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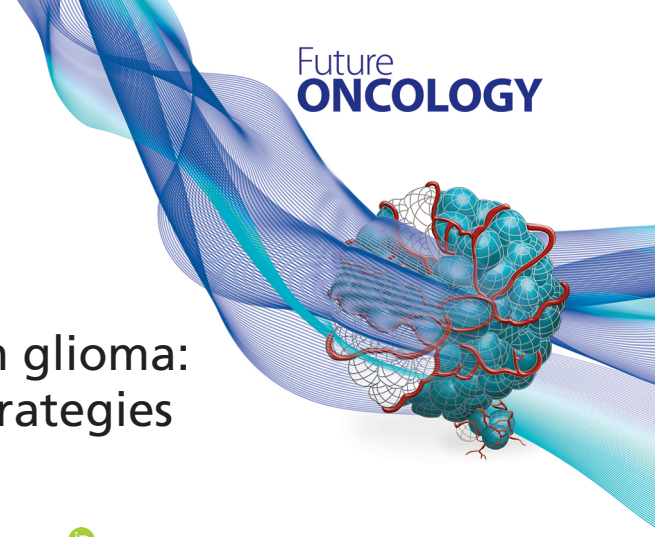

Pediatric low grade focal brainstem glioma: outcomes of different treatment strategies and prognostic factors

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Background: This study explores the prognostic factors and outcomes of different treatment modalities in focal brain stem glioma (FBSG). **Materials & methods:** Pediatric FBSG patients diagnosed during 2010–2017 were retrospectively reviewed for clinical and therapeutic data. **Results:** A total of 71 cases were identified and the median age was 6.4 years. The 5-year overall- and progression-free survival were 74.5 and 70.6%, respectively. Radiotherapy was the main line of treatment (66.2%) and there were no survival differences between radiotherapy, chemotherapy and surveillance groups. Two independent poor prognostic factors were identified on multivariate analysis: age <8 years and cervicomedullary tumor site ($p = 0.02$ for both). **Conclusion:** Surveillance, radiotherapy and chemotherapy have comparable clinical outcomes in pediatric FBSG.

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Keywords: cervicomedullary glioma • focal brainstem glioma • intrinsic glioma • low-grade glioma • overall survival • pediatric • progression-free survival

The global incidence of pediatric brain tumors is estimated to be 2.28 per 100,000 persons, while it is 1.77 per 100,000 persons in the Middle East and North Africa [1]. Brainstem tumors comprise 10–20% of the pediatric central nervous system tumors and they are broadly grouped into two main entities: diffuse intrinsic pontine glioma (DIPG) comprising 80% of patients and focal brainstem glioma (FBSG) constituting 20% [2,3]. Following MRI establishment, Choux *et al.* subclassified brainstem tumors into four types: type I, DIPG; type II, focal intrinsic; type III, exophytic; and type IV, cervicomedullary tumors [4,5]. DIPG is a highly aggressive tumor with a short duration of symptoms (≤3 months) and dismal prognosis where median survival is usually <1 year [6]. Conversely, FBSG (types II, III and IV) is characterized by insidious onset, low-grade histology and excellent prognosis [2]. While surgery has no role in DIPG treatment, it is often an upfront treatment modality option in FBSG [5]. Radiotherapy and chemotherapy are more controversial treatment options and no consensus has been reached yet, mainly due to the limited patient population [2,6]. The present study evaluates the management and clinical outcomes of FBSG in a single large tertiary cancer center.

Materials & methods

Following institutional review board approval, we retrospectively identified pediatric patients (≤18 years old) with the diagnosis of FBSG treated at our hospital from January 2010 to December 2017. We thoroughly reviewed electronic patients' records for clinical, treatment and survival data. Computed tomography (CT) and MRI scans were reviewed by a specialized neuro-radiologist on picture archiving and communication system for accurate determination of tumor type (II, III or IV, denoting low grade tumor) and site. The extent of surgical resection was identified by surgeons' reports and postoperative MRI performed within 48 h of surgery. Subtotal resection was defined by the presence of any postoperative residual disease.

