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Brainstem Low-Grade Gliomas in Children—Excellent Outcomes With Multimodality Therapy

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Abstract

Safe maximal surgical resection is the initial treatment of choice for pediatric brainstem low-grade gliomas. Optimal therapy for incompletely resected tumors or that progress after surgery is uncertain. We reviewed the clinical characteristics, therapy, and outcomes of all children with nontectal brainstem low-grade gliomas treated at the University of Michigan between 1993 and 2013. Median age at diagnosis was 6 years; histology was confirmed in 23 of 25 tumors, 64% were pilocytic astrocytoma. Nineteen patients underwent initial tumor resection; 14/19 received no

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Author Contributions

SAU and PLR contributed in caring for the patients, study design, obtaining the data, data analysis, writing the manuscript, and reviewing the final manuscript. CK contributed in caring for the patients, data analysis, and reviewing the manuscript. SV, BLB, NAB, and DW contributed in performing data collection, data analysis, and writing the manuscript. HCW, KED, and ASL performed data collection. KM, HJG, DAH, and COM contributed in caring for the patients, data analysis and reviewing the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The study was reviewed and approved by the Institutional Review Board of the University of Michigan (IRB approval number: HUM00088512).

upfront adjuvant therapy. Eight patients in the study had progressive disease; 5 initially resected tumors received chemotherapy at tumor relapse, all with partial or complete radiographic responses. Ten-year progression-free survival is 71% and overall survival, 100%. This single-institution retrospective study demonstrates excellent survival rates for children with brainstem low-grade gliomas. The efficacy of the well-tolerated chemotherapy in this series supports its role in the treatment of unresectable or progressive brainstem low-grade gliomas.

Keywords

brainstem tumors; low-grade glioma; progressive tumors; chemotherapy; overall survival

Neoplasms that arise in the brainstem constitute approximately 15% of pediatric brain tumors.[1] The majority (80%) of these brainstem tumors are malignant diffuse intrinsic pontine gliomas, but most of the balance are brainstem low-grade gliomas.[2] Children with diffuse intrinsic pontine gliomas present with rapidly progressive cranial nerve deficits, weakness or ataxia, have characteristic magnetic resonance imaging (MRI) findings and abysmal outcomes, with very short survival.[3] Conversely, brainstem low-grade gliomas are generally slow growing with an indolent course and more favorable prognosis.

Brainstem low-grade gliomas can be classified by location, as tectal midbrain, tegmental midbrain, focal pontine, pontomedullary, medullary, and cervicomedullary. Children with tectal gliomas typically present with hydrocephalus from obstruction of the cerebral aqueduct and can usually be managed with cerebrospinal fluid diversion (shunt or endoscopic third ventriculostomy) and radiographic surveillance, without other treatment.[4] Brainstem low-grade gliomas in locations other than tectal midbrain often require more definitive therapy. With the advent of the MRI and advances in operative techniques, neurosurgical resection is attempted for many nontectal brainstem low-grade gliomas, and outcomes have greatly improved. However, complete resection is not always possible because of the critical location of these tumors. As well, in a subset of patients with minimal signs or symptoms, the potential for operative deficits may be great enough to favor a conservative approach of watchful waiting. Unresected or incompletely resected brainstem low-grade glioma tumors have the potential for gradual growth, estimated in one series at an average of 4 mm increase in tumor diameter per year.[5] There is lack of consensus regarding optimal adjuvant therapy for tumors that are incompletely resected or those that progress after initial resection. Both radiotherapy and chemotherapy can be effective treatment, but optimal management in various specific settings remains uncertain.

The goal of this study was to evaluate the tumor characteristics, clinical features, management and outcomes of all children with nontectal brainstem low-grade gliomas treated at our institution over a 20-year period (1993–2013). This included the safety and efficacy of surgical intervention, adjuvant and salvage chemotherapy and/or radiation therapy, survival outcomes, treatment sequelae, and molecular characterization of the tumors.

Methods

Study Subjects

A retrospective review of the medical records was conducted on all children <21 years of age with a diagnosis of nontectal brainstem lowgrade gliomas, treated and followed at the University of Michigan C. S. Mott Children's Hospital from 1993 to 2013. The study was approved by the institutional review board. Subjects were eligible for the study if they had imaging findings consistent with a brainstem lowgrade glioma—a well circumscribed or exophytic lesion that is hypointense on T_1-weighted images, hyperintense on T_2-weighted images and enhancing with contrast, or if there was a histologic confirmation of a low-grade glioma in brainstem. Tumor location was identified as nontectal midbrain, pontine, pontomedullary, medullary or cervicomedullary. Patients with tectal gliomas were excluded from the study because these tumors are usually treated with cerebrospinal fluid diversion and radiographic surveillance, without need for definitive tumor therapy. Tumor treatment may have included surgical resection or biopsy, chemotherapy and radiotherapy.

