17]. Because DIPG is rapidly fatal, most children do not survive for an extended period to manifest delayed-late RT complications. As a consequence, the benefit of stereotactic radiosurgery, intensity-modulated RT, or proton beam RT is uncertain but may be efficacious in selected patients in the recurrent setting (see the discussion below).

In the hope of improving on standard RT, various radiation sensitizers (such as platinoids, etoposide, and nitrosureas) have been investigated [5, 18, 19]. The use of concurrent RT with standard or metronomic dosed temozolomide (TMZ) failed to provide benefit despite its success in adult supratentorial GB [20•, 21••, 22, 23]; the use of concurrent topotecan was similarly disappointing [24]. The Children's Oncology Group performed a phase 2 study using the potent radiosensitizer motexafin gadolinium in combination with fractionated RT (total 54 Gy in 30 fractions) [25]. Compared with historic controls, there was no benefit from the addition of motexafin gadolinium.

Various chemotherapeutic strategies, including pre-RT chemotherapy, RT with concurrent chemotherapy, and adjuvant chemotherapy, have been employed in the hope of improving survival [5]. To date, no agent or regimen has improved survival over RT alone. TMZ, which has shown benefit in other high-grade gliomas in children, failed in multiple DIPG phase 2 studies [20•, 21•, 22, 23, 26]. A summary of agents that have been investigated for initial treatment of DIPG as part of phase II clinical trials is given in Table 2.

Treatment at Progression

There is no standard therapy for DIPGs that progress following RT as clinical studies have failed to identify a regimen with antiglioma activity. DIPGs have been included in multiple pediatric brain tumor clinical trials investigating the use of single-agent (PCNU, ifosfamide, carboplatin, orally administered etoposide, thiotepa, topotecan) or multiagent (8-in-1; 5-fluorouracil, lomustine, hydroxyurea, 6-mercaptopurine; MOPP; ifosfamide, etoposide, mesna; cisplatin, cytosine arabinoside, etoposide) chemotherapy regimens [27]. The small number of DIPG patients in these studies precludes demonstration of efficacy, although the lack of radiographic responses suggests that in general these agents are ineffective. A recent study of bevacizumab in combination with irinotecan for recurrent DIPG demonstrated minimal efficacy [28]. Wolff et al. [29] reported a retrospective study of the MD Anderson Cancer Center experience treating DIPG at progression. They identified 31 patients who were treated with 26 different agents in 31 different regimens. The most frequently used options were etoposide (14), bevacizumab (13), irinotecan (13), nimotuzumab (13), valproic acid (13), and additional RT (7). Additional RT resulted in the highest radiographic response rate (4/7) and the longest progression-free-survival.

Targeted Therapy

There is optimism that targeted therapy based on molecular characterization of DIPG will be an effective strategy for selected tumors [9••]. A summary of phase 1 and phase 2 clinical trials using targeted therapy for the treatment of DIPG is given in Table 3. To date, the results have been overwhelmingly disappointing, although a small number of patients with surprisingly long progression-free survival have been reported; three patients were without progression more than 36 months from diagnosis after being treated with gefitinib and RT [30]. Most of the studies were not enriched with patients known to have a molecular abnormality of interest. To obtain tissue for molecular characterization, stereotactic needle biopsy will play an increasing role in the management of DIPG, although tumor heterogeneity and sampling issues complicate its utility. Active study protocols are collecting cerebrospinal fluid, serum, urine, and tumor tissue to analyze them for genome-wide expression patterns of RNA, proteomic profiling, and genome-wide analysis. An ongoing clinical trial headed by Kieran is using biopsy tissue to allocate patients to treatment arms —(1) bevacizumab, RT, and erlotinib, (2) bevacizumab and RT, (3) bevacizumab, RT, and TMZ, and (4) bevacizumab, RT, erlotinib, and TMZ—based on the molecular marker EGFR and the promoter methylation status of the DNA repair enzyme O^6-methylguanine-DNA methyltransferase. Other targeted agents under investigation for treatment of DIPG include bevacizumab, crenolanib, cilengitide, vandetanib, dasatinib, crizotinib, and cetuximab (Table 4).

