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Pediatric Neurosurgery; Dec 2003; 39, 6; Research Library
pg. 314

Original Paper

Pediatric Neurosurgery

Pediatr Neurosurg 2003;39:314–322
DOI: 10.1159/000075260

Received: February 21, 2003
Accepted: May 27, 2003

Surgical Outcome following Resection of Contrast-Enhanced Pediatric Brainstem Gliomas

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Key Words
Pediatric brainstem tumors · Radiology · Pathology · Surgery

Abstract
Background: The role of surgery in the management of gadolinium-enhancing pediatric brainstem lesions on magnetic resonance imaging (MRI) has been a matter of open debate. This clinical series correlates radiological and pathological findings to assess the role of contrast enhancement as an indication for surgery with respect to clinical outcome. ***Methods:*** We retrospectively reviewed the charts of all pediatric patients admitted to the Johns Hopkins Hospital with a diagnosis of a brainstem tumor between January 1985 and December 2000. ***Results:*** There were a total of 89 patients who met the inclusion criteria. Fifty-seven patients (64.0%) underwent surgical resection while 32 (36%) were treated with radiation and/or chemotherapy. Of the surgical candidates, 57 (100%) had an accompanying MRI scan significant for an enhancing lesion in the midbrain, pons or the medulla. The pathology was consistent with juvenile pilocytic astrocytoma in 30 patients (52.6%) and glioblastoma multiforme in 12 patients (21.1%). The remaining cases consisted of 10 patients (17.5%) with fibrillary astrocytomas, 3 (5.3%) with gangliogliomas, 1 (1.8%) with an oligodendroglioma and 1 (1.8%) with a primitive neuroectodermal tumor. A total of 29 patients had a total surgical resection, 8 a near total resection (>90%), 15 a subtotal resection (50–90%) and 5 a partial resection (<50%). The progression-free survival of all patients was 71.9% at 3 years and 45.6% at 5 years. ***Conclusions:*** This case series illustrates that contrast-enhanced MRI has positive prognostic value in the management of pediatric brainstem gliomas. In our study, the majority of enhancing tumors were low grade and amenable to surgical intervention. Consequently, we recommend surgical resection and pathological diagnosis of all enhancing brainstem tumors with adjuvant therapy reserved for recurrent or unresectable cases.

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Introduction

Pediatric brain tumors arise at an annual rate of 3.6 per 100,000 children, with brainstem gliomas comprising 10–20% [1, 2]. Neoplasms localized to the brainstem tend to present at an average age of 6–9 years. They carry no predilection for race, gender or geographic location [3, 4], with one report proposing a possible genetic basis [5]. This heterogeneous group of tumors covers the spectrum of prognosis and efficacy of treatment. One form of classi-

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1016–2291/03/0396–0314$19.50/0

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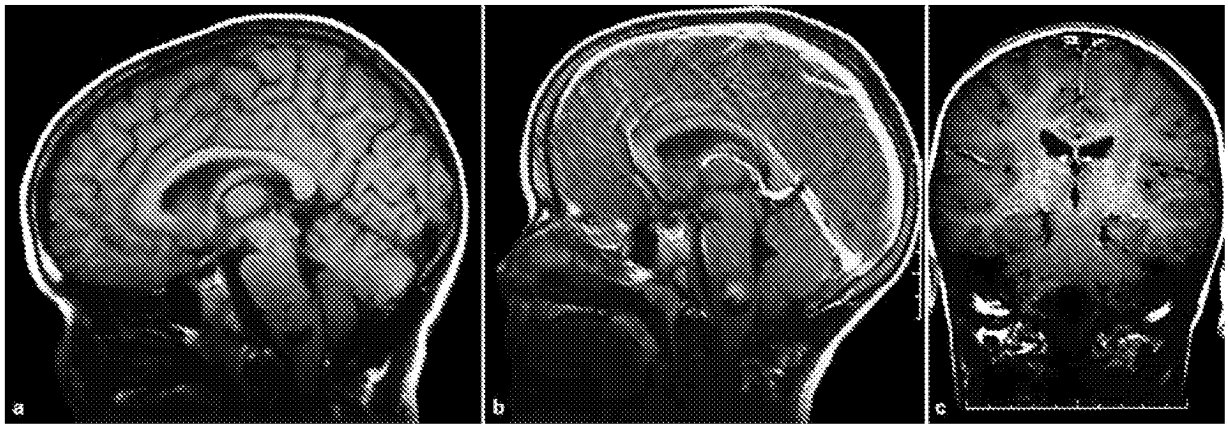

Fig. 1. A representative brain MRI without (**a**) and following (**b**) contrast administration, showing an enhancing brainstem lesion, a pilocytic astrocytoma. A postoperative coronal image is shown in **c**.

fication divides these lesions into diffuse and focal brainstem tumors [2, 5].