Chemotherapeutic regimen

The chemotherapy regimen consisted of two phases: induction and maintenance. The former comprised 10 weeks of an intravenous pulse of 1.5 mg/m^2 vincristine (maximum 2 mg) on day 1 of the first 10 weeks, together with a single dose of carboplatin 550 mg/m^2 as a 1-h infusion on day 1 of weeks 1, 4, 7 and 10. The maintenance phase started at week 13, where both drugs were administered simultaneously in a 4-weekly regimen until completion of 53 weeks.

Radiotherapy technique

CT simulation was performed after thermoplastic head mask immobilization, with 2 mm slice thickness. Patients younger than 4 years, or those who could not lie still, were treated under general anesthesia. High-resolution T2 weighted MRI was fused with the CT planning set to delineate the gross target volume. Clinical target volume (CTV) was created by the addition of a 1 cm margin to the gross target volume, after adjusting for bony structures and tentorium. A 5 mm margin was further added to CTV to create the planning target volume as per our departmental policy [7]. Dosimetric plans, dose distribution and calculation were carried out using Monaco (version 5.11.01) treatment planning software (Elekta Inc, Stockholm, Sweden) and assessed via dose–volume histograms. Set-up verification was performed using electronic portal imaging or cone-beam computed tomography. Patients underwent clinical examination once weekly during radiotherapy for detailed general and neurological examination and toxicity assessment.

Toxicity assessment

Common Terminology Criteria for Adverse Events version 4.0 was used to score acute radiation and chemotherapy toxicity. The Radiation Therapy Oncology Group Late Radiation Morbidity Scoring Criteria was used to score radiation toxicity appearing beyond 90 days from radiotherapy [8].

Response assessment

Bimonthly follow-up visits were arranged upon completion of therapy for the first year and every 4–6 months thereafter. Radiological progression was defined as a ≥25% increase in tumor volume, the appearance of new lesions or leptomeningeal spread. Neurological assessment was regularly performed and MRI was performed at 6–12-month intervals.

Statistical analysis

Overall survival (OS) was calculated from the date of registration to the date of death due to any cause or the date of last follow-up. Progression-free survival (PFS) was calculated from the date of registration to the date of tumor progression, death or last follow-up. The Kaplan-Meier method was used for survival analysis with 95% confidence intervals. A Cox proportional hazards model was used to identify prognostic variables associated with OS and PFS at a p-level of 0.2 for bivariable selection and 0.05 for multivariable analysis. χ^2 and Fisher's exact tests were used for categorical variables, while t test and analysis of variance test (ANOVA) were used for continuous variables. The maximally selected rank statistics method was used to categorize the age and duration of symptoms. All statistical analyses were performed using R statistical environment (version 3.4.0), R packages survival (version 2.41–3) and IBM SPSS version 22. A p-value ≤ 0.05 was considered significant.

Results

During the period 2010–2017, we identified 71 radiographically confirmed low-grade FBSG cases, after the exclusion of tectal tumors as they represent a unique entity with indolent behavior. The patients had a median age

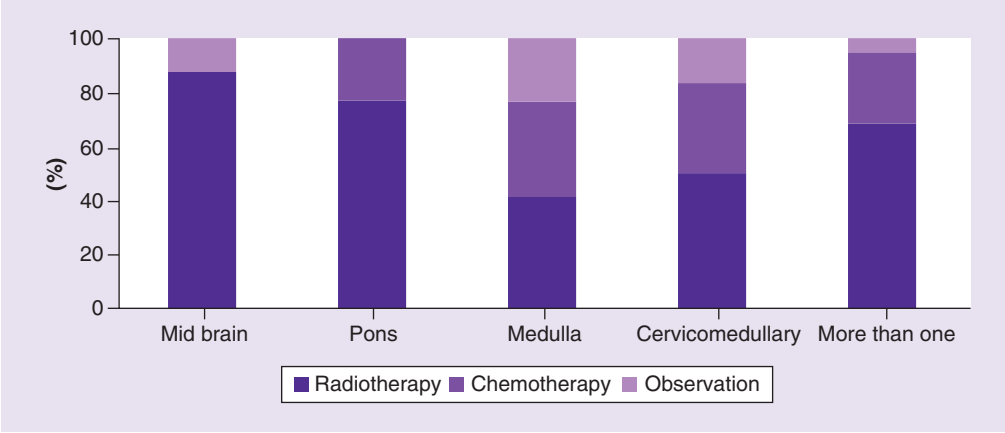

Figure 1. Treatment modalities in different brainstem subsites.

of 6.4 years (range 0.66–18) with a slight male predominance (53.5%). The most common presenting manifestations were cranial nerve palsy (50.4%) and increased intracranial pressure (45%) and 29.6% of our cases underwent ventriculo-peritoneal shunt insertion due to hydrocephalic changes. The majority of tumors either involved more than one brainstem subsite (26.8%) or the medulla (23.9%). A total of 13 tumors (18.3%) were cervicomedullary (type IV) and almost half of the tumors (49.2%) were of the focal intrinsic type (type II; Table 1). The median follow-up for all patients was 47.9 months (95% CI: 34.2–57.6).