Immunotherapy

Various vaccine approaches are being evaluated for other high-grade gliomas, including autologous-tumor-lysate-pulsed dendritic cell vaccine and peptide vaccines [31]. The use of dendritic cell vaccines is limited in DIPG given the need for tumor lysate to be used as the source of tumor-associated antigens. There are two ongoing phase 2 DIPG vaccine studies (Table 3): a tumor lysate vaccine using the established brain tumor initiating cell line GBM-6 as the antigen source and an EGFRvIII peptide antigen vaccine.

Midbrain Tectal Glioma

Epidemiology and Diagnosis

In contrast to the highly malignant DIPGs, midbrain tectal gliomas are typically low-grade astrocytomas that follow a relatively benign course. The tumor is usually diagnosed in childhood, although not infrequently it manifests itself in adults. Mean age at diagnosis is 7–10 years [32, 33]. Because of the proximity of the tumor to the cerebral aqueduct, symptoms associated with these tumors include increased intracranial pressure from obstructive hydrocephalus, which is the commonest mode of presentation. Alternatively, the tumor is found incidentally in the workup of headache, head trauma, or other unrelated neurologic symptoms. On MRI, the tumor appears as a T1 hypointense, T2 hyperintense lesion localized to the midbrain tectum; enhancement after administration of intravenous contrast medium is present in a small minority of tumors [33–36]. Given the appearance on imaging, midbrain tectal glioma is sometimes referred to as a "pencil" glioma, as the tumor is columnar with a long axis paralleling the periaqueductal gray matter. World Health Organization (WHO) grade I or grade II astrocytoma is the commonest lesion encountered in the midbrain tectum, but rarer entities include high-grade astrocytoma, oligodendroglioma, ependymoma, ganglioglioma, medulloblastoma, primitive neuroectodermal tumor, metastases, and other lesions such as vascular

Table 2 Summary of up-front phase 2 studies for diffuse intrinsic pontine glioma (DIPG)

Study	Regimen	Number of patients (median age, years)	Results
Levin et al. [46]	5-fluoroaracil and lomustine plus RT with hydroxyurea and misonidazole	28	mEFS 32 weeks mOS 44 weeks
Jenkin et al. [47]	RT followed by lomustine, VCR, and prednisone vs no treatment (randomized)	RT: 35 RT and CT: 39	mPFS 7 vs 8 months 5-year OS 17 % vs 23 % (not significant)
Kretchmar et al. [48]	Cisplatin and cyclophosphamide, then hyperfractionated RT	37	PR 3 mOS 9 months
Jennings et al. [49]	CT (A or B) followed by RT A: carboplatin, etoposide, and VCR B: cisplatin, etoposide, VCR, and cyclophosphamide	A: 32 B: 31	1-year EFS (17±5) % 2-year EFS (6±3) %
Bernier-Chastagner et al. [24]	IV topotecan plus RT	32 (7 years)	40 % PR, 9-month OS (34.4±8) % 12-month OS (25.5±8) % mOS 8.3 months
Jalali et al. [22]	TMZ plus RT followed by TMZ	20 (8.3 years)	mOS 9.15 months mPFS 6.9 months
Sirachainan et al. [26]	TMZ plus RT followed by TMZ and *cis*-retinoic acid	12 (4.2 years)	mOS 13.5±3.6 months 12-month OS (58±14.2) %
Korones et al. [50]	VCR and orally administered etoposide plus RT followed by VCR and etoposide	30 (8 years)	PR 7 (23 %) 1-year OS (27±7) % 2-year OS (3±2) % mOS 9 months
Kim et al. [51]	TMZ and thalidomide plus RT followed by TMZ and thalidomide	17 (8 years)	PR 10 mPFS 7.2 months (95 % CI, 3.6–10.7) mOS 12.7 months (95 % CI, 10.4–15.1) 1-year OS 58.3 % 2-year OS 25 %
Sharp et al. [23]	TMZ plus RT followed by TMZ	15 (6.4 years)	mOS 9.8 months (95 % CI, 6.4-10.8) 12-month OS (20±10.3) %
Cohen et al. [21•]	TMZ plus RT followed by TMZ	63 (7.7 years)	1-year EFS (14±4.5) % 1-year OS (40±6.5) % mOS 9.6 months
Wolff et al. [52]	IV MTX followed by RT plus cisplatin, etoposide, VCR, and ifosfamide followed by VCR, lomustine, and prednisone	30 (10.8 years)	1-year EFS 43 % 2-year EFS 20 %
Pollack et al. [30]	Gefitinib plus RT followed by gefitinib	43 (7 years)	1-year PFS (20.9±5.6) % 2-year PFS (9.3±4) % 1-year OS (56.4±7.6) % 2-year OS (19.6±5.9) %
Haas-Kogan et al. [53]	Tipifarnib plus RT followed by tipifarnib	40 (5.5 years)	mPFS 6.8 months mOS 8.3 months 1-year PFS (12.9±4.9) % 1-year OS (34.3±7.4) %
Massimino et al. [54]	Nimotuzumab plus RT	47	mOS 9.6 months
Chassot et al. [20•]	TMZ plus RT followed by TMZ	21 (6.4 years)	mOS 11.7 months mPFS 7.5 months 1-year OS 50 % 1-year PFS 33 %