The majority of brainstem gliomas infiltrate the surrounding brain [6, 7] and are termed diffuse pontine gliomas. Histologic diagnosis is usually consistent with well-differentiated fibrillary astrocytoma (WHO grade II) or its higher-grade counterpart, anaplastic astrocytoma (WHO grade III). Malignant growth by interweaving between normal axons renders this group of tumors unfavorable to surgical intervention. As such, conventional radiotherapy and/or chemotherapy provide only temporary disease control with inevitable neurological deterioration.

In contrast to typical gliomas, certain brainstem tumors demonstrate substantially improved outcome following aggressive surgical resection. These focal tumors are believed to account for a small proportion of brainstem gliomas. One such tumor, the juvenile pilocytic astrocytoma (JPA), carries an especially favorable prognosis [8]. Given the generally benign nature of JPAs, it is important to distinguish between diffuse and focal brainstem tumors in order to provide the best medical and surgical care.

Since diffuse and focal brainstem gliomas exhibit different behaviors, we reviewed all patients presenting to our institution over the past 15 years with brainstem lesions. Our aim was to correlate the radiological and pathological findings and to assess the role of contrast enhancement as an indicator of potential management and surgical outcome.

Patients and Methods

We retrospectively reviewed the charts of all patients admitted to the Johns Hopkins Hospital between January 1985 and December 2000 with the diagnosis of a brainstem tumor. The definition of a brainstem tumor was limited to intra-axial lesions within the midbrain, pons or the medulla (fig. 1). Patients were excluded if they had received prior surgical intervention or adjuvant chemo/radiotherapy. For all surgical procedures, our approach was via a subtemporal, suboccipital or midline incision. We routinely utilized microsurgical techniques as well as electrophysiological monitoring.

For determination of treatment efficacy, survival was the primary endpoint. Survival was plotted using Kaplan-Meier survival analysis and statistical significance was determined by the Kruskal-Wallis nonparametric analysis of variance followed by the nonparametric analog of the Newman-Keuls multiple comparison test [9].

Neurologic outcome was assessed for each surgical patient at the time of discharge and was based on the Glasgow Outcome Scale. At 6-month follow-up, each patient was also assessed based on the Karnofsky scale.

Results

Patient Demographics

A total of 89 patients were identified. There were 46 males and 43 females who ranged in age from 3 months to 20 years with an average age of 7.3 years at time of diagnosis. The majority (72; 80.9%) presented with complaints of headache, nausea, vomiting, ataxia and cranial neuropathies (table 1).

Fifty-seven children (64.0%) underwent surgical resection, while the remaining 32 (36.0%) were treated medically, with radiation and/or chemotherapy. Of the surgical candidates, 57 (100%) had an accompanying magnetic

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Table 1. Patient demographics

a General characteristics of the total patient population (n = 89)

Males	46
Females	43
Age (mean), years	7.3 (range 3 months to 20 years)
Enhancing lesions	57 (64)
Nonenhancing lesions	32 (36)

b Surgical group of enhancing lesions (n = 57)

	Location		
	midbrain	pons	medulla
Total	7 (12)	21 (37)	29 (51)
Symptoms			
Headache	4 (57)	17 (81)	26 (90)
Nausea/vomiting	2 (29)	15 (71)	24 (83)
Ataxia	2 (29)	18 (86)	12 (41)
Hemiparesis	3 (43)	16 (76)	5 (17)
CN palsy			
III	3 (43)	6 (28)	–
VI	1 (14)	16 (76)	14 (48)
VII	1 (14)	14 (66)	10 (34)
VIII	–	3 (14)	1 (5)
IX/X	–	1 (5)	7 (24)
Exophytic	1 (14)	6 (28)	10 (35)
Nonexophytic	6 (86)	15 (71)	19 (65)

Figures in parentheses represent percentages. CN = Cranial nerve.

resonance imaging (MRI) scan significant for an enhancing lesion within the midbrain, pons or medulla. Forty-four of the 57 patients (77%) had diffuse rather than focal T2 signal changes within the brainstem on magnetic resonance studies.