Data Collected

Data pertaining to the clinical presentation, tumor imaging characteristics and histopathologic diagnosis, treatment and treatment-related complications or toxicities including long-term neurologic sequelae, and survival outcomes, were collected for all patients. The extent of surgical resection was based on the neurosurgeon's intraoperative estimate and findings on postoperative imaging and defined as gross total resection, no residual disease; near total resection, >90% resection; subtotal resection, 50% to 90% resection; partial resection, <50% resection; and biopsy only. Chemotherapy was used as upfront adjuvant or neoadjuvant therapy or when there was tumor progression; chemotherapy regimens included (1) carboplatin/vincristine; (2) thioguanine/procarbazine/lomustine/vincristine; (3) cyclic oral temozolomide (TMZ) at a dosing schedule of 150 to 200 mg/m^2/day × 5 days in 28-day cycles. Administration of carboplatin/vincristine and thioguanine/procarbazine/lomustine/vincristine were patterned on Children's Cancer Group protocol A9952.[6] Conventionally fractionated radiation to the site of the primary tumor using 6-to 15-MeV photons was administered to those treated with radiotherapy as upfront therapy or at tumor progression. No patients were treated with proton therapy.

BRAF Mutation Analysis

Unstained slides and a corresponding hematoxylin-eosin (H&E) slides were prepared from formalin-fixed paraffin-embedded tissue blocks. Areas containing high tumor content were selected by a pathologist (N.A.B). Genomic DNA was extracted from 2–6 unstained slides within the selected area using the Pinpoint Slide DNA Isolation System (Zymo Research). RNA was extracted from 10-mm scrolls using TRIzol LS (Thermo Fisher Scientific). $BRAF^{V600E}$ mutation testing was performed on extracted DNA as previously described.[7] KIAA1549-BRAF fusion testing was performed on RNA using a reverse transcription–polymerase chain reaction assay designed with forward primers within exons 15 and 16 of KIAA1549 and reverse primers within exons 9 and 11 of BRAF. The assay was validated to detect the 3 most common fusion transcripts—exon 16/exon 9, exon 15/exon 9, and exon 16/exon 11—as well as the more unusual exon 15/exon 11 transcript. Together, these cover

approximately 98% of KIAA1549-BRAF fusions occurring in pilocytic astrocytoma according to the COSMIC database (http://cancer.sanger.ac.uk/cosmic).

Analysis

The primary outcome measures were 10-year progression-free survival and overall survival. Progression-free survival was defined as the time from diagnosis to progression or death; overall survival was defined as the time from diagnosis to death or end of study period. Kaplan Meier curves were used to estimate both progression-free survival and overall survival.

Results

Between 1993 and 2013, a total of 25 children with a diagnosis of nontectal brainstem low-grade glioma consecutively treated at the University of Michigan C. S. Mott Children's Hospital were eligible for the study. Three additional children with brainstem low-grade gliomas were excluded from the analysis because they had received the majority of their care at other institutions and datasets were insufficient. There were 13 boys/12 girls, with a median age at diagnosis of 6 years (range, 4 months to 16 years); none of the children had a diagnosis of neurofibromatosis type 1 (or type 2). Patient demographics, presenting symptoms, tumor location, and histopathologic diagnosis are shown in Table 1. Sixty-four percent of the tumors were pilocytic astrocytoma and 68% were dorsally exophytic tumors. Histopathologic diagnosis was made in 23/25 patients. No tissue was available in 2/25 patients in whom the diagnosis was based on MRI findings that were strongly suggestive of a brainstem low-grade glioma (Figure 1).

Twenty-two patients underwent an initial surgery, either biopsy (3) or surgical resection (19); extent of resection was gross total resection/near total resection (10), subtotal resection (7), partial resection (2) (Table 2). One additional patient underwent a gross total resection after tumor progression following upfront radiotherapy and chemotherapy. Among the 19 patients who underwent tumor resection at diagnosis, 14 patients received no further upfront treatment, whereas 5 patients received adjuvant therapy (chemotherapy [3], radiotherapy [2]). Among the 6 patients who underwent no tumor resection at diagnosis (biopsy [3], no surgery [3]), 1 patient received no initial therapy and 5 received (neo)adjuvant therapy (radiotherapy [3], radiotherapy + chemotherapy [2]).

A total of 8/25 patients experienced progressive disease at a median of 5 months from diagnosis (range, 3 months to 16 years). Seven of these had undergone tumor resection at diagnosis (3 near total resection, 3 subtotal resection, and 1 partial resection + adjuvant chemotherapy). One of the 8 patients with progressive disease underwent no initial surgery but had a gross total resection after progression following failed radiotherapy plus 1 cycle of chemotherapy. Only 2 of the 8 patients with progressive disease received adjuvant therapy at diagnosis (chemotherapy [1] and radiotherapy + chemotherapy [1]).