Table 2 (continued)

Study	Regimen	Number of patients (median age, years)	Results
Warren et al. [55]	RT followed by SQ PEGylated interferon α-2b weekly	32 (5.3 years)	2-year OS 14 % mPFS 7.8 months

IV intravenously administered, *RT* radiation therapy, *CT* chemotherapy, *PR* partial response, *OS* overall survival, *mOS* median overall survival,, *TMZ* temozolomide, *PFS* progression-free survival, *mPFS* median progression-free survival, *EFS* event-free survival, *mEFS* median event-free survival, *SQ* subcutaneously administered; *VCR* vincristine, *MTX* methotrexate, *CI* confidence interval

malformations (angioma, cavernoma), abscess, hamartoma, granulomatous disease, and periaqueductal stenosis [34]. The following discussion refers to low-grade astrocytomas of the midbrain tectum.

Treatment

Treatment of hydrocephalus is usually necessary since most patients present with obstructive hydrocephalus due to aqueductal stenosis. Hydrocephalus is surgically managed by the implantation of a ventriculoperitoneal (VP) shunt or by an endoscopic third ventriculostomy. Endoscopic third ventriculostomy is preferable as a biopsy can be obtained during the procedure and the complications of a VP shunt (device infection, cerebrospinal fluid overdrainage, subdural fluid collection, and shunt malfunction) can be abrogated [32, 37]. Because of the typical benign course of midbrain tectal gliomas, most patients may be followed with serial MRI, without treatment. Radiographic tumor progression occurs in 15–25 % of cases [32]. To best define treatment at tumor recurrence, a biopsy is recommended at the time of tumor progression. On tumor recurrence, the recommendation is to treat low-grade astrocytomas with fractionated, external beam RT; the long-term prognosis remains excellent in most patients. Median progression-free survival and overall survival extend beyond the follow-up period of most studies (median follow-up period range of 4–10 years) [32, 33, 38]. If a high-grade glioma is demonstrated at recurrence, salvage therapies using alkylator-based chemoradiotherapy are most often employed.