Surgical intervention was performed in 25 patients (35.2%), where the majority underwent biopsy (n = 16/25, 64%). From the 23 cases with proven pathology, ten cases had ganglioglioma grade I or II, which is a relatively uncommon finding. A strategy of careful observation was adopted in eight patients; four had subtotal resection followed by observation, while the remaining four patients were followed up without any surgical intervention. Chemotherapy was the treatment of choice in 16 patients (22.5%), while radiotherapy was delivered to 47 children (66.2%) at a median dose of 54 Gy. The decision of treatment for each case was based on multidisciplinary team discussions, guided primarily by the patient's age, performance status, clinical presentation, physician's discretion and patient's preference. Patients who suffered from significant neurological symptoms were mostly chosen in the multidisciplinary team meetings to receive radiotherapy, while those with less or no symptoms or of young age either received chemotherapy or were put under close follow-up. A total of 11 patients who were presented by mild symptoms (no motor weakness, no ataxia, no cranial nerve palsy), were treated as follow: three were kept under follow-up, four received chemotherapy and four received radiotherapy. The previous is showing that the initial condition is not the only factor that leaded the choice of treatment, as all the treatment modalities are acceptable options while we do not have a specific protocol for low-grade brainstem glioma. Of note, 78.6% of patients older than 8 years and 53% of the younger cases, received radiotherapy. Therefore, radiotherapy was the treatment of choice in the majority of cases in both groups. The distribution of different treatment modalities according to the tumor subsite is shown in Figure 1.

Treatment toxicity

Acute grade 2 radiation-induced toxicities were nausea/vomiting (n = 5/47, 10.7%) and fatigue (n = 7/47, 14.9%). Grade 3 toxicities were nausea/vomiting in one patient (2.1%) and acute otitis media in another patient (2.1%). Minimal late toxicities were observed, only grade 2 skin pigmentation in one patient (2.1%). Acute chemotherapy-induced grade 2 toxicities included nausea/vomiting (n = 3/16, 18.7%), diarrhea (n = 3/16, 18.7%) and oral mucositis (n = 2/16, 12, 5%). Acute grade 3 toxicities included myelosuppression (n = 3/16, 18.7%), thrombocytopenia (n = 2/16, 12.5%), skin rash (carboplatin allergy; n = 3/16, 18.7%) and febrile neutropenia (n = 1/16, 6.3%). It is noteworthy that the acute toxicity did not statistically differ between chemotherapy and radiotherapy, whereas two patients suffered from long-term moderately retarded school achievement, one in each of the radiotherapy and chemotherapy treatment groups.

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Table 1. Baseline characteristics and treatment of 71 patients.

Variable	n (%)
Age (years), median (range)	6.44 (0.66–18)
Gender:	
– Male	38 (53.5)
– Female	33 (46.5)
NF-1	3 (4.2)
Duration of symptoms (months), median (range)	3 (0.2–36)
Clinical presentation†:	
– Increased intracranial pressure	32 (45)
– Motor weakness	29 (40.8)
– Cranial nerve palsy	36 (50.4)
– Ataxia	19 (26.8)
– Hydrocephalus	16 (22.5)
– Others	15 (21.1)
– Not known	9 (12.7)
VP shunt	23 (32.4)
Tumor site:	
– Midbrain	9 (12.6)
– Pons	13 (18.3)
– Medulla	17 (23.9)
– More than one subsite	19 (26.8)
– Cervicomedullary	13 (18.3)
Tumor type:	
– Focal intrinsic	35 (49.2)
– Exophytic	19 (26.8)
– Cervicomedullary	13 (18.3)
– Diffuse (nonpontine)	1 (1.4)
– Not known	3 (4.22)
Pathology (WHO grade):	
– Pilocytic astrocytoma (grade I)	9 (12.7)
– Ganglioglioma (grade I)	4 (5.6)
– Ganglioglioma (grade II)	6 (8.4)
– Pilomyxoid (grade II)	1 (1.4)
– Low grade glioma, NOS	3 (4.2)
– Nonrepresentative sample	2 (2.8)
– Not available	46 (64.8)
Surgery:	
– STR	9 (12.6)
– Biopsy	16 (22.5)
– None	46 (64.8)
Management:	
– Observation	8 (11.3)
– Chemotherapy	16 (22.5)
– Radiotherapy	47 (66.2)