Salvage therapy for the 8 patients with progressive disease included a first surgery/resection (gross total resection) in 1 patient; repeat resection in 2 patients (followed by radiotherapy in 1 and by chemotherapy in 1); chemotherapy only in 4 patients; radiotherapy only in 1

patient. None of these 8 patients have since progressed and are alive with stable disease in 4 or no evidence of disease in 4. Likewise, the 17 of 25 patients who did not progress are all alive with stable disease or no evidence of disease. Thus, the Kaplan-Meier estimates of 10-year survival for the entire cohort are progression-free survival of 71% and overall survival of 100% (Figure 2). Although none of the 4 patients who underwent a gross total resection at diagnosis experienced tumor progression, neither gross total resection nor any other extent of resection correlated with progression-free survival ($P = .44$) (Figure 3). A schema of the therapy used and outcomes for all those with progressive disease is outlined in Figure 4.

Chemotherapy was generally well tolerated. Only 1 of the 10 patients who received chemotherapy (5, adjuvant at diagnosis; 5, salvage at progression), experienced grade 3 myelosuppression that delayed chemotherapy and required dose reduction for prolonged myelosuppression. Two patients developed manageable hypersensitivity reactions to carboplatin toward their end of therapy. One patient developed grade 3 constipation on vincristine that required dose reduction.

At last follow up, at a median of 9 years, 5 patients had persistent, moderately severe adverse neurologic sequelae that were first noted shortly after surgical resection. All 5 had undergone surgical resection at outside institutions without pediatric neurosurgical expertise, prior to transfer to our institution; one also received subsequent adjuvant radiotherapy, and 3 salvage chemotherapy at tumor progression. Among the 9 children who received radiotherapy (at a median age of 11 years, range, 3.3–16 years), 5 had no adverse sequelae during the study period, one developed hypothyroidism and one, growth hormone deficiency, both requiring hormonal supplementation and 4 sustained neurocognitive dysfunction of varying severity. One patient had language impairment in the form of mild fluent dysphasia, and another had learning difficulties that required special education support in school. Two others had more severe deficits, one with severe psychiatric disturbance that precluded independent living, and the other with moderate cognitive impairment (IQ 65 on formal neuropsychometric testing).

Determination of tumor BRAF mutation status was attempted in this cohort and was successful in 7 tumors; but tissue was not available/inadequate or of poor quality in the remaining tumors. We detected a KIAA1549-BRAF fusion in 4/7 tumors whereas all 7 were negative for the $BRAF^{V600E}$ mutation (Table 2).

Discussion

Brainstem low-grade gliomas are relatively rare brain tumors of childhood and, despite their benign histopathology, have the potential to cause significant neurologic morbidity because of their location.[2, 8–10] Whenever feasible, surgical gross total resection has been proposed as the treatment of choice for pediatric brainstem low-grade gliomas. Several studies that report sustained disease control after complete tumor resection support this view, as does our finding of no recurrences among the 5 patients (4 at diagnosis, 1 at progression) whose tumors were totally resected.[11–14]

Although our data support that a complete resection is desirable, because these tumors arise near critical brainstem structures, cranial nerve nuclei, sensory and motor long tracts, an aggressive attempt at total resection can leave the child with significant neurologic deficits.[15] Five patients in our cohort developed new major neurologic deficits following surgical resection of their tumors. Three of these involved the pons, perhaps suggesting increased potential for morbidity from tumor resection in this location. Moreover, these patients underwent surgery at nonpediatric centers before transfer to our institution for further management, underscoring the critical importance of optimal pediatric neurosurgical expertise in the management of brainstem low-grade gliomas in children. The decision about the extent of an attempted resection rests on the neurosurgeon's expertise/experience and knowledge of risk for operative injury weighed against the safety and efficacy of other available therapies for tumor control.

When a brainstem low-grade glioma cannot be totally resected but the extent of residual tumor is modest and the child has minimal deficits, expectant management with close radiographic surveillance seems a reasonable approach. But for patients with significant and symptomatic residual tumor, the prudence of watchful waiting is less certain. The decision to employ adjuvant therapy upfront after an incomplete resection or biopsy hinges on the risk of irreversible injury from further tumor growth balanced against the potential toxicity of adjuvant therapies, as well as their effectiveness for rescue at tumor relapse.

