Brain (2001), **124,** 2528–2539

Brainstem gliomas in adults: prognostic factors and classification

Jean-Sébastien Guillamo,[1] Annick Monjour,[3] Luc Taillandier,[4] Bertrand Devaux,[2] Pascale Varlet,[2] Christine Haie-Meder,[5] Gilles-Louis Defer,[6] Patrick Maison,[7] Jean-Jacques Mazeron,[1] Philippe Cornu[1] and Jean-Yves Delattre[1] for the Association des Neuro-Oncologues d'Expression Française (ANOCEF)

[1]*Service de Neurologie, Service de Radiothérapie, Service de Neurochirurgie, Hôpital Pitié-Salpêtrière and* [2]*Service de Neurochirurgie, Service d'Anatomopathologie, Hôpital Saint-Anne, Paris,* [3]*Service de Neurologie, Hôpital Pasteur, Colmar,* [4]*Service de Neurologie, CHU Nancy, Nancy,* [5]*Service de Radiothérapie, Institut Gustave Roussy, Villejuif,* [6]*Service de Neurologie Dejerine, CHU Côte de Nacre, Caen and* [7]*Service de Pharmacologie clinique, CHU Henri Mondor, Créteil, France*

Correspondence to: Professor J.-Y. Delattre, Service de Neurologie Mazarin, Hôpital Pitié-Salpêtrière, 75651 Paris Cedex 13, France
E-mail: jean-yves.delattre@psl.ap-hop-paris.fr

Summary

In contrast to childhood brainstem gliomas, adult brainstem gliomas are rare and poorly understood. The charts of 48 adults suffering from brainstem glioma were reviewed in order to determine prognostic factors, evaluate the effect of treatment and propose a classification of these tumours. Mean age at onset was 34 years (range 16–70 years). The main presenting symptoms were gait disturbance (61%), headache (44%), weakness of the limbs (42%) and diplopia (40%). Four patterns were identified on MRI, representing non-enhancing, diffusely infiltrative tumours (50%), contrast-enhancing localized masses (31%), isolated tectal tumours (8%) and other patterns (11%). Treatment consisted of partial resection (8%), radiotherapy (94%) and chemotherapy (56%). Overall median survival was 5.4 years. On univariate analysis, the following favourable prognostic factors were identified ($P < 0.01$): age of onset <40 years, duration of symptoms before diagnosis >3 months, Karnofski performance status >70, low-grade histology, absence of contrast enhancement and 'necrosis' on MRI. On multivariate analysis, the duration of symptoms, the appearance of 'necrosis' on MRI and the histological grade of the tumour remained significant and independent prognostic factors ($P < 0.05$). Eighty-five percent of the tumours could be classified into one of the following three groups on the basis of clinical, radiological and histological features. (i) Diffuse intrinsic low-grade gliomas (46%) usually occurred in young adults with a long clinical history before diagnosis and a diffusely enlarged brainstem on MRI that did not show contrast enhancement. These patients were improved by radiotherapy in 62% of cases and had a long survival time (median 7.3 years). Anaplastic transformation (appearance of contrast enhancement, 27%) and relentless growth without other changes (23%) were the main causes of death. (ii) Malignant gliomas (31%) occurred in elderly patients with a short clinical history. Contrast enhancement and necrosis were the rule on MRI. These tumours were highly resistant to treatment and the patients had a median survival time of 11.2 months. (iii) Focal tectal gliomas (8%) occurred in young patients and were often revealed by isolated hydrocephalus. The course was indolent and the projected median survival period exceeded 10 years. In conclusion, adult brainstem gliomas are different from the childhood forms and resemble supratentorial gliomas in adults. Low-grade tumours have a clinicoradiological pattern that is so characteristic that the need for a potentially harmful biopsy is debatable. The optimum timing of treatment for supratentorial low-grade tumours remains unclear. In high-grade gliomas, the prognosis remains extremely poor despite aggressive treatment with radiotherapy and chemotherapy.

Keywords: brainstem; glioma; adult; classification; prognostic factors

Abbreviations: CI = confidence interval; NF1 = neurofibromatosis type 1

Introduction

In children, brainstem gliomas constitute ~10% of brain tumours and are usually classified in three main groups (Farwell *et al.*, 1977; Freeman and Farmer, 1998; Walker *et al.*, 1999). The largest subgroup is diffuse intrinsic pontine glioma, which is characterized by a striking diffuse enlargement of the brainstem on MRI, with or without heterogeneous contrast enhancement, an aspect that obviates the need for biopsy according to many authors (Albright *et al.*, 1993; Constantini and Epstein, 1996). These tumours carry the worst prognosis of any brain tumour in childhood, with a median survival of <1 year (Kaplan *et al.*, 1996; Mandell *et al.*, 1999). The second subgroup (10% of tumours) comprises slow-growing low-grade gliomas arising at the cervicomedullary junction or from the floor of the fourth ventricle (Hoffman *et al.*, 1980; Pollack *et al.*, 1993). These tumours most often have a posterior contrast-enhancing exophytic development that may be amenable to surgical resection (Bricolo *et al.*, 1991; Constantini and Epstein, 1996). Long survival is common and the median survival time is over 5 years. The third subgroup consists of indolent focal tectal gliomas, which are often heralded by hydrocephalus (Squires *et al.*, 1994; Bowers *et al.*, 2000).

In contrast, brainstem gliomas in adults are poorly understood because they are quite unusual, accounting for $<2\%$ of gliomas (White, 1963). Most reported studies belong to an era when MRI was not available at diagnosis (White, 1963; Grigsby *et al.*, 1989; Selvapandian *et al.*, 1999). However, some data suggest that survival is much longer in adults than in children (Linstadt *et al.*, 1991; Landolfi *et al.*, 1998; Selvapandian *et al.*, 1999).

To improve our understanding of the natural history of these tumours, to identify prognostic factors and to propose a scheme of classification for them, a retrospective study of adult brainstem gliomas was undertaken.

Patients and methods

Inclusion criteria

Patients were included if they met the following criteria: (i) they were older than 16 years at the first symptom; (ii) the epicentre of the tumour, defined as the centre of the tumour bulk, was located in the brainstem (midbrain, pons and medulla oblongata) (this criterion excluded tumours originating in the thalamus, the cerebellar peduncles or the cervical spinal cord); (iii) the diagnosis was based on histological confirmation or on clinical history with characteristic MRI appearance, consisting of an infiltrative expansive process, with or without contrast enhancement (when the lesion had contrast enhancement and when an infectious process could not be ruled out, pathological examination of a biopsy was mandatory); and (iv) a complete medical record, including clinical data, repeated MRI, and detailed treatment data, was available.

Ependymomas, which constitute a distinct nosological group, were excluded from the study.

Data collection

The following clinical data were collected: (i) at the time of diagnosis: age, sex, ethnic origin, time between the date of the first symptom and the date of the diagnosis (i.e. duration of symptoms), main symptoms and signs, Karnofski performance status, description of the tumour on MRI (T_1- and T_2-weighted images in at least two planes before and after gadolinium contrast enhancement), and pathological reports when available; (ii) treatment administered at diagnosis of the tumour; (iii) during follow-up: clinical and radiological course, complications (hydrocephalus, haemorrhage, leptomeningeal dissemination, bulbar involvement with swallowing impairment), treatment at recurrence, and date and cause of death or date of the last visit if the patient was alive.

The radiological response to radiotherapy and chemotherapy was reported as: (i) a complete response, i.e. disappearance of all visible tumour; (ii) a partial response, i.e. a decrease of $>50\%$ in the axial cross-section of the greatest surface area (contrast enhancement or T_2 hypersignal for non-enhancing tumours); (iii) progressive disease, i.e. $>25\%$ increase in axial cross-section of the greatest surface area; or (iv) stable disease, i.e. all other situations (Macdonald *et al.*, 1990; Bauman *et al.*, 1999). The response was evaluated while the patients were receiving a stable or decreasing dose of corticosteroids.

Statistical analysis

Survival time was measured from the date of symptom onset to the date of last follow-up or death. Survival was estimated by the Kaplan–Meier method and its 95% confidence interval (CI) by the Rothman method. Survival curves were compared with the log rank test. The following parameters were evaluated for their association with survival: age of onset, sex, duration of symptoms, motor impairment, Karnofski performance status, location of the epicentre of the tumour, contrast enhancement on MRI after gadolinium infusion, MRI evidence of necrosis, histological grade and radiotherapy schedule (conventional versus hyperfractionated). The Cox proportional hazards model was used to test prognostic factors in multivariate analysis. Results are expressed with relative risk and its 95% CI.

Results

Patient population

Between 1985 and 1999, 48 patients from seven centres of the French association of neuro-oncologists [ANOCEF (Association des Neuro-Oncologues d'Expression Française)] fulfilled the criteria described above and were included in the database.

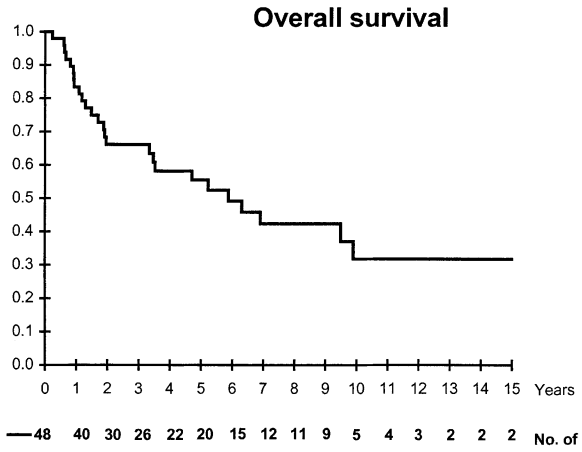


Fig. 1 Kaplan–Meier survival curve for the 48 patients. The median survival was 5.4 years and 3-year survival was 66% (95% CI 52–78%).

Overall survival and general characteristics of the population

Mean follow-up was 5 years (range 3 months to 22 years) and 26 (54%) patients were dead at the time of analysis. Overall median survival for the entire group was 5.4 years (Fig. 1) and 3-year survival was 66% (95% CI 52–78%). Mean age at onset was 34 years (range 16–70, median 29 years); there was a trend towards a biphasic age distribution, with a first peak in the third decade and a second peak in the sixth decade. An age of >40 years at diagnosis was associated with a significantly shorter survival time compared with a younger age ($P = 0.009$; Fig. 2). There was a predominance of males (33 males/15 females) but sex was not related to survival ($P = 0.42$). The medical histories revealed that three patients (6%) had neurofibromatosis type 1 (NF1) and one patient with a pathologically proven brainstem oligodendroglioma had received cranial radiotherapy (15 Gy) 17 years earlier (at the age of 1 year) for histiocytosis X of the occipital bone.

Clinical presentation

Median Karnofski performance status at diagnosis was 80 (range 50–100). Performance status ⩽70 was associated with a shorter survival time ($P = 0.002$; Fig. 2). The median symptom duration before diagnosis was 4 months (range 1 week to 7 years). The onset of the disease was sudden (stroke-like) for five patients, and was related in three of them to intratumoral haemorrhage. Among the other patients, 20 (42%) had a short duration of symptoms (<3 months) and 23 (48%) had a long duration of symptoms (>3 months) before diagnosis, a feature strongly related to survival ($P < 0.0001$; Fig. 2). The main symptoms and signs at presentation are presented in Table 1. Briefly, gait disturbance (61%), due to ataxia and/or weakness of the lower limbs, was the most frequent complaint, followed by diplopia (40%) and diffculty in swallowing (15%). Isolated facial paresis,

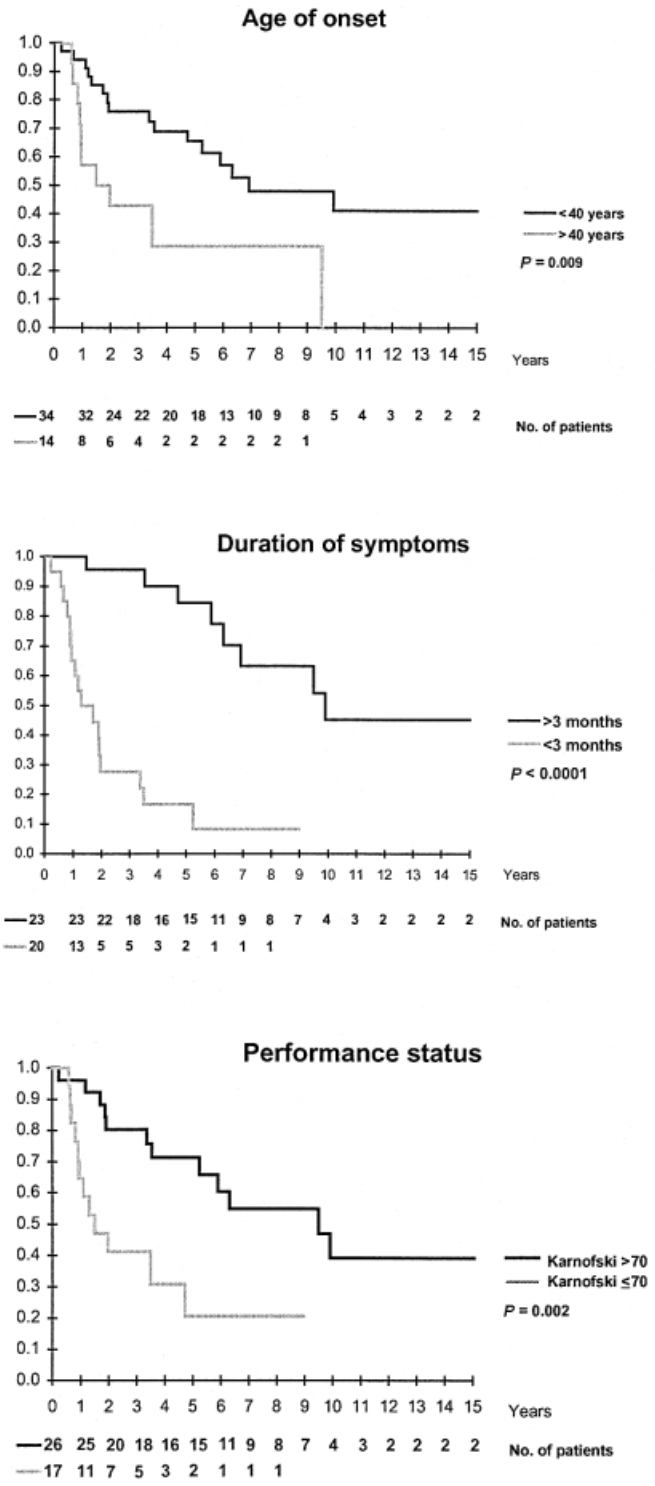


Fig. 2 Comparison of Kaplan–Meier survival curves according to clinical prognostic factors. Age of onset <40 years, symptom duration >3 months and Karnofski performance status >70 were significantly associated with longer survival (log-rank test).

lasting several months before diagnosis, occurred in seven cases (15%) and was associated with hemifacial spasm in five cases. Of interest is one patient who presented with fluctuating weakness of the upper limbs, with fatigability and

Table 1 *Symptoms and signs at presentation (*n = *48)*

Symptoms (%)	
Gait disturbance	61
Headache	44
Weakness of the limbs	42
Diplopia	40
Dysphagia	15
Vomiting	12
Deafness	10
Paraesthesia	6
Tinnitus	6
Nasal voice	6
Hiccup	2
Signs (%)	
Cranial nerve involvement	87
VII	37
VI	33
VIII	33
IX, X, XI	33
V	21
III	4
IV	2
XII	2
Pyramidal signs	58
Cerebellar syndrome	37
Nystagmus	31
Sensory loss	25

Table 2 *MRI features at presentation (*n = *48)*

MRI characteristics (%)	
T_1-weighted images	
Hyposignal	98
Isosignal	2
T_1-weighted images with gadolinium infusion	
Contrast enhancement	46*
Contrast enhancement with 'necrosis'	20*
T_2-weighted images	
Hypersignal	100
Heterogeneous	75
Homogeneous	25
General patterns	
Non-enhancing, diffusely infiltrative	50
Enhancing localized mass	31
Isolated tectal tumour	8
Others	11
Posterior exophytic	2
Diffusely infiltrative with enhanced nodule	4
Miscellaneous unclassified	5
Associated features	
Mass effect	80
Hydrocephalus	15
Exophytic	12
Prepontine	10
Posterior	2
Cystic component	12
Haemorrhage	6

*Contrast enhancement and 'necrosis' seen on MRI were associated with worse prognosis (Fig. 6). 'Necrosis' was defined as a zone of irregularly shaped T_1 hyposignal surrounded by contrast enhancement.

improvement after rest. She also had intermittent nasal voice, swallowing impairment and a positive neostigmine test, which led to a tentative diagnosis of myasthenia gravis, and she was treated accordingly. However, 3 months later, cerebellar signs and nystagmus appeared and MRI showed an infiltrative brainstem tumour corresponding to a glioma on pathological examination of a biopsy specimen.

MRI features at diagnosis

The main findings are summarized in Table 2. In an attempt to simplify the anatomical classification of these infiltrating tumours, their location was defined according to the site of the tumour epicentre. Using this criterion, 60% of tumours were located in the pons, 25% in the medulla and 15% in the mesencephalon. Most tumours extended outside their main location, and were most frequently pontomedullary (57%). Tumour site did not appear to affect survival (P = 0.38).

Four patterns were identified on MRI, namely patterns representing non-enhancing diffusely infiltrative tumours (50%) (Fig. 3), contrast-enhancing localized masses (31%) (Fig. 4), isolated tectal tumours (8%) (Fig. 5) and other patterns (11%). Forty-six per cent of tumours had contrast enhancement that was associated with a shorter survival time (P = 0.001; Fig. 6). Presumed 'necrosis' on MRI, defined as a zone of irregularly shaped T_1 hyposignal surrounded by contrast enhancement, was found in 20% of cases and was strongly associated with shorter survival ($P < 0.0001$; Fig. 6).

Surgical procedures

Thirty-four patients (71%) had surgery, including 22 stereotactic biopsies and 12 craniotomies. In the latter group, partial resection was performed in only four patients. Minor postoperative neurological complications were reported in four (12%) patients; these consisted of transient worsening of pre-existing cranial nerve palsies. CSF shunts were performed in four patients at presentation and in six patients during the course of the disease (total n = 10, 20%). Infiltration of the mesencephalon was a constant feature in patients who developed symptomatic hydrocephalus that required a shunt at diagnosis or during follow-up.

Pathology

Among 34 pathological specimens, two (6%) were non-diagnostic. The histological information (Table 3) fell into three groups: astrocytic gliomas (56%), oligodendrocytic and oligoastrocytic gliomas (25%) and unspecified gliomas (19%). Low-grade tumour (grade I or II) was associated with longer patient survival ($P < 0.0001$; Fig. 6).

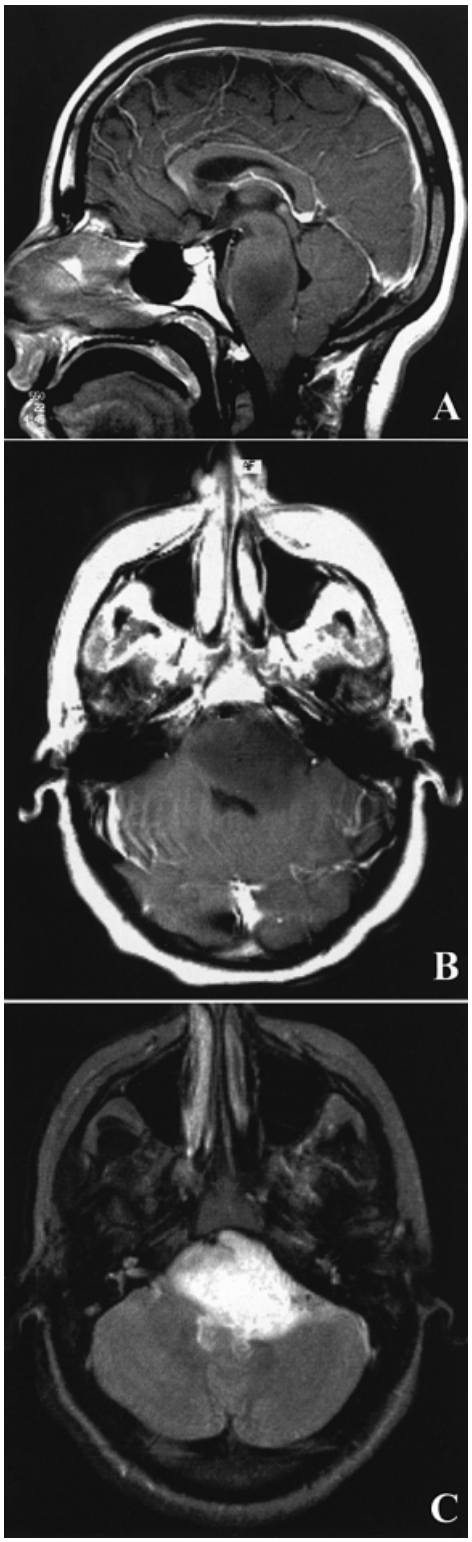


Fig. 3 MRI of a patient with non-enhancing, diffusely infiltrative tumour classified as an intrinsic diffuse low-grade brainstem glioma. (**A**) Sagittal T_1-weighted image after gadolinium infusion. (**B**) Axial T_1-weighted image after gadolinium infusion. (**C**) Axial T_2-weighted image.

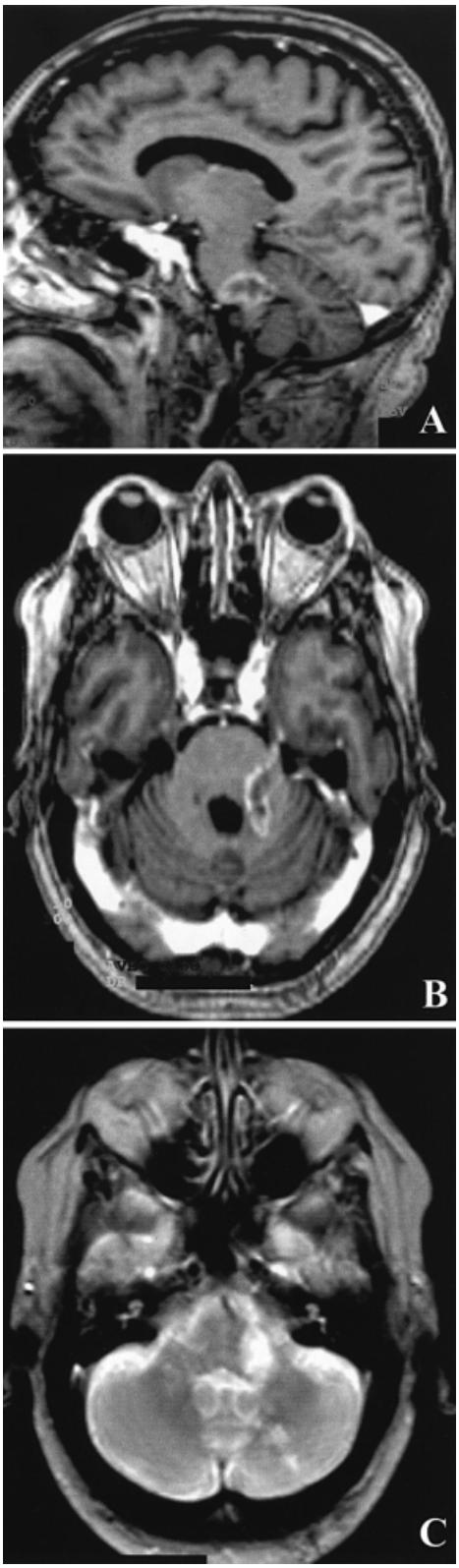


Fig. 4 MRI of a patient with a contrast-enhancing localized mass classified as a malignant brainstem glioma. (**A**) Sagittal T_1-weighted image after gadolinium infusion. (**B**) Axial T_1-weighted image after gadolinium infusion. (**C**) Axial T_2-weighted image.

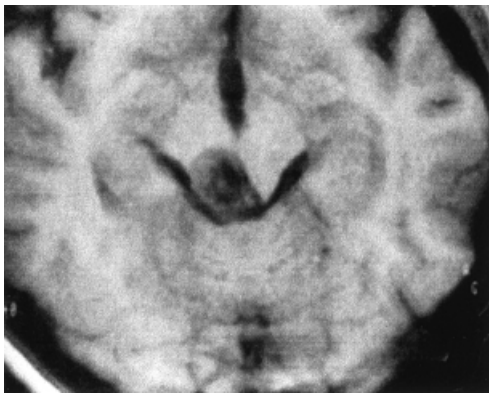