A total of 29 patients had a total surgical resection, 8 a near total resection (>90%), 15 a subtotal resection (50–90%) and 5 a partial resection (<50%). The degree of resection was determined on a postoperative MRI with contrast obtained in the first 48 h after surgery.

Surgical Histopathology

The pathology was consistent with JPA in 30 patients (52.6%) and glioblastoma multiforme (GBM) in 12 patients (21.1%). The remaining cases consisted of 10 patients (17.5%) with fibrillary astrocytomas, 3 (5.3%) with ganglioglioma, 1 (1.8%) with an oligodendroglioma and 1 (1.8%) with a primitive neuroectodermal tumor (PNET) (fig. 2).

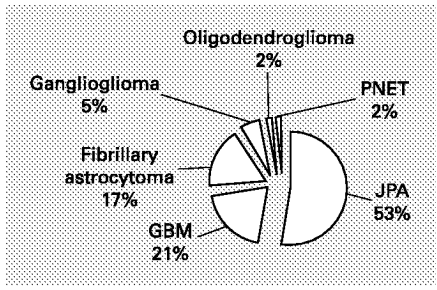

Fig. 2. Pathologic distribution of enhancing tumors in the surgical group.

Of the 30 patients who harbored JPAs, 22 (73%) had diffuse T2 signal abnormalities within the brainstem on MRI scans. Twenty-five had a total resection while 5 received a near total resection. There were 11 dorsally exophytic tumors (36%). Over the course of 10 years, 16 patients had evidence of local recurrence and were treated by additional surgery and adjuvant radiotherapy. Twelve patients were diagnosed with GBM, 7 of whom had a subtotal resection and 5 a partial resection. All of these patients went on to receive postoperative radio/chemotherapy. Of the 10 patients with fibrillary astrocytomas, 2 had a near total resection while 8 had a subtotal resection. Four received additional radiotherapy, 2 underwent chemotherapy and 4 more had both. Finally, there were 3 patients with gangliogliomas, 1 with an oligodendroglioma and 1 with a PNET. With the exception of a single oligodendroglioma patient, all received total resection. Two patients with gangliogliomas and 1 with oligodendroglioma also received postoperative radiotherapy.

Patient Survival

The Kaplan-Meier survival curves illustrate the overall disease progression of patients with nonenhancing versus contrast-enhancing tumors (fig. 3). The median survival for patients with nonenhancing lesions was 17 months versus >120 months for patients with enhancing tumors ($p < 0.001$).

In the surgical group, the survival rates were directly related to tumor pathology (fig. 4). All of the patients diagnosed with JPAs are alive after 10 years. For patients with GBM, the median survival was 8 months versus 22 months ($p < 0.005$) for those with fibrillary astrocytoma. A total of 3 patients with gangliogliomas had a median survival of 3 years, with 1 long-term survivor. There is 1 patient with a PNET who is alive after 10 years and 1 with an oligodendroglioma who was lost to follow-up.

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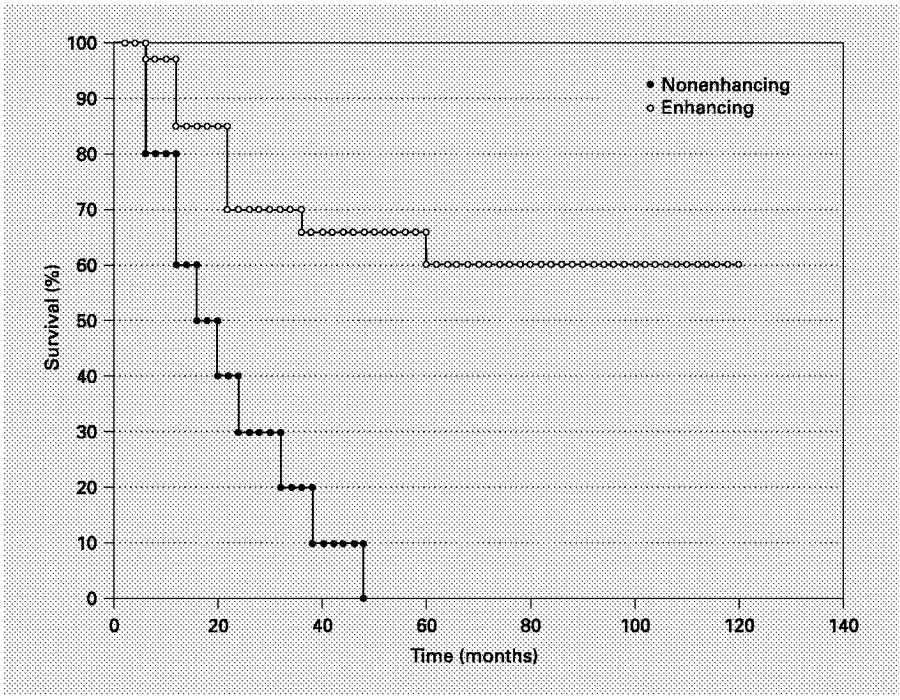