A retrospective review of 96 patients treated at Hospital for Sick Children in Toronto, reported a favorable outcome after upfront observation as a first-line management in some patients with brainstem low-grade gliomas and significant residual tumor after resection. Although 54% of 42 tumors progressed after observation following incomplete resection, there was no difference in their progression-free survival compared to a subgroup of 24 patients who received upfront chemotherapy or radiotherapy in the presence of significant residual disease. Moreover, there was no survival disadvantage for the observation group in whom the progression-free survival and overall survival were 57% and 93%, comparable to 57% and 89% for the entire cohort.[16] A very good progression-free survival of 70% was similarly noted for cervicomedullary low-grade gliomas following surgical resection alone, by Robertson et al.[17] Lundar et al demonstrated a favorable 47% progression-free survival in 15 patients with low-grade midbrain tumors that were surgically resected upfront. No further adjuvant therapy or repeat resection was required in these patients, the majority of whom had not undergone a total resection.[12] Thus, expectant surveillance is a safe approach for many brainstem low-grade gliomas with residual tumor after diagnosis. However, a significant fraction of these tumors do progress and require additional treatment, for which both chemotherapy and radiotherapy have been effective therapies.

The radiotherapy required for pediatric brainstem low-grade gliomas can be delivered to a focal tumor volume, and taken together with the infratentorial location of these tumors, this should decrease the potential for severe neurologic/neurocognitive sequelae compared with irradiation of supratentorial tumors or the whole brain. No neurocognitive deficits were reported among 4 children with focal pontine tumors conformally irradiated to a dose of 54 Gy by Edward et al.[18] However, Freeman et al found school performance difficulties, seizures, hearing, and neuroendocrine deficits in 7 of 8 long-term survivors of brainstem

gliomas treated with radiotherapy.[19] As well, young children treated with radiotherapy for posterior fossa ependymomas, tumors very close to brainstem, were reported to have emotional/behavioral function below the mean, as well as attention deficits and academic achievement problems, even with the use of conformal radiotherapy.[20] Development of anaplastic astrocytomas and late-occurring stroke are additional concerns in children who receive cranial irradiation for low-grade tumors.[21–23] Moreover, in the largest study of long-term outcomes of pediatric low-grade gliomas, from the SEER database (4040 children with low-grade gliomas, 12% brainstem low-grade gliomas), for the entire cohort, not only was the 20-year overall survival inferior in children who received radiotherapy, but the increased 2.4 hazard ratio of death due to nontumor causes in the irradiated group suggests that radiotherapy-induced mortality accounted for some of the deaths.[24]

In our study, at a median follow-up of 9 years, among the 9 patients who received radiotherapy, 5 patients had no adverse sequelae attributable to radiotherapy, but 2 patients acquired neuroendocrine deficits and 4 patients developed varying degrees of neurocognitive or psychiatric dysfunction. These long-term sequelae further emphasize prudence when considering radiotherapy for these tumors, even with focal administration.

Despite these limitations constraining its use with impunity, radiotherapy has substantial efficacy in the treatment of brainstem low-grade gliomas, either as initial therapy (with or without surgical resection) and for salvage of relapsed tumors.[25–28] In the Toronto series of 96 children with brainstem low-grade gliomas, radiotherapy was used in 22 patients (either as adjuvant or salvage treatment) with 5-year progression-free survival and overall survival of 66% and 83%, respectively, comparable to that of the entire cohort.[16] From another single institution review of 52 pediatric brainstem low-grade gliomas at St Jude Children's Research Hospital, in which 5-year event-free survival and overall survival were 59% and 98%, upfront radiotherapy provided prolonged progression-free survival in 17/21 patients with incompletely resected or biopsied tumors, and more than 70% of relapsed patients were successfully salvaged with radiotherapy.[9] The use of radiotherapy was more limited, but also effective in our study. Six of seven patients who received upfront adjuvant radiotherapy have not experienced tumor progression (after incomplete resection [2], biopsy [3], or no surgery [1]); all but one was older than 7 years at the time of irradiation. Additionally, 2 patients were successfully salvaged with radiotherapy (+/− re-resection) at progression, at ages 27 years and 4 years. Nevertheless, given the potential long-term side effects of cranial irradiation, postponement, at least until the child is older and can tolerate it with fewer sequelae, seems a desirable goal.

Chemotherapy may also be effective as adjuvant therapy against relapse/progression of brainstem low-grade gliomas, and as salvage therapy for recurrent or progressive tumors. In these settings, chemotherapy may obviate high-risk surgical tumor resection or repeat resection, and may permit deferral of radiotherapy in a young child until an older age when it is better tolerated. Chemotherapy seems particularly advantageous for the treatment of tumors in young children deemed high risk for surgical resection, but with neurologic deficits that may worsen with any further tumor growth.