Exophytic Medullary Glioma

Medullary brainstem tumors are typically focal or dorsally exophytic as defined by MRI, although infrequently they are diffuse. In the rare instance of diffuse medullary BG, the behavior recapitulates that of a DIPG. Exophytic BG typically arises from the subependymal glial tissue [39]. Young patients present insidiously with failure to thrive, whereas older patients present with symptoms of increased intracranial pressure [40]. The classic imaging appearance is a well-demarcated tumor residing primarily in the fourth ventricle; enhancement after administration of contrast medium is seen in most tumors [40–42]. Nearly all exophytic medullary gliomas are low-grade gliomas, with WHO grade I astrocytoma (pilocytic astrocytoma) being commoner than WHO grade II astrocytoma [3, 42]. Patient course is relatively benign. If progression occurs, tumor growth is usually along the path of least resistance and most often into the fourth ventricle or surrounding cisterns [39]. Asymptomatic patients can be followed closely with serial MRI, without treatment. Surgical resection is the treatment of choice for symptomatic cases and cerebrospinal fluid diversion (VP shunting) is necessary in some [43]. Maximal tumor

Table 3 Summary of phase 1 and phase 2 clinical trials using targeted therapy for the treatment of DIPG

Study	Phase	Agent	No. of patients	Results
Pollack et al. [56]	1	Imatinib plus RT	35	1-year OS 45 %
Fouladi et al. [57]	1	lapatinib		
Broniscer et al. [58]	1	Vandetanib plus RT	35	1-year OS 37 %
Geyer et al. [59]	1	Gefitinib plus RT	20	1-year OS 48 %
Geoerger et al. [60]	1	Erlotinib plus RT	20	mOS 12 months
Gururangan et al. [28]	2	Bevacizumab plus irinotecan	16	Recurrent disease—no radiographic responses
Pollack et al. [30]	2	Gefitinib plus RT	43	1-year OS 56.4 %
Haas-Kogan et al. [53]	2	Tipfiarnib plus RT	40	mOS 8.3 months 1-year OS 34.3 %
Massimino et al. [54]	2	Nimotuzumab plus RT	47	mOS 9.6 months

RT radiotherapy, *OS* overall survival, *mOS* median overall survival

Table 4 Ongoing DIPG clinical trials using targeted therapy and immunotherapy

Principle investigator	Phase	Title	Agent
C. Wetmor	1	PDGFR Inhibitor Crenolanib in Children/Young Adults with DIPG or Recurrent HGG	Crenolanib
P. Leblond	1	Cilengitide in Combination with RT in Children with DIPG	Cilengitide plus RT
A. Broniscer	1	Clinical Trial Evaluating the Combination of Vandetanib and Dasatinib During and After RT in Children with Newly Diagnosed DIPG	Vandetanib and dasatinib during and after RT
A. Broniscer	1	Study of the Combination of Crizotinib and Dasatinib in Pediatric Research Participants with DIPG and HGG	Crizotinib plus dasatinib (after RT)
M.W. Kieran	2	Molecularly Determined Treatment of DIPG	Arm 1: bevacizumab plus RT plus erlotinib Arm 2: bevacizumab plus RT Arm 3: bevacizumab plus RT plus TMZ Arm 4: bevacizumab plus RT plus erlotinib plus TMZ
C.M. Kramm	2	Cilengitide and Metronomic TMZ for Relapsed or Refractory HGG or DIPG in Children and Adolescents	Cilengitide plus metronomic dosed TMZ
M. Fouladi	2	A Study of Bevacizumab Therapy in Patients with Newly Diagnosed HGG and DIPG	Bevacizumab plus RT plus TMZ
I. Dunkel	2	External Beam RT and Cetuximab Followed by Irinotecan and Cetuximab for Children and Young Adults with Newly Diagnosed DIPG and HGG	Cetuximab plus RT followed by cetuximab plus irinotecan
C. Moertel	1	Imiquimod/Brain Tumor Initiating Cell Vaccine in DIPG	Tumor lysate vaccine—established brain tumor initiating cell line GBM-6 as the antigen source
P. Fisher	1	Phase I Rindopepimut after Conventional RT in Children with DIPG	Rindopepimut—EGFRvIII antigen peptide vaccine

RT radiotherapy, *TMZ* temozolomide, *HGG* high-grade glioma, *PDGFR* platelet-derived growth factor receptor, *EGFRvIII* epidermal growth factor receptor variant III

debulking with preservation of neurologic function is the goal of surgery [39]. The 5-year survival rate was 100 % in one series [3].