Fig. 3. Kaplan-Meier survival curves for enhancing and nonenhancing brainstem tumors. The median survival for patients with nonenhancing lesions was 17 months versus >120 months for patients with enhancing tumors ($p < 0.001$).

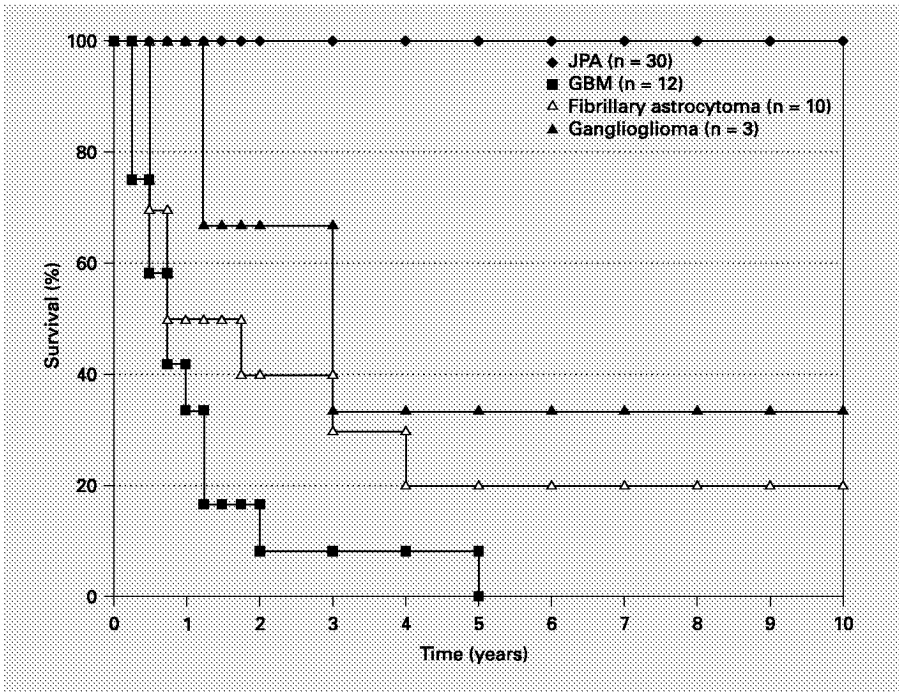

Fig. 4. Kaplan-Meier survival curves for different enhancing brain tumors based on histopathology.

A total of 28 patients (49%) received additional postoperative adjuvant therapy. Sixteen patients (57%) with JPA were treated with radiotherapy alone. An additional 12 (43%) with grade II–IV astrocytomas received radiation, chemotherapy or both. Of the grade II–IV astrocytoma patients treated with radiation therapy alone, the median survival was 20 months versus 6 months for patients receiving chemotherapy alone (fig. 5; $p < 0.001$). The median survival following combination radiotherapy plus chemotherapy was also significantly longer than for