However, data for the safety and efficacy of chemotherapy for brainstem low-grade gliomas is limited. This data in children is derived mainly from studies of incompletely resected or progressive low-grade gliomas in any brain location, the majority of which are hypothalamic/optic pathway tumors, with few brainstem gliomas. Various combinations of chemotherapeutic agents have been successfully used in these studies, but outcomes for the small numbers of brainstem tumors are not separately reported.[6, 8, 29–34] A randomized phase III CCG study of 102 incompletely resected or progressive low-grade gliomas demonstrated a 50% event-free survival with no difference between the 2 regimens (carboplatin and vincristine vs thioguanine, procarbazine, CCNU [lomustine], and vincristine).[6] A large multicenter German HIT 96 study also successfully used carboplatin/vincristine to avoid radiotherapy in a large majority of children with low-grade gliomas, and reported 75% 5-year progression-free survival.[8] In both studies, the carboplatin and vincristine regimen was generally well tolerated, with hypersensitivity reaction to carboplatin being the most common reason for patients to come off therapy.

Rhonge et al reported the outcome of 16 unresectable or recurrent brainstem low-grade gliomas treated with carboplatin/vincristine at 2 Canadian centers. The chemotherapy was well tolerated and afforded a 5-year 70% progression-free survival and 100% overall survival.[2] Our data also support efficacy of chemotherapy for brainstem low-grade gliomas. Ten of our 25 patients received chemotherapy (6 carboplatin/vincristine; 3 thioguanine, procarbazine, lomustine, vincristine; 1 temozolomide), either as adjuvant therapy in 5, or at the time of tumor progression in 5. There was tumor progression in 2/5 patients who received adjuvant chemotherapy, but all 5 patients who received chemotherapy for salvage of progressive tumor are alive and progression-free at a median of 8 years' follow-up after initial progression.

There have been recent major advances in understanding the molecular mechanisms that underlie the oncogenesis of pediatric low-grade gliomas. These include very frequent *BRAF* gene fusions in pilocytic astrocytomas, as well as other *BRAF* mutations and various downstream MAP kinase pathway alterations in other low-grade gliomas, depending on location and including brainstem low-grade gliomas.[35] Molecular evaluation was possible in 7 tumors in this cohort, 4 of whom had the KIAA1549-BRAF fusion; all 7 patients were negative for the $BRAF^{V600E}$ mutation. These findings are consistent with those found among pediatric pilocytic astrocytomas and other low-grade gliomas in previous studies, but meaningful clinical correlations in our brainstem low-grade glioma cohort is not possible because of the small number of molecular analyses. However, with the emerging development of personalized medicine, integration of this molecular information into diagnostic evaluation of brainstem low-grade gliomas as well as of other pediatric low-grade gliomas, will be increasingly important for treatment decision making, as more targeted therapies become available.

Conclusions

Although there remain challenges in the management of brainstem low-grade gliomas, it is heartening to confirm the findings of others, that the combination of skilled surgery, radiotherapy, and chemotherapy results in excellent survival of children with brainstem low-

grade gliomas, with a 10-year 71% progression-free survival and 100% overall survival of our study patients, all alive with stable disease or no evidence of disease.

Findings of this study support the view that totally resected brainstem low-grade glioma tumors have an excellent chance of cure without other therapy, but also that many tumors with residual disease after resection or even biopsy may be safely followed and further treated at the time of progression without jeopardizing ultimate tumor control and long-term survival. An exception to this latter conclusion may be for patients with significant neurologic deficits that are likely to worsen with any tumor progression.

There is already good evidence supporting the efficacy of radiotherapy for brainstem low-grade gliomas, also corroborated by the results of our study. The findings in our cohort also strengthen previously limited data, that chemotherapy useful in the treatment of low-grade gliomas in other locations is valuable for brainstem low-grade gliomas, as well. These results reinforce a role for chemotherapy in the treatment of these tumors, especially when it is important to avoid the potential long-term sequelae of radiotherapy in younger children, and to obviate aggressive surgery for tumors at very high risk for surgical morbidity. Nevertheless, in view of the overall favorable prognosis of these tumors, sometimes even after minimal surgical intervention and with no adjuvant therapy, the potential for treatment-related long-term morbidity should be kept prominently in mind when making therapeutic decisions. Going forward, molecular characterization of these tumors will be important to individualize targeted therapies with the hope of reducing adverse effects of chemotherapy and radiation therapy.