Adult BGs

BGs account for less than 2 % of intracranial tumors in adults [1]. In a retrospective series of 19 adults (median age 40 years) with a BG—13 pontine (68 %), two midbrain tectum (11 %), and four cervicomedullary junction (22 %)—the median survival and the 5-year survival rate were 54 months (range 3–98 months) and 45 %, respectively, suggesting that the disease may be less aggressive than in children [44]. Most patients were treated with fractionated, external beam RT.

Another series of 48 adults (mean age 34 years) with BG (60 % pontine, 25 % medulla, and 15 % midbrain) demonstrated similar results; median survival was 5.4 years .[45] The vast majority of these patients (94 %) were treated with fractionated RT. Six favorable prognostic factors were identified: young age (less than 40 years); duration of symptoms more than 3 months; Karnofsky performance status more than 70 %; absence of contrast enhancement or "necrosis" on imaging; and low-grade tumor. In this series, BGs were separated into three categories: adult diffuse intrinsic low-grade BG; adult malignant BG; and focal tectal midbrain BG.

Adult diffuse intrinsic low-grade BG (46 % of the total adult BG cases in the series) presented in adults in their third decade. Symptom duration was more than 3 months and sometimes several years prior to diagnosis. Isolated facial palsy with hemispasm was the commonest prolonged presenting syndrome. Most of these tumors appeared as infiltrative, diffuse, nonenhanced lesions in the pontomedullary region on MRI. RT significantly improved the clinical neurologic status in 13 of 21 patients (62 %). Presumed anaplastic transformation characterized by contrast enhancement occurred in 27 % of patients at the time of tumor recurrence. Median overall survival was 7.3 years.

Adult malignant BG (31 % of the total) occurred in older patients (older than 40 years in ten of 15 patients). Presentation was of rapid onset and performance status was impaired in most patients. Contrast enhancement (15/15) and necrosis (10/15) were present at diagnosis. All tumors had evidence of anaplasia on pathologic examination. Treatment was relatively ineffective as only two patients had improvement after RT and median overall survival was11.2 months.

Patients with focal tectal midbrian gliomas (8 % of all BGs) had an indolent course. Hydrocephalus was the only presenting syndrome. All patients were alive at the last follow-up (more than 5 years in one patient and 8 years in three patients).

The results from this study suggest that diffuse, infiltrative, nonenhanced brainstem tumors in adults can be followed or

treated without biopsy. Symptomatic patients should be treated with RT. Focal midbrain tectal tumors can be followed closely without treatment (except for hydrocephalus in clinically appropriate cases). Contrast-enhanced and necrotic pontine tumors in adults should be considered for biopsy and treated with RT or chemoradiotherapy.

Conclusions

The prognosis for DIPG patients remains dismal. In contrast to other malignant gliomas, for which active chemotherapeutic agents have been identified, RT remains the only effective therapy. Future advances will occur through improved knowledge of the tumor biology that will require acquisition of tumor tissue. Although currently lacking therapeutic benefit, sterotactic needle biopsy provides an opportunity to further understand the molecular characteristics of these highly malignant tumors and should be increasingly used as part of clinical trials.

In contrast to DIPG, the prognosis for tectal midbrain gliomas and exophytic medullary gliomas is relatively good. Although these tumors can be associated with significant morbidity, tumor progression occurs in comparatively few cases. Future studies should be designed to clarify which tectal midbrain gliomas and exophytic medullary gliomas should be treated early and to define the optimal treatment modality. Improved understanding of the biology of these two tumor types is necessary through molecular characterization of tumor tissue obtained in those undergoing biopsy and from postmortem studies.

Conflict of Interest Sean A. Grimm declares no conflict of interest. Marc C. Chamberlain declares no conflict of interest.

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- •• Of major importance

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