Favorable Outcome With Conservative Treatment for Children With Low Grade Brainstem Tumors

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Background. Pediatric brainstem tumors (BST) comprise a heterogeneous group of entities. Data regarding treatment options and outcome of BST, specifically brainstem low grade tumors (BSLGT) are limited. In order to better define risk groups and evaluate treatment options for pediatric BST, we performed a comprehensive analysis of all BST patients treated in our hospital during the MRI era. **Procedures.** We retrospectively analyzed clinical, imaging, and pathology data at presentation, treatment, and outcome of all BST patients followed at the Hospital for Sick Children in Toronto over the last 25 years. **Results.** Of 1,801 children with brain tumors, 223 (12%) had a brainstem primary location. Tumors without pontine involvement were BSLGT in 98.3%, whereas 75% of tumors involving the pons were high grade ($P = 0.0001$). Patients with BSLGT had 5-year progression-free survival (PFS) and overall survival (OS) of $57 \pm 3\%$ and $89 \pm 5\%$, respectively. Upfront observation of tumor residual conferred no survival disadvantage with 5-year PFS and OS of $57 \pm 5\%$ and $93 \pm 3\%$, respectively. In the group of patients requiring further treatment, 5-year PFS and OS were comparable between chemotherapy and radiotherapy with $53 \pm 12\%$ and $93 \pm 4\%$ and $66 \pm 11\%$ and $83 \pm 6\%$, respectively ($P = 0.26$ and 0.3, respectively). **Conclusion.** BST without pontine involvement are almost invariably BSLGT. Children with BSLGT have an excellent outcome even with careful initial observation. No clear benefit was observed for radiotherapy over chemotherapy when adjuvant treatment was needed. A conservative approach may be warranted for children with non-pontine brainstem lesions. Pediatr Blood Cancer © 2011 Wiley-Liss, Inc.

Key words: CNS tumors; brainstem tumors; low grade glioma; pediatric

INTRODUCTION

Brainstem tumors (BST) comprise 10–15% of pediatric brain tumors [1,2]. Over the last 2 decades the outcome of patients diagnosed with the most common pediatric brain tumors has improved significantly (3–6). Unfortunately, there has been no such progress with BST. Since resection is often impossible and biopsies are not routinely performed, pathological and biological data are scarce. Clinical data from sufficiently large patient cohorts are limited, and management varies widely between centers.

BST in the pre-MRI era were considered to be among the deadliest diseases in childhood, with pathology most often consistent with high grade gliomas [3,4]. The main treatment modality used was focal irradiation, with palliative intent in most cases [5]. The introduction of MRI over the last 3 decades, along with additional data from biopsies and autopsies, has allowed a more accurate definition of risk groups.

Diffuse intrinsic pontine gliomas (DIPG) comprise a distinct clinical entity defined by clinical presentation and imaging findings (14). DIPG carries a dismal prognosis regardless of pathological diagnosis [6]. Patients are treated with radiation with short-term responses and a median OS of 9–12 months [1,7,8].

Other lesions of the brainstem are less clearly defined. Tectal lesions may be indolent. Therefore, first line treatment consists of CSF diversion with no biopsy or further tumor-specific treatment in most cases [9–11]. Dorsally exophytic and focal pontomedullary lesions may be pathologically low grade and are frequently associated with long-term survival [12–15].

To better define and characterize specific risk groups and outcome of pediatric brainstem tumors we performed a comprehensive population-based study focused on imaging, pathological, and outcome data from a large cohort of patients followed and treated in the Hospital for Sick Children in Toronto over the last 25 years.

PATIENTS AND METHODS

The Hospital for Sick Children (Sickkids) has a catchment area of over 5 million residents in Southern Ontario. Since patient referral is uncommon, incidence and prevalence of tumor subtypes are unbiased. Data were collected from all relevant sources within the hospital, including the hospital medical records, databases of the brain tumor program, department of neurosurgery, and the pathology and radiology archives.