†Numbers do not add to 71 as some patients had more than 1 presenting symptom/sign.
NF-1: Neurofibromatosis type 1; STR: Subtotal resection; VP: Ventriculoperitoneal.

Clinical outcomes

The 5-year OS and PFS were 74.5% (95% CI: 64.4–86) and 70.6% (95% CI: 60.4–82.5), respectively. The median survival for the whole cohort and all subtypes were not reached. It was not possible to identify the cause of death as the majority of the cases died outside the hospital. Only four cases died in hospital, one died postoperatively and

Table 2. Characteristics of patients with disease progression.

Case n	Age (years)	Pathology	Extent of surgery	Tumor site	Initial treatment	Time to progression (months)	Second-line treatment	Status at last FU	OS (months)
1	7.5	LGG	Biopsy	Midbrain	RT 54 Gy	3.2	None	Dead	72.8
2	7.6	NA	None	Pons	RT 54 Gy	20.9	None	Alive	19.4
3	12	NA	Biopsy	Pons	RT 54 Gy	7.9	Chemotherapy	Dead	14
4	7.8	Ganglioglioma G2	Biopsy	Pons	RT 54 Gy	5.6	None	Dead	14.2
5	2.9	Ganglioglioma G2	Biopsy	Medulla	Observation	10	Surgery	Alive	16.8
6	10	Ganglioglioma G1	Biopsy	Medulla	Chemotherapy	19.7	None	Alive	19.7
7	11.9	Ganglioglioma G2	STR	Cervicomedullary	RT 54 Gy	6.1	None	Dead	9.3
8	1.6	NA	None	Cervicomedullary	Chemotherapy	31.8	RT	Dead	36.9
9	6.5	NA	None	>1 subsite	RT 54 Gy	6.2	None	Dead	10
10	5.1	NA	None	>1 subsite	RT 54 Gy	5.3	None	Dead	8.5
11	4.9	NA	None	>1 subsite	RT 54 Gy	1	None	Dead	6.5

FU: Follow-up; LGG: Low-grade glioma; NA: Not applicable; OS: Overall survival; RT: Radiotherapy; STR: Subtotal resection.

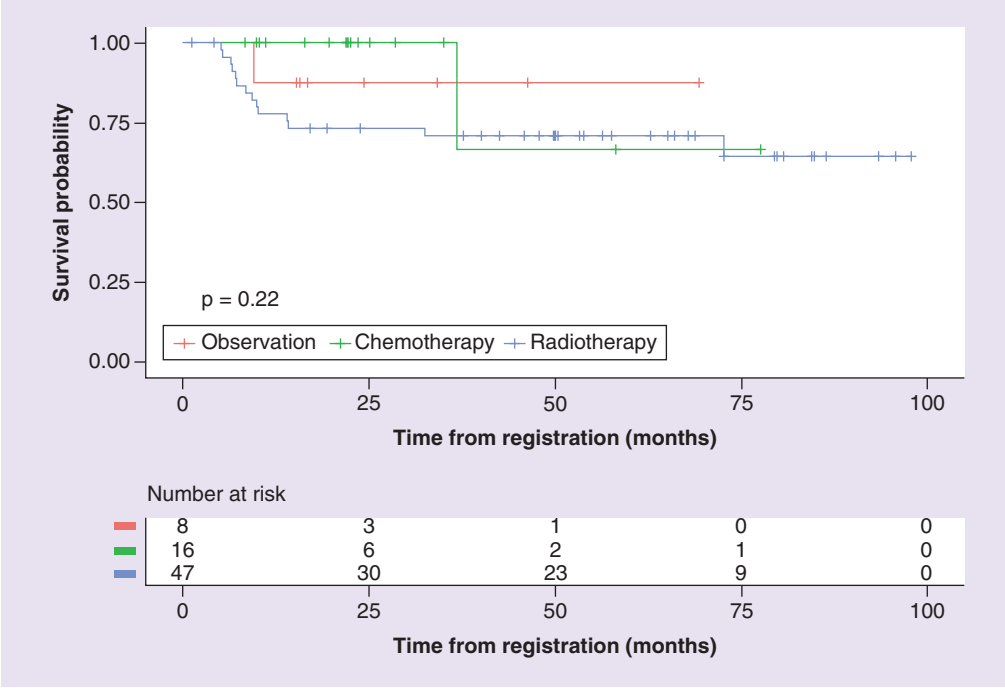

Figure 2. Overall survival of focal brainstem glioma according to treatment modality.

the other three died due to progression of neurological symptoms (persistent convulsions, disturbance of conscious or bulbar palsy that leaded to severe chest infection). 11 patients (n = 11/71, 15.5%) developed disease progression after a median of 7.6 months. Of these, eight had received radiotherapy, two had received chemotherapy and one was under active surveillance at the time of progression (Table 2).

Observation, radiotherapy and chemotherapy yielded comparable mean OS results (69 vs 68.1 vs 64 months, respectively; p = 0.15), while the median survival was not reached in any of these treatment subgroups. The 5-year OS was 87.5% (95% CI: 67.3–100), 66.7% (95% CI: 30–100) and 70.9% (95% CI: 58.7–85.6) for observation, chemotherapy and radiotherapy, respectively (p = 0.22). The 5-year PFS was 75% (95% CI: 50.3–100), 68.2% (95% CI: 37.6–100) and 68.8% (95% CI: 56.5–83.8), respectively (p = 0.341; Figure 2). Of note, the mean age of patients who received radiotherapy was 8.3 year, which was significantly older than those who received chemotherapy (Figure 3).

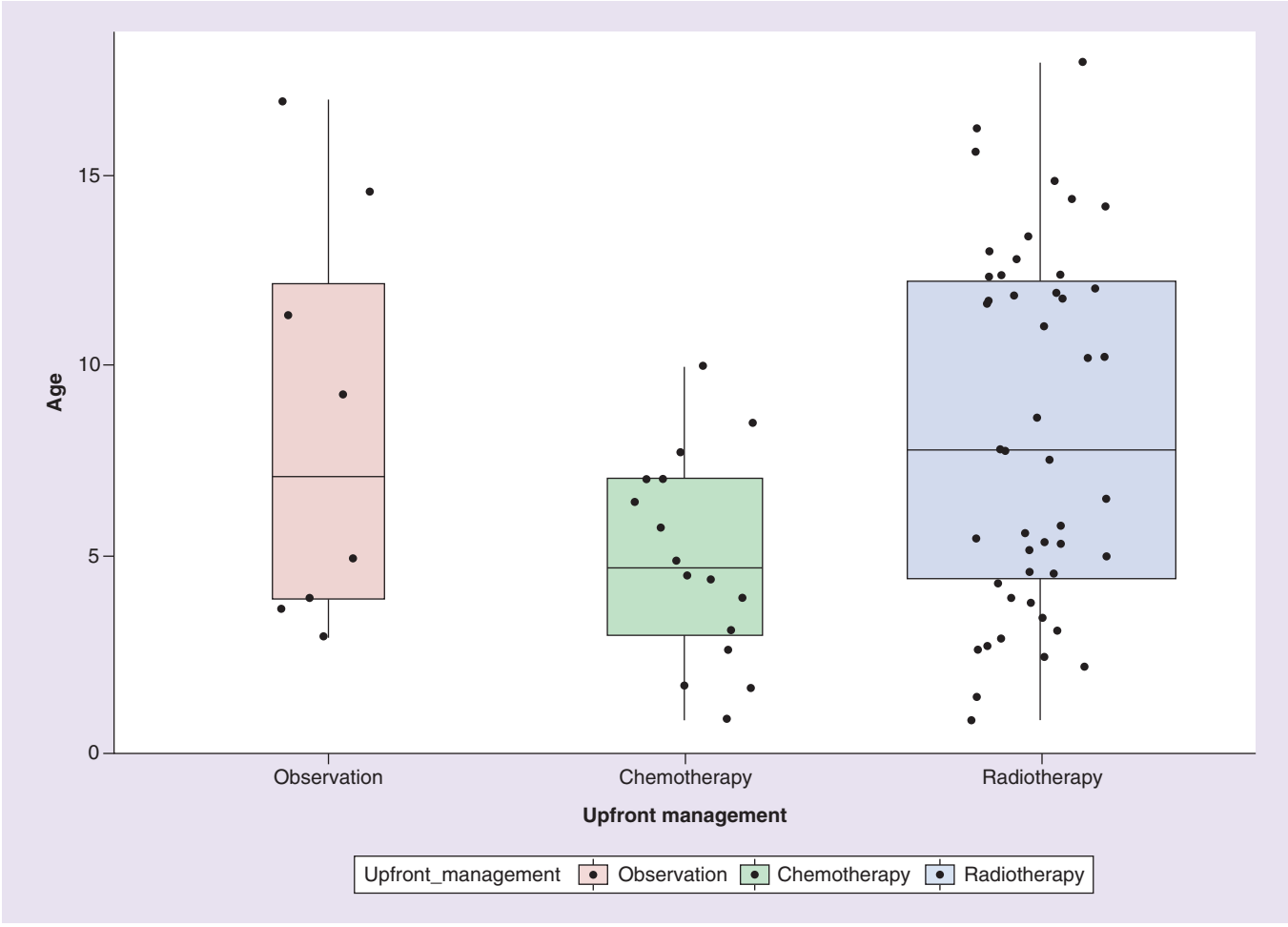

Figure 3. Age of the patients in different adjuvant management.

Subgroup analysis of the 23 pathologically-proven patients revealed that 12 cases received chemotherapy, six patients received radiotherapy and the remaining five were put under active surveillance. The 5-year OS and PFS of those patients were 81.1% (95% CI: 64.2–98) and 73.2% (95% CI: 52.4–94), respectively, which were not statistically significant from the survival outcomes of the whole cohort. Ganglioglioma (grades I and II) was the most predominant histology (43.5%) among the pathologically-proven patients and it conferred worse survival compared with the remaining low-grade pathologies (mean survival 24 months [95% CI: 15–33] vs 78 months [95% CI: 67–88], respectively; p = 0.06).

On Cox regression multivariate analysis, patients aged ≥8 years had significantly better OS than younger patients (HR: 0.211, 95% CI: 0.06–0.79; p = 0.02; Table 3). In addition, cervicomedullary tumors conferred worse OS as compared with other brainstem locations (HR: 5.376, 95% CI: 1.32–21.82; p = 0.02). Conversely, none of the remaining patients' demographics, tumor or treatment characteristics had a significant prognostic impact. In our cohort, 13 patients (18.3%) had the diagnosis of cervicomedullary BSG and the median of the largest diameter of cervicomedullary tumors was 5.5 cm (range 2.3–6.5 cm). On a *post hoc* analysis comparing the mean of the largest diameter of tumors, cervicomedullary tumors were significantly larger compared with other brainstem subsites (p = 0.05). Of 13 cervicomedullary patients, six received radiotherapy, four received chemotherapy, two were kept under observation and one died postoperatively. Stepwise multivariate analysis revealed that both older age and cervicomedullary site were independent prognostic factors (p = 0.02 for both).

Table 3. Cox regression analysis for overall survival.

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p-value†	Hazard ratio	95% CI	p-value
Age						
<8 years	1 (reference)	–	0.05	1 (reference)	–	
≥8 years	0.36	0.12–1.10		0.21	0.06–0.79	0.02*
Gender						
Male	1 (reference)	–	0.48	–	–	–
Female	1.4	0.55–3.55				
Tumor site						
Brainstem	1 (reference)	–	0.19	1 (reference)	–	0.028
Cervicomedullary	2.1	0.75–5.90		5.38	1.32–21.82	
Symptom duration						
<1 month	1 (reference)	–	0.23	–	–	–
≥1 month	0.38	0.08–1.77				
Tumor type						
Focal intrinsic	1 (reference)	–		–	–	–
Focal exophytic	0.85	0.26–2.77	0.46			
Cervicomedullary	1.87	0.62–5.58				
Management						
Follow-up	1 (reference)	–		1 (reference)	–	
Chemotherapy	0.52	0.03–8.3	0.16	0.26	0.02–4.29	0.34
Radiotherapy	2.35	0.31–17.98		3.62	0.44–29.63	0.23

† All factors with p = 0.2 in univariate analysis were included in the multivariate analysis.
*p-values considered significant at 0.05 level.

Discussion

This retrospective study, on a relatively large cohort of patients, reports the clinical outcomes of a rare pediatric disease. Although pediatric low-grade FBSG, radiologically or pathologically-proven, has a good prognosis, it lacks standard treatment guidelines with no prospective randomized studies. This urges for more efforts to reach a worldwide consensus on the optimal management.

Surgery

In the present study, the 5-year OS of all 71 patients was 74.5% (95% CI: 66.4–86.0) and the 5-year PFS was 70.6% (95% CI: 60.4–82.5). Our results show a lower OS than that of St. Jude Hospital and Sick Children Hospital (OS: 74.5 vs 98 vs 89%, respectively) [9,10]. On the contrary, our study shows a higher 5-year PFS (70.6 vs 59 vs 57%, respectively). Of note, those studies included tectal gliomas; however, we focused on nontectal FBSG in our analysis as tectal tumors are usually successfully managed with observation without any intervention. Only 35.2% of our patients were pathologically proven, either by biopsy or surgery, compared with the St Jude study in which all tumors were biopsied and proven to be low-grade. The absence of gross total resection (GTR) within our patients might have contributed to the lower OS outcomes. In the St Jude study, 17 and 50% of patients underwent GTR and subtotal resection, respectively, with a trend toward better 5-year PFS for those who underwent GTR compared with less extensive resection [9]. Sandri *et al.* also showed that the extent of surgery (total/subtotal vs partial) was the most relevant prognostic factor for PFS in FBSG [11]. Moreover, Garzón *et al.* emphasized in a study including 43 FBSG pediatric patients that surgery is the most significant predictor of better prognosis [12]. Similarly, Upadhyaya *et al.* reported an excellent 10-year OS of 100% and PFS of 71% in 25 brainstem low-grade glioma (LGG) patients [13]. Collectively, these results highlight the importance of surgical resection in FBSG, whenever feasible. The recent advancements in neuroimaging and the availability of intraoperative imaging have improved the safety and accuracy of neurosurgery in brainstem tumors.

Adjuvant treatment

In contrast to surgery, the role of adjuvant treatment and its optimal timing, whether to be delivered upfront or deferred until progression, are still controversial. In the present study, there were no differences in survival between those who were kept under observation and those who received upfront adjuvant chemotherapy or radiotherapy, both in the whole cohort and the pathologically-proven subgroup. These findings are comparable to that of the Sick Children Hospital where noninferior outcomes were reported for observation compared with the entire cohort (PFS: 57 vs 57%, respectively; and OS: 93 vs 89%, respectively). They also reported that 46% of patients who underwent biopsy or partial resection did not progress and did not require further treatment. Moreover, delay of treatment till progression had no impact on survival [10]. Similar results were reported by the St Jude Hospital study, where no survival differences were observed between different treatment modalities [9].

The use of chemotherapy in low-grade FBSG has similar goals and benefits to that in LGG elsewhere, mainly to prevent tumor progression while avoiding radiotherapy toxicity, especially in young children. It is noteworthy that the optimal choice of chemotherapy regimen is still controversial too. The Children's Oncology Group compared weekly vincristine/carboplatin regimen and TPCV combination (thioguanine, procarbazine, lomustine and vincristine) in patients younger than 10 years and concluded no difference in PFS or OS, with more toxicity in the TPCV group [14]. In a small series of 16 FBSG patients, Ronghe *et al.* reported 5-year PFS and OS of 70 and 100%, respectively, using vincristine/carboplatin chemotherapy [15]. Unfortunately, these findings were not consistent in other studies where the response was not durable and the 5-year PFS ranged from 30 to 40% [16]. The large multicenter German HIT-LGG 96 study, including 86 FBSG out of 1031 LGG cases, offered immediate adjuvant therapy (chemotherapy or radiotherapy) only in symptomatizing non- or incomplete surgical cases or those having risk of progression at a critical site. Complete response was achieved in 3.8%, partial response in 31.6% and stable disease in 56.5%, while 8.1% had tumor progression. The 5- and 10-year PFS in the chemotherapy group were 47 and 44%, respectively, as opposed to higher values in those who received radiotherapy (5- and 10-year PFS of 65 and 62%, respectively) [17].

In the present study, 22.5% of cases received chemotherapy and they were all younger than 10 years. However, a protracted chemotherapy regimen for 1 year may represent a significant burden to families. The Pediatric Oncology committee in Developing Countries recommends the use of vincristine and monthly carboplatin for children younger than 8 years in low- and middle-income countries, whereas the choice of adjuvant treatment for children above 8 years is individualized, bearing in mind that radiotherapy yields better PFS at the expense of additional late side-effects [18]. Radiotherapy was the adjuvant treatment of choice in 66.2% of our patients using conformal or intensity-modulated radiotherapy techniques. In young children, radiotherapy carries the risk of significant late toxicities including cognitive impairment, visual and endocrinological deficits [19]. A small study on four FBSG cases who received radiotherapy did not report any neurocognitive deficits [20]. However, in another small series, hearing and neuroendocrine deficits, seizures and school performance difficulties were found in seven out of eight FBSG survivors [21]. Nevertheless, owing to its good local control results, radiotherapy is recommended in selected cases based on the symptomatic burden, patient's age, general condition, the size and location of the tumor [22,23]. In an attempt to mitigate radiation-induced toxicities, the Children Oncology Group reduced the CTV margin to 0.5 cm with acceptable 5-year PFS and OS of 71 and 93%, respectively, and no increase in marginal failure [24].

Prognostic variables

The only prognostic factors adversely affecting survival, in our study, were young age (<8 years) and cervicomedullary tumor site. Many small studies of LGG in children have looked at age as a prognostic factor, with inconsistent results. A British series showed that young age groups showed poor clinical outcomes, which is consistent with our finding [25]. Contrary, The German Study HIT-LGG 96 reported inferior outcomes for children >11 years this is in contrast with our observation [17]. A third large study with 278 LGG patients concluded that age < or >5 years did not affect OS [26]. In our study, on the Cox regression analysis for overall survival, the HR was significant in younger age groups in both univariate and stepwise multivariate analysis suggesting that the effect is probably independent of the treatment received.

The prognostic impact of tumor site in brainstem gliomas is poorly defined because only a few studies subdivided FBSG by subsite. In a study by Garzón *et al.* including only four cervicomedullary tumors out of 43 cases, there was no significant impact of tumor site on clinical outcomes [12]. However, McAbee *et al.* analyzed 31 cervicomedullary cases and reported a high rate of recurrence (45%) with an estimated 5-year PFS and OS of 64.7 and 86.7%, respectively [27]. Of note, a study by Ahmed *et al.* showed that aggressive surgery in cervicomedullary tumors

yielded better outcomes with 10- and 20-year OS of 75 and 64%, respectively [28]. Collectively, these findings might indicate that cervicomedullary tumors exhibit worse outcomes owing to the difficulty of achieving GTR.

Limitations of this study include its retrospective nature, limited histopathological data with the possibility of having high-grade gliomas, relatively low surgical rates, lack of specific patients' criteria to lead the choice of treatment modality and the lack of rigorous systemic assessment of long-term toxicities.

Conclusion

The present study provides valuable data on a relatively large series of patients with a rare disease. Our survival results are comparable to those reported in the literature, taking into consideration the lower percentage of patients who underwent surgical resection compared with other studies. These results emphasize the importance of safe surgical intervention in FBSG. Different treatment strategies yielded comparable clinical outcomes and the choice of chemotherapy or radiotherapy largely depends on the patient's age and symptomatic burden. Thus, we recommend careful close observation in non- or minimally symptomatic cases. Of various clinicopathological factors, only young age and cervicomedullary tumors predicted for worse survival outcomes.

Summary points

- Pediatric focal low-grade brainstem tumors have a good prognosis.
- The gender, tumor type and duration of symptoms were not shown to be of prognostic value.
- Compared with different brainstem locations, cervicomedullary tumors showed worse prognosis.
- Young age (<8 years) showed worse prognosis.
- Surgical resection is advised, whenever feasible.
- Active surveillance, chemotherapy and radiotherapy result in comparable clinical outcomes.
- The choice of treatment should be largely guided by patients' age, performance status and symptomatic burden.
- Large, multicenter studies are required to standardize treatment guidelines in pediatric focal brain stem glioma.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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