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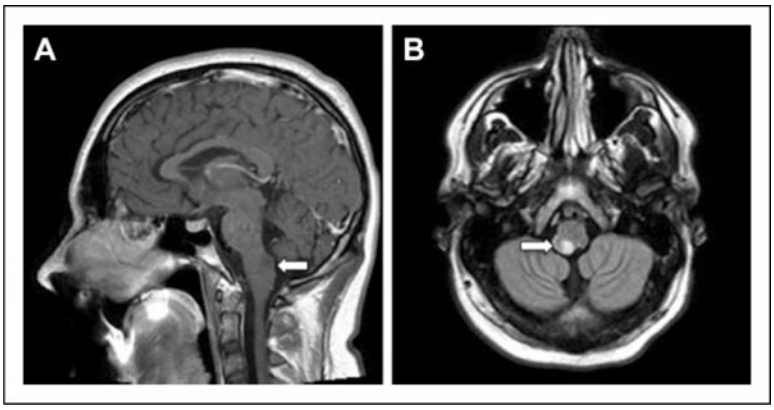

Figure 1.

Magnetic resonance images (MRIs) in an 11-year-old boy who has been followed closely, with no biopsy for confirmation and has not had any therapeutic intervention (Table 2). (A) T1-weighted sagittal non contrast image and (B) T1 axial flair image showing a dorsally exophytic medullary brainstem lesion.

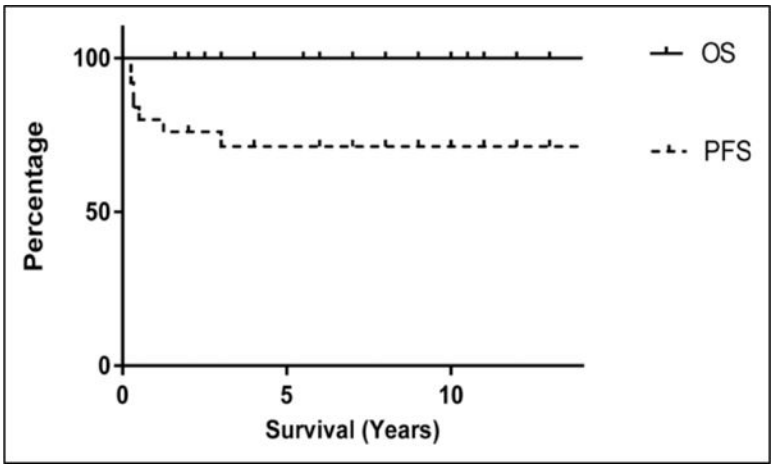

Figure 2.
Kaplan-Meier Survival curves for all patients.

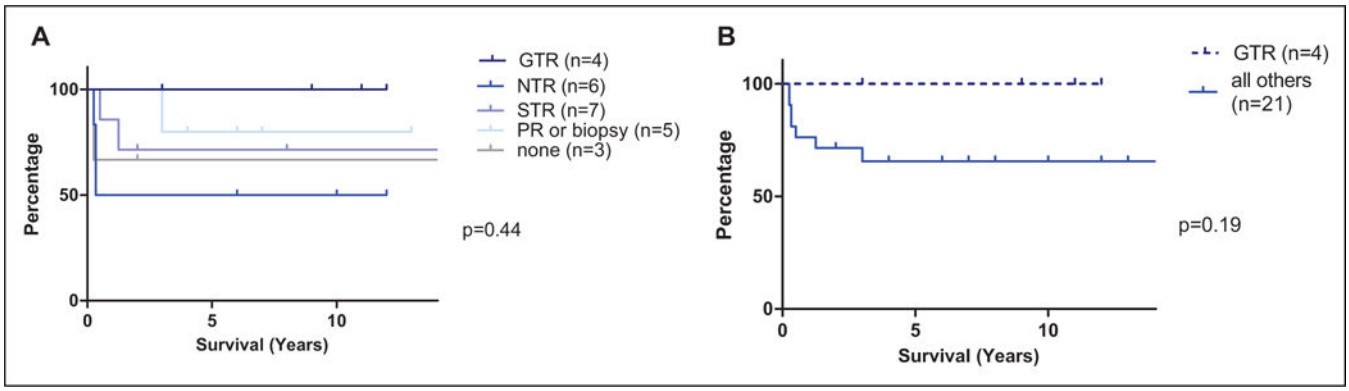

Figure 3.

Progression-free survival based on extent of resection: (A) gross total resection vs the individual groups and (B) gross total resection vs the rest.

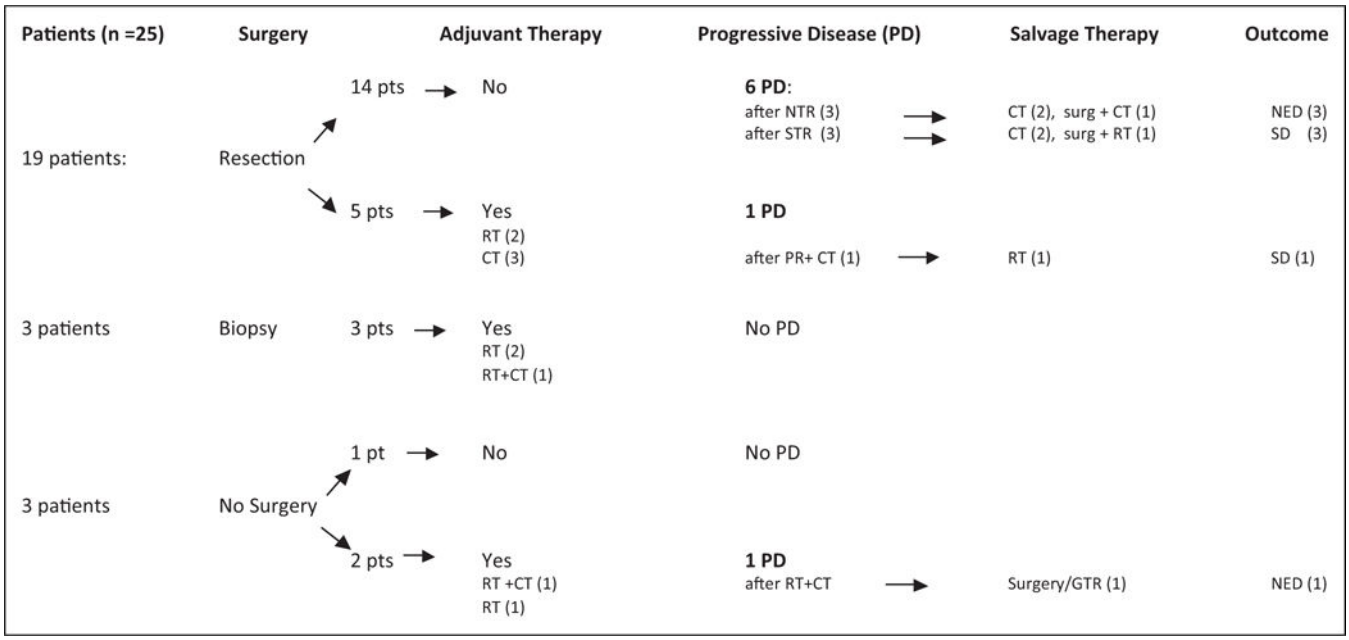

Figure 4.

Brainstem low-grade glioma therapy schema and salvage therapy/outcomes after progressive disease.

Table 1

Characteristics of Study Subjects (N = 25).

Characteristic	
Age	
Median age at diagnosis	6 years (range: 4 mo–16 y)
Gender	
Male	13
Female	12
Tumor location	
Nontectal midbrain	6
Pontine	3
Pontomedullary	7
Medullary	3
Cervicomedullary	6
Histology	23/25
Pilocytic astrocytoma	16 (64%)
WHO Grade II astrocytoma	3 (12%)
Ganglioglioma	2 (8%)
Mixed oligoastrocytoma	2 (8%)
Diagnosis by MRI only	2/25 (8%)
Presenting features	
Headache	12 (48%)
Vomiting	11 (44%)
Hydrocephalus	14 (56%)
Cranial nerve or extremity paresis (Including dysphagia)	16 (64%)
Failure-to-thrive	5 (20%)
Central sleep apnea	1 (4%)

Table 2

Clinical Presentation and Outcome of the Study Subjects.

Surgery at diagnosis	Extent of resection	Age at diagnosis in years	Tumor location	Histology	BRAF alteration	Neurologic deficits at presentation	Hydrocephalus/ VP shunt	Adjuvant therapy	Progression/ PFS	Salvage therapy	Disease outcome	Follow-up, (in years)	Sequelae	Clinical outcome (compared with status at diagnosis)
Yes, n = 22	GTR = 4	6	Cervicomedullary, DE	Ganglioglioma	Inadequate	- R hemiparesis - Ataxia	No/no	None	No	–	NED	11	Right hemiparesis	No change
		16	Pontomedullary, DE	PA	NA	- Ataxia	Yes/yes	None	No	–	NED	3	-Tracheostomy - Multiple cranial nerve palsy - Ataxia - G tube dependent	Worse
		5	Pontomedullary, DE	PA	Negative	- Dysphagia - FTT	Yes/no	None	No	–	NED	9	None	Better
		1.8	Medullary, DE	PA	Negative	- Abnormal tongue movements -FTT	Yes/no	None	No	–	NED	12	Hemiatrophy and fasciculation of tongue	Better
	NTR = 6	5	Pontine, focal	PA	NA	- Right sensorineural hearing loss	No/no	None	Yes/3 mo	CT VCR/carboplatin	NED	2.5	- U/L deafness - Right facial nerve paresis	Worse
		1.6	Cervicomedullary, DE	PA	Inadequate	- Dysphagia -FTT - Quadriparesis	Yes/no	None	Yes/4 mo	Resection + CT VCR/carboplatin	NED	18	Central sleep apnea	Better
		0.8	Cervicomedullary, DE	PA	Inadequate	- Torticollis - R sixth nerve palsy -RUE monoparesis	No/no	None	No	–	SD	10	None	Better
		6	Pontomedullary, DE	PA	Inadequate	- L sixth nerve palsy - L hearing loss - L seventh nerve palsy - L hemiparesis	Yes/no	None	No	–	SD	12	- L seventh nerve palsy - L sensorineural hearing loss - L hemiparesis	No change
		5.5	Pontomedullary, DE	Ganglioglioma	KIAA1549- BRAF	- Dysphagia	No/no	None	No	–	SD	6	None	Better
		2	Midbrain tegmentum	PA	KIAA 1549- BRAF	- L hemiparesis	No/no	None	Yes/4 mo	CT VCR/carboplatin	NED	1.6	None	Better
	STR = 7	2	Midbrain tegmentum, LE	PA	NA	- Dysphagia - Diplopia - Ataxia - FTT	Yes/yes	None	Yes/15 mo	CT TPCV	SD	10.5	- Dysphagia - Left hemiparesis	Worse
	STR = 7	16	Cervicomedullary, DE	PA	Inadequate	- None	No/no	None	No	–	SD	2	None	No change
		11	Pontine, focal DE	PA	Negative	- None	Yes/no	None	Yes/16 y	Resection +RT	SD	17	None	No change

Surgery at diagnosis	Extent of resection	Age at diagnosis in years	Tumor location	Histology	BRAF alteration	Neurologic deficits at presentation	Hydrocephalus/ VP shunt	Adjuvant therapy	Progression/ PFS	Salvage therapy	Disease outcome	Follow-up, (in years)	Sequelae	Clinical outcome (compared with status at diagnosis)
		4.25	Cervicomedullary, DE	PA	NA	- Apnea - Ataxia - Dysphagia - Right hemiparesis	No/no	None	Yes/6 mo	CT VCR/carboplatin	SD	14.5	- Sleep apnea - Bulbar dysfunction - Right hemiparesis - Tracheostomy - G tube dependent	Worse
		16	Pontomedullary, DE	PA	Inadequate	None	Yes/no	RT	No	–	SD	15	Mild ataxia	Worse
		5	Pontomedullary, LE	PA	KIAA 1549- BRAF	- None	Yes/no	CT TPCV	No	–	NED	2	None	No change
		8	Cervicomedullary, DE	Mixed OA	NA	- Obstructive sleep apnea - Stridor	No/no	RT	No	–	SD	8	Obstructive sleep apnea	No change
	PR = 2	14	Pontine, focal	Grade II Astro	Inadequate	- R seventh nerve palsy - B/L abductor palsy	No/no	CT TMZ	No	–	SD	7	- R seventh nerve palsy - B/L abductor palsy	No change
		0.3	Pontomedullary, DE	Mixed OA	NA	- Dysphagia - FTT	Yes/yes	CT VCR/carboplatin	Yes/3 y	RT	SD	13	- Central sleep apnea - T racheostomy	Worse
	Biopsy = 3	11	Midbrain tegmentum, DE	Grade II Astro	NA	- Dysphagia - B/L ptosis - Ataxia - Dysarthria	Yes/no	RT+CT TPCV	No	–	SD	6	None	Better
		13	Midbrain tegmentum	PA	KIAA 1549- BRAF	- Ataxia - Right hemiparesis	Yes/yes	RT	No	–	SD	13	Right hemiparesis	Better
		8	Midbrain	Grade II Astro	NA	-Left hemiparesis	No/no	RT	No	–	SD	4	None	Better
None, n = 3		11	Medullary, DE	NA		- None	No/no	None	No	–	SD	2	None	No change
		14	Midbrain tegmentum	PA	Inadequate	-Left hemiparesis - Right third nerve paresis	Yes/yes	RT+ 1 cycle CT VCR/carboplatin	Yes/3 mo after RT, during CT	Resection after failure of RT and CT	NED	5.5	- Left hemiparesis - Right third nerve paresis	No change
		7	Medullary, DE	NA		- Hyponasal speech	Yes/yes	RT	No	–	SD	15	Hyponasal speech	No change

Abbreviations: CCNU, lomustine; CT, chemotherapy; DE, dorsally exophytic; FTT, failure to thrive; GTR, gross total resection; LE, laterally exophytic; NA, not available; NED, no evidence of disease; NTR, near total resection; OA, oligoastrocytoma; PA, pilocytic astrocytoma; PFS, progression-free survival; PR, partial resection; RT, radiotherapy; SD, stable disease; STR, subtotal resection; TMZ, temozolomide; TPCV, thioguanine, procarbazine, lomustine, vincristine