Records of all patients diagnosed with brain tumors since 1985 (MRI era) were reviewed, to identify patients with brainstem tumors. Patients with midbrain, pons, medulla, or cervicomedullary tumors according to radiologic/surgery reports were included. Patients with thalamic-midbrain or cerebellopontine lesions were included only if multiple radiological reports/surgical report or

review of the scan confirmed that more than 50% of the tumor was located in the midbrain/pons. For biopsied tumors pathology was reported as per the WHO criteria [16]. For non-biopsied tumors, a tumor was defined as high grade if it was compatible with the classic clinical and imaging diagnosis of DIPG [17]. Non-biopsied tumors were reported to be low grade if tumor location was tectal/posterior pontomedullary involving less than 40% of the pons, and the patient was observed without additional treatment. All progressive lesions were biopsied to confirm their nature. Tumor resection was considered to be total if no residual tumor was seen on postoperative MRI. Resection of more than 95% was graded near total, resection of 50–95% was graded as sub-total, 25–50% as partial, and less than 25% was graded as a biopsy. Tumor progression was defined as more than 25% tumor growth in consecutive MRI scans and/or clinical progression for which the patient was started on a second line of treatment. Survival curves were obtained using the Kaplan Meier method. Univariate analyses were performed using the Chi-square or Fisher exact test.

RESULTS

One thousand eight hundred one children were diagnosed with brain tumors between 1985 and 2009. Two hundred twenty-three of them (12%) had tumors located within the brainstem. The median age at diagnosis was 6.2 years (range 1-day old–17 years old). Male to female ratio was 1.05:1. Seven patients were diagnosed with underlying cancer predisposition conditions—all of them had neurofibromatosis type 1 (NF-1). All NF-1 patients had low grade lesions, four of them tectal. All seven patients are alive and only two required active adjuvant treatment (one child received radiation therapy and the other was treated with chemotherapy).

Prevalence of High and Low Grade Tumors in the Brainstem Is Equal

One hundred fifteen patients within the study group were diagnosed with high grade tumors, and 104 patients with low grade tumors. Four patients had non-informative biopsies. The median age at diagnosis and male to female ratio were not significantly different between high and low grade tumor patients.

The group of high grade lesions consisted of 95 patients with DIPG, diagnosed according to clinical and imaging criteria [3,17] 3 patients with primitive neuroectodermal tumors (PNET), and 17 patients with biopsied high grade astrocytoma.

Low grade tumors included 86 biopsied low grade glioma and 18 non-biopsied low grade tumors. Biopsied low grade glioma included 74 lesions (85%) consistent with WHO grade I astrocytoma, 4 (4.7%) lesions consistent with WHO grade II astrocytoma and 8 (9%) consistent with ganglioglioma.

Twenty-one patients were initially diagnosed with low grade tumors according to clinical and imaging characteristics with no biopsy. Three patients within this group, all with tectal lesions, were ultimately biopsied due to progression. All pathological specimens were consistent with WHO grade I astrocytoma. Median time of follow-up within this group is 3.6 years (0.27–10.55 years).

There were only 4 (3%) long-term survivors within the 115 patients with high grade tumors (median follow-up of survivors 6.22 years, range 3.98–13.6 years), In contrast, 87 out of the 104

Location and rate of high grade lesions

High grade tumors:
1/ 58 tumors not involving the pons (Pnet)
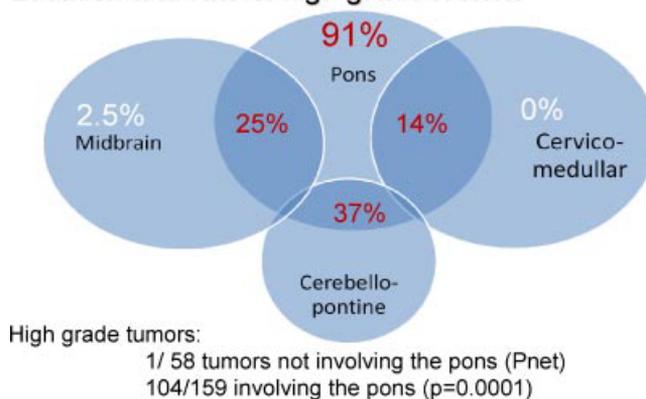104/159 involving the pons (p=0.0001)

Fig. 1. Percentage of malignant tumors in each site within the brainstem. Note that 91% of tumors involving only the pons are malignant compared to only 2% of the non-pontine lesions. Tumors with partial pontine involvement are malignant in 14–37% of the cases. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/pbc]

(84%) patients with low grade tumors survived their disease (median follow-up 4.8 years range 0–19.7).