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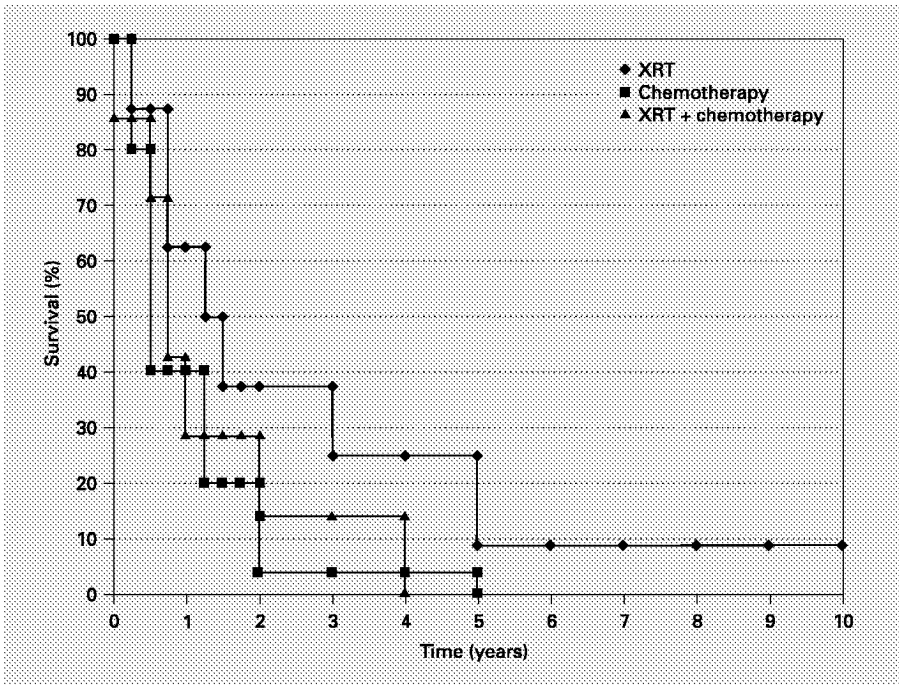

Fig. 5. Kaplan-Meier survival curves for patients with grade II–IV astrocytomas receiving postoperative adjuvant therapy. In the grade II–IV astrocytoma patients treated with radiation therapy alone, the median survival was 20 months versus 6 months for patients receiving chemotherapy alone ($p < 0.001$). The median survival following combination radiotherapy (XRT) plus chemotherapy was also significantly longer than for chemotherapy alone (median survival 11 months; $p < 0.006$).

Table 2. Survival by clinical characteristics

Characteristic	3-year overall survival	Log rank p value
Duration of symptoms		
<6 months		
Nonenhancing tumors	1 (3)	<0.005
Enhancing tumors	12 (21)	
>6 months		
Nonenhancing tumors	5 (16)	<0.005
Enhancing tumors	25 (44)	
Location of enhancing tumors		
Midbrain (n = 7)	4 (57)	<0.001
Pons (n = 21)	5 (24)	
Medulla (n = 29)	23 (80)	

Figures in parentheses represent percentages.

chemotherapy alone (median survival 11 months; $p < 0.006$).

The duration of symptoms appeared to make a difference to the overall 3-year survival for both nonenhancing and enhancing lesions. For patients with symptoms lasting less than 6 months prior to diagnosis, the presence of an enhancing lesion was associated with greater survival than for nonenhancing lesions (table 2). The same holds true for patients with symptoms lasting longer than 6 months, where 44% of the patients survived for 3 years. Furthermore, symptom duration of less than 6 months was associated with an overall worse survival rate for patients with both nonenhancing and enhancing brainstem lesions. Finally, within the category of enhancing tumors, survival was related to the location of the lesion, as 80% of patients with medullary lesions were long-term survivors compared to 57% of those with midbrain lesions and only 24% of patients with pontine tumors (table 2).

Taken together, the progression-free survival of all patients with enhancing brainstem tumors was 71.9% at 3 years and 45.6% at 5 years.

Neurological Outcome

The neurological outcome following resection of the brainstem lesions in the present series is shown in table 3. There was good recovery in 45 patients (78.9%), moderate disability in 10 patients (17.5%), severe disability in 2 patients (3.5%) and vegetative state in 1 patient (1.7%). There were no immediate postoperative deaths.

At 6 months, 40 patients (70%) had a score of 80 or higher on the Karnofsky scale. There were 4 patients (7%) with scores of 60–80, 10 (17.5%) with scores of 40–60 and 3 (5.2%) who scored below 40.

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Table 3. Neurologic outcome

Time point	n
At hospital discharge (GOS)	
GR	45 (78.9)
MD	10 (17.5)
SD	2 (3.5)
VS	1 (1.7)
Dead	1 (1.7)
At 6 months (Karnofsky scale)	
100–80	40 (70.1)
80–60	4 (7.0)
40–60	10 (17.5)
<40	3 (5.2)

Figures in parentheses represent percentages. GOS = Glasgow Outcome Scale; GR = good recovery; MD = moderate disability; SD = severe disability; VS = vegetative state.

Discussion

Intra-axial brainstem tumors have been traditionally regarded as surgically inaccessible lesions with a uniformly poor prognosis. However, increasing data [5, 10–13] indicate that distinct subgroups of brainstem tumors may be amenable to surgical intervention. To further address this question, we reviewed our experience in the operative management of 57 patients with intra-axial brainstem tumors. In particular, we focused on the role of gadolinium contrast enhancement at the time of preoperative MRI as a possible predictor of histology and patient survival.

Although several groups have recently looked at the prognostic value of contrast-enhanced MRI in brainstem gliomas, the results of those studies have been mixed and confusing. For instance, Moghrabi et al. [14] retrospectively reviewed 26 newly diagnosed pediatric patients with diffuse brainstem glioma and found no difference in the median survival between patients with or without contrast enhancement. Similarly, Albright et al. [8] reviewed 84 pediatric patients with brainstem gliomas and found that tumor enhancement was not associated with any alteration in survival time. However, in the same study, a hypodense tumor prior to contrast administration or a tumor that involved the entire brainstem correlated poorly with long-term survival.

In our series, we identified a total of 89 patients who presented with a newly diagnosed intra-axial brainstem lesion. Of these, 32 had nonenhancing lesions on MRI while 57 had lesions that enhanced with gadolinium. While the former group was treated with standard radiation and/or chemotherapy for a presumed diffuse brainstem glioma, the latter 57 patients underwent surgical intervention. Our results indicate that enhancing brainstem lesions occur within a distinct group of patients, the majority of whom have low-grade tumors. This finding is in contrast to the studies discussed above. One possible reason for this discrepancy is that Moghrabi et al. [14] looked only at contrast enhancement within diffuse pontine gliomas, ignoring all other brainstem tumors. Another explanation could lie in the fact that Albright et al. [8] relied exclusively on computed tomography. Since MRI is known to be more sensitive in detecting infratentorial enhancing lesions [15–17], it may be that a larger percentage of patients with benign tumors were missed in that study. We utilized only MRI in newly diagnosed patients, and our results suggest that enhancement may serve as a potential predictor of pathology and thus the need for early surgical intervention.

Previously, Barkovich et al. [18] developed a classification scheme for brainstem gliomas based on T2-weighted MRI. In their study involving 87 pediatric patients with brainstem gliomas, the authors found that diffuse tumors were associated with diffuse T2 abnormalities while focal gliomas had a pattern of enhancement that corresponded only to the area of T2 signal abnormality. Our data show that the majority of patients with enhancing brainstem tumors had diffuse rather than focal T2 signal abnormalities. Moreover, the majority of patients with focal tumors such as JPA had diffuse T2 changes rather than focal abnormalities corresponding to the area of gadolinium enhancement. Although we do not have a clear reason for the discrepancy between the two studies, we postulate that the observed differences could be a function of numerous factors, including the size of the tumor, the timing of the MRI and the duration of treatment with steroids prior to MRI imaging. Clearly, more controlled studies are needed to further clarify this important issue, which can have an impact on the selection of patients deemed appropriate for surgery.

The Kaplan-Meier survival curve based on the histopathological diagnosis of the tumors shows the excellent prognosis of patients with pilocytic astrocytomas. This finding further corroborates the benign nature of these lesions [19, 20]; however, our study also adds new data regarding the intra-axial nature of JPAs without an exo-

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phytic component. Of the 30 patients with JPAs, only 11 presented with radiologically exophytic tumors (36%). The remainder were completely circumscribed within the midbrain, pons or the medulla. It would thus appear that JPAs can assume many different shapes, and their true incidence may be underestimated if one only considers these lesions in the context of an exophytic component. Indeed, JPAs have been thought to represent only 20–30% of pediatric brainstem tumors [21, 22], compared to the 50% in our study. Nevertheless, our findings – confirmed with a pathologic diagnosis – would support the notion that these tumors may occur with a greater incidence than previously thought. Since JPAs are benign, slow-growing and treatable tumors, we propose that all enhancing brainstem tumors warrant surgical exploration.

One important argument that can be raised with respect to surgical intervention relates to the relatively high level of morbidity reported in this series (17.5% of patients had moderate disability, 3.5% severe disability and 1.7% vegetative state). Certainly, one possible alternative to open surgical resection is stereotactic biopsy followed by focal radiotherapy/radiosurgery. The feasibility and safety of stereotactic biopsy involving brainstem lesions are well established [23–25], as is the benefit of radiosurgery for the treatment of brainstem tumors [26–30]. Nevertheless, our high level of morbidity must be interpreted in the context of preoperative neurologic deficits. Twenty-four of our patients (42%) presented with some degree of hemiparesis. Thirty-seven (65%) had deficits involving CN VII–X. The majority improved followed surgical resection and decompression of the brainstem lesion. As a result, the benefits of stereotactic biopsy and radiosurgery must be carefully weighed in the context of a benign lesion which can be safely resected with overall acceptable levels of morbidity and mortality.

Our results provide further insight into the prognosis of patients with brainstem lesions. Clearly, those patients with rapid onset of symptoms (<6 months) have a poorer outcome than patients with a prolonged clinical presentation (>6 months). Regardless of the timing, however, the presence of an enhancing lesion correlates with improved survival as compared with nonenhancing lesions. Furthermore, for patients with enhancing tumors, the location of the tumor within the brainstem is predictive of long-term survival. Nearly 80% of the children in our study who presented with medullary enhancing lesions were alive at 3 years versus only 57% of those with midbrain lesions and only 24% of those with pontine lesions. These findings further confirm the generally benign nature of enhancing brainstem tumors located within the medulla and suggest that tumors involving the midbrain or the pons are more aggressive or simply invasive into vital cardiorespiratory centers of the brainstem.

In contrast to JPAs, patients with a GBM have a relatively poor prognosis. Despite aggressive treatment with both adjuvant radiation and chemotherapy, all of these patients eventually die as result of this disease. As our study indicates, the poor survival of patients with brainstem GBMs mirrors that of patients with supratentorial GBMs. The other single large group in our cohort, patients with fibrillary astrocytomas, had a longer survival than patients with GBMs. In fact, the median survival of these patients was 22 months, and 20% are long-term survivors at 10 years. Three of our patients with gangliogliomas were also followed in this study and one is still alive at 10 years. The remaining two patients, 1 with a PNET and 1 with oligodendroglioma, represent insufficient data to draw any meaningful conclusions.

In order to compare the effects of radiotherapy and/or chemotherapy on the survival of pediatric patients with brainstem gliomas, we further analyzed all of the astrocytoma patients in our study based on the respective treatment strategy. While all patients ultimately succumbed to their disease, only radiotherapy appeared to show any potential treatment benefit. Indeed, patients treated with chemotherapy and radiotherapy fared worse than patients treated with radiotherapy alone, and chemotherapy by itself offered the least benefit of all. While there is some evidence that chemotherapy is beneficial for opticohypothalamic low-grade gliomas [31–35], no data exist with regard to similar tumors located in the brainstem. Overall, our data further support previous reports [36–39] on the beneficial aspects of adjuvant radiotherapy and show no role for additional chemotherapy in the management of patients with diffuse gliomas.

While the lack of success with chemotherapy in the treatment of brainstem tumors is becoming increasingly more apparent [40–43], an increasing number of studies have focused on the combination of chemo- and radiotherapy. Recently, Lopez-Aguilar et al. [44] tested a preir-radiation dose of ifosfamide, carboplatin and etoposide for the treatment of anaplastic astrocytoma and GBM and found that while it exerted a small effect in supratentorial tumors, brainstem tumors responded poorly to treatment. Similarly, results from a Brazilian cooperative study utilizing high-dose tamoxifen and radiotherapy in patients with diffuse brainstem gliomas found no significant change in the overall prognosis of these patients [45]. The effects of carboplatin and etoposide have been equally

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disappointing, with neither agent showing any improvement in survival when administered with radiotherapy [46]. Moreover, a recent study by Freeman et al. [47] has shown a possible detrimental effect of a combined chemotherapy-radiotherapy approach in children with diffuse brainstem gliomas, suggesting that radiotherapy may remain the mainstay treatment of patients with these aggressive tumors.

Conclusions

Surgery of primary intra-axial tumors of the brainstem can present serious problems, and until recently, most of these tumors have been considered unremovable and even untreatable. In spite of recent surgical and radiologic advances, the indications for surgery remain controversial.

The main goal of our study was to examine the role of contrast enhancement during MRI and to decide whether it could be used as a potential indicator for surgical intervention. To do so, we operated on all patients who presented with enhancing brainstem tumors. Our results suggest that in the majority of cases, the histology was consistent with a low-grade lesion. Consequently, we propose that there is an important prognostic value in contrast-enhanced MRI and that it should be used routinely when deciding whether or not to proceed with surgical exploration of a brainstem lesion.

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