High Grade Tumors Are Extremely Rare in Non-Pontine Lesions

We analyzed tumor characteristics according to the epicenter location in the brainstem (Fig. 1). Fifty-one percent of the tumors (114 tumors) were centered in the pons, 16% (37 tumors) involved the midbrain and 9.4% (21 tumors) were located in the cervicomedullary region. Tumors involved more than one brainstem region in 34 cases (15.2%). Data regarding specific location were unavailable in 17 cases (7.3%). Further data regarding patients and tumor characteristics are presented in Table I. Age was not associated with tumor location (median age at diagnosis

TABLE I. Brainstem Tumors Patients and Tumor Characteristics

Patients characteristics	
Median age at diagnosis	6.2
Male/female ratio	1.05:1
Tumor location	
Midbrain-thalamus	9
Midbrain	28
Midbrain-pons	12
Pons	114
Pontomedullar	14
Cerebellopontine	8
Cervicomedullar	21
Brainstem—not specified	17
Tumor pathology	
WHO Grade 1 astrocytoma	74
WHO Grade 2 astrocytoma	4
High grade glioma	17
Ganglioglioma	8
PNET	3
Non-informative biopsies	4
Non-biopsied low grade tumors	18
Non-biopsied DIPG	95

was 6.2 years within the whole cohort (range 1-day old–17.85 years old), 6.7 years within the non-DIPG patients with pontine involvement (range 0.05–17.85 years) and 7.7 years in the group of patients with non-pontine tumors (range 0.76–17 years)).

Out of 58 tumors with no pontine involvement, only 1 (1.7%) was a high grade lesion (PNET). In contrast, 112/148 (75%) tumors involving the pons were high grade ($P = 0.0001$). Furthermore, the rate of high grade tumors correlated with the extent of pontine involvement. Tumors located exclusively in the pons were high grade in 104/114 (91%) compared to only 8/34 (24.6%) tumors located partially in the pons and partially in other brainstem regions ($P = 0.0005$).

Favorable Outcome of Upfront Observation in BSLGT

We separately analyzed data regarding our 96 patients with brainstem low grade tumors (BSLGT) since clinical course and treatment modalities are distinct from other brainstem tumors. Patients with ganglioglioma were not included in this cohort. Within the BSLGT patients 78 were diagnosed with low grade astrocytoma and 18 had non-biopsied low grade tumors.

The median age at diagnosis was 6.2 years. Median follow-up was 4.8 years (0–19.7). Further data regarding tumor and patient characteristics are presented in Table I. Supplemental Table I summarizes the initial management and outcome of BSLGT patients.

One patient within the whole cohort underwent gross total resection and no further treatment was needed. We divided the rest of the BSLGT to three groups. Sixty-three patients did not receive initial medical therapy despite significant residual tumor. Of these, 42 were observed following upfront partial resection/biopsy (group I) and 21 patients with tectal (15 patients) or focal pontomedullary lesions (6 patients) had no biopsy prior to observation (group II). Group III consisted of 24 patients with BSLGT that received medical treatment (chemotherapy/radiotherapy) upfront. Treatment initiation was at the discretion of the treating physician (Supplemental Table I). Data regarding the extent of resection and follow-up of eight more patients were insufficient and therefore, not included in the groups.

Five-year progression-free survival (PFS) and OS of the entire BSLGT cohort were $57 \pm 3\%$ and $89 \pm 5\%$, respectively (Fig. 2A). The progression rate tended to be higher for patients younger than 3 years old (17/23 (74%) of young patients experienced tumor progression compared to 40/73 (54%) older patients ($P = 0.08$)). No other clinical factor including tumor location, size, and extent of surgery predicted progression.

Surprisingly, excellent survival was observed for patients with residual tumor undergoing observation only (group I). Progression was observed in 23/42 (54%) patients. Five-year PFS and OS for these patients were $50 \pm 6\%$ and $92 \pm 3\%$, respectively. Furthermore, no significant difference in PFS was observed between patients with tumor residual following surgery only (group I) and patients treated with medical treatment upfront (group III). The outcome of patients in group II comprising of patients observed without upfront biopsy was excellent. At a median of 3.48 years (0.55–10.5), only 3/21 (14%) tumors progressed. One patient died due to infection 3.59 after diagnosis with no tumor progression. For all patients who did not receive adjuvant therapy (groups I and II, n = 63) 5-year PFS and OS were $57 \pm 5\%$ and $93 \pm 3\%$, respectively (Fig. 2B).

Chemotherapy Versus Radiotherapy: Outcome Analysis

Sixty-six of our 96 patients with BSLGT underwent adjuvant treatment. Twenty-four were treated upfront and the rest were treated at progression. Forty-three patients received either chemotherapy or radiotherapy as a single intervention allowing us to conduct an outcome analysis of each treatment modality (Supplemental Table I).

Twenty-one patients were treated with chemotherapy as a first option. Treatment protocols included vincristine and carboplatin (10 patients), vinblastine (8 patients), thioguanine, procarbazine, lomustine, and vincristine (TPCV) (2 patients), and Baby POG (1 patient). Twenty-two patients were treated with focal radiotherapy with a total dose of 54–59 Gy to the tumor. Median age at diagnosis of patients in the chemotherapy group was 3.24 years (0.5–15.58) and median age at treatment was 5 years (0.5–15.58). Patients in the radiotherapy group were significantly older with median age at diagnosis of 11.79 years (1.08–19.64) and median age at treatment of 11.89 years (3.08–17.64). Tumor location and treatment timing (upfront/on progression) were comparable between chemotherapy and radiation groups (Supplemental Table II). Five-year PFS and OS for patients receiving chemotherapy and radiotherapy were $53 \pm 12\%$ and $93 \pm 4\%$ and $66 \pm 11\%$ and $83 \pm 6\%$, respectively, with no significant difference between the two groups ($P = 0.26$ and 0.3, respectively, Fig. 2C,D).

Four patients treated with adjuvant therapy died during follow-up. One out of the 21 children treated with chemotherapy died due to tumor transformation. The patient was treated with the TPCV protocol for a biopsied low grade glioma in the prepontine region. Eighteen months after completion of treatment (3 years after diagnosis) his tumor progressed and revealed clinical and imaging features of DIPG. Postmortem analysis revealed a high grade glioma. Three of 22 patients treated with radiotherapy died. Two patients died due to progression of lesions involving the pons, in these two cases lesions were suggestive of DIPG on radiology but biopsy revealed low grade glioma. The third patient had a cervicomedullary lesion and died due to aspiration pneumonia with no evidence of tumor progression.

DISCUSSION

Data extraction from our large cohort of brainstem patients allowed us to document unbiased incidence of different pathological and clinical subtypes as well as tumor occurrence within each brainstem region. Our data demonstrate a highly significant correlation between tumor location and malignant behavior. Tumors without pontine involvement were low grade in 98.3% of the cases (57/58) whereas tumors involving the pons were low grade in only 25% of the cases (36/148). Ninety-nine percent of the high grade tumors within our cohort involved the pons (112/113). Presence of a high grade tumor conferred poor prognosis with only 4/112 patients in our cohort being long-term survivors.

Prior studies delineated risk groups among brainstem tumor patients based on tumor pathology, location, growth extent, growth direction, and multiple other imaging-based features [12–15,17]. Though this allowed identification of risk group, patients' grading was frequently cumbersome, terminology was study specific and some of the criteria used to differentiate between low- and high-risk groups were subjective. In agreement with our results all these studies pointed to diffuse pontine
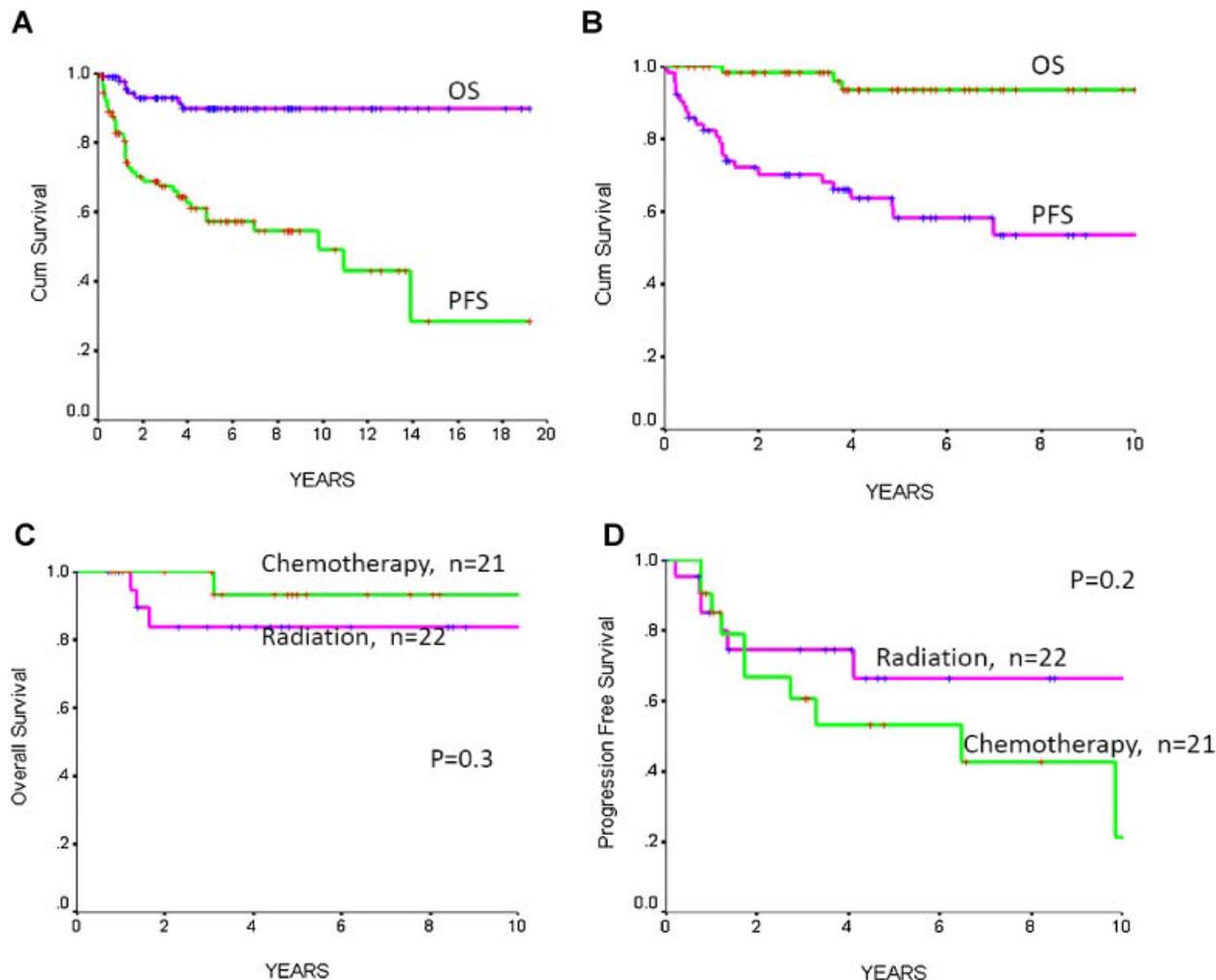
Fig. 2. Five years overall and progression-free survival for brainstem low grade tumor patients. **A**: Outcome of all patients with brainstem low grade tumors (N = 96, OS = 89 ± 5%, PFS = 57 ± 3%). **B**: Outcome of children with brainstem low grade tumors undergoing observation (N = 63, OS = 93 ± 3%, PFS = 57 ± 5%). **C**: Overall survival following radiotherapy compared to chemotherapy (83 ± 6% and 93 ± 4%, respectively). **D**: Progression-free survival following radiotherapy compared to chemotherapy (66 ± 11% and 53 ± 12%, respectively). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/pbc]

involvement as the highest risk group, but none of these earlier studies identified the rarity of high grade lesions in non-pontine tumors [12–15,17,18]. Fisher et al. [17] summarized data regarding 76 patients with brainstem glioma. In agreement with our findings, tumor grade was significantly associated with location. Out of 48 cases with available pathological specimens, fibrillary astrocytomas (FA) were observed outside the pons only twice, whereas pilocytic astrocytoma (PA) occurred throughout the brainstem. Pathology was highly predictive of survival with 5-year overall survival (OS) of 95% and 15% for PA and FA, respectively. Pontine location was found to be an independent negative prognostic factor. Two more recent studies did not demonstrate similar findings [19,20]. Both these studies included 27–48% adult patients, possibly confounding results. Our study, summarizing data from a large pediatric cohort, suggests that unlike pontine lesions, tumors not involving the pons may be considered as low grade ones and their management as BSLGT is appropriate, even in the absence of a biopsy sample.

Initial management of BSLGT is still controversial. Complete tumor resection which is the mainstay of treatment for low grade glioma in other brain locations, is associated with a risk of significant morbidity in the context of brainstem tumors. Jallo et al. [21] described an extremely high morbidity rate following 41 total or subtotal cervicomedullary surgeries. Following resection, 41% of the patients required tracheostomy insertion and 46% required gastrostomy. Due to the high morbidity rate a cautious approach, consisting of tumor biopsy or limited debulking is widely used, thus most patients are left with residual disease.

Data regarding outcome of different treatment modalities for patients with residual BSLGT are limited and variability of treatment between centers precludes meaningful conclusions. Our findings suggest a favorable outcome of upfront observation as first line treatment in patients with BSLGT. Within our cohort 46% of the patients with biopsied/partially resected tumors had no progression during observation of their residual tumor, and active treatment was not needed. Furthermore, treatment delay to time of

progression (median 1.21 years, range 0.05–13.95) conferred no survival disadvantage for these patients. In agreement with our results, Weiner et al. [22] reported PFS and OS of 60% and 89% in 39 patients with partially resected cervicomedullary lesions with varied pathologies undergoing observation. Similar outcomes were reported by other authors [23,24]. Furthermore, Fouladi et al. [25] summarized similar favorable results of observation in optic pathway glioma. Many physicians consider immediate treatment (radiation most often) because of the risk of neurological deficit associated with progression. Our observation may contribute to a shift in the paradigm as observation appears to be an appropriate and safe alternative.

A significant number of patients with residual low grade glioma, require administration of chemotherapy or radiotherapy to control disease progression. Studies summarizing outcome of low grade glioma patients receiving adjuvant therapy in other locations report 12–78% 5-year EFS following chemotherapy and 63–87% 3- and 5-year EFS, respectively, following radiotherapy [25–27]. Tumors included in these studies involve the optic pathway/hypothalamus in most cases. Patients treated with radiotherapy are frequently older than those treated with chemotherapy due to the increased risk of radiation related side effects in early childhood. Since early age is associated with higher progression rate in patients with low grade glioma [28], comparison of outcome may be biased, suggesting a worse outcome for chemotherapy treated patients. In our cohort, no significant difference in 5 years OS or EFS was found between similar groups of chemotherapy and radiotherapy treated patients. Taken together, these observations suggest that a staged approach to BSLGT without aggressive surgery or upfront radiation therapy is not associated with survival disadvantage.

Since survival rate is high in patients with BSLGT, long-term functional outcome of these patients is critical. Data regarding long-term toxicity of radiotherapy were reported in multiple studies. However, very few patients with BSLGT were included in these studies [26,29]. Edwards et al. reported excellent short-term functional outcome following irradiation in five patients with focal brainstem astrocytomas [30]. Unfortunately these data were not available within our study and further research as well as longitudinal studies evaluating treatment sequelae in other patients cohorts are needed for this group of patients.

This study has the limitation of being a retrospective study as it reports the outcome of patients diagnosed and followed over the last 25 years, thus, data may be confounded due to changes in diagnosis and treatment techniques that took place during that time and further studies are needed to confirm our results.

In summary, we demonstrate that non-pontine brainstem lesions are almost invariantly BSLGT. As such, initial observation followed by treatment at progression, may be warranted. Prospective multicenter studies and longer follow-up for functional outcome are needed to better define role of chemotherapy and radiotherapy in the treatment of pediatric brainstem tumors.

REFERENCES

1. Frazier JL, Lee J, Thomale UW, et al. Treatment of diffuse intrinsic brainstem gliomas: Failed approaches and future strategies. J Neurosurg 2009;3:259–269.
2. Farwell JR, Dohrmann GJ, Flannery JT. Central nervous system tumors in children. Cancer 1977;40:3123–3132.
3. Littman P, Jarrett P, Bilaniuk LT, et al. Pediatric brain stem gliomas. Cancer 1980;45:2787–2792.
4. Berger MS, Edwards MS, LaMasters D, et al. Pediatric brain stem tumors: Radiographic, pathological, and clinical correlations. Neurosurgery 1983;12:298–302.
5. Tomita T, McLone DG, Naidich TP. Brain stem gliomas in childhood. Rational approach and treatment. J Neurooncol 1984;2:117–122.
6. Fangusaro J. Pediatric high-grade gliomas and diffuse intrinsic pontine gliomas. J Child Neurol 2009;24:1409–1417.
7. Mohanty A. Role of surgery in brainstem gliomas. Neurol India 2009;57:231–232.
8. Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: Critical review of clinical trials. Lancet Oncol 2006;7:241–248.
9. Pollack IF, Hoffman HJ, Humphreys RP, et al. The long-term outcome after surgical treatment of dorsally exophytic brainstem gliomas. J Neurosurg 1993;78:859–863.
10. Bowers DC, Georgiades C, Aronson LJ, et al. Tectal gliomas: Natural history of an indolent lesion in pediatric patients. Pediatr Neurosurg 2000;32:24–29.
11. Stark AM, Fritsch MJ, Claviez A, et al. Management of tectal glioma in childhood. Pediatr Neurol 2005;33:33–38.
12. Stroink AR, Hoffman HJ, Hendrick EB, et al. Diagnosis and management of pediatric brain-stem gliomas. J Neurosurg 1986;65:745–750.
13. Epstein F. A staging system for brain stem gliomas. Cancer 1985;56:1804–1806.
14. Barkovich AJ, Krischer J, Kun LE, et al. Brain stem gliomas: A classification system based on magnetic resonance imaging. Pediatr Neurosurg 1990;16:73–83.
15. Fischbein NJ, Prados MD, Wara W, et al. Radiologic classification of brain stem tumors: Correlation of magnetic resonance imaging appearance with clinical outcome. Pediatr Neurosurg 1996;24:9–23.
16. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. World Health Organization classification of tumours of the central nervous system, 4th edition. Lyon: IARC; 2007.
17. Fisher PG, Breiter SN, Carson BS, et al. A clinicopathologic reappraisal of brain stem tumor classification. Identification of pilocystic astrocytoma and fibrillary astrocytoma as distinct entities. Cancer 2000;89:1569–1576.
18. Epstein F, Wisoff JH. Intrinsic brainstem tumors in childhood: Surgical indications. J Neurooncol 1988;6:309–317.
19. Ueoka DI, Nogueira J, Campos JC, et al. Brainstem gliomas—Retrospective analysis of 86 patients. J Neurol Sci 2009;281:20–23.
20. Combs SE, Steck I, Schulz-Ertner D, et al. Long-term outcome of high-precision radiotherapy in patients with brain stem gliomas: Results from a difficult-to-treat patient population using fractionated stereotactic radiotherapy. Radiother Oncol 2009;91:60–66.
21. Jallo GI, Shiminski-Maher T, Velazquez L, et al. Recovery of lower cranial nerve function after surgery for medullary brainstem tumors. Neurosurgery 2005;56:74–77. discussion 78.
22. Weiner HL, Freed D, Woo HH, et al. Intra-axial tumors of the cervicomedullary junction: Surgical results and long-term outcome. Pediatr Neurosurg 1997;27:12–18.
23. Pollack IF, Pang D, Albright AL. The long-term outcome in children with late-onset aqueductal stenosis resulting from benign intrinsic tectal tumors. J Neurosurg 1994;80:681–688.
24. Robertson PL, Allen JC, Abbott IR, et al. Cervicomedullary tumors in children: A distinct subset of brainstem gliomas. Neurology 1994;44:1798–1803.
25. Fouladi M, Wallace D, Langston JW, et al. Survival and functional outcome of children with hypothalamic/chiasmatic tumors. Cancer 2003;97:1084–1092.

26. Merchant TE, Li C, Xiong X, et al. Conformal radiotherapy after surgery for paediatric ependymoma: A prospective study. Lancet Oncol 2009;10:258–266.

27. Marcus KJ, Goumnerova L, Billett AL, et al. Stereotactic radiotherapy for localized low-grade gliomas in children: Final results of a prospective trial. Int J Radiat Oncol Biol Phys 2005;61:374–379.

28. Janss AJ, Grundy R, Cnaan A, et al. Optic pathway and hypothalamic/chiasmatic gliomas in children younger than age 5 years with a 6-year follow-up. Cancer 1995;75:1051–1059.

29. Merchant TE, Conklin HM, Wu S, et al. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: Prospective evaluation of cognitive, endocrine, and hearing deficits. J Clin Oncol 2009;27:3691–3697.

30. Edwards MS, Wara WM, Ciricillo SF, et al. Focal brain-stem astrocytomas causing symptoms of involvement of the facial nerve nucleus: Long-term survival in six pediatric cases. J Neurosurg 1994;80:20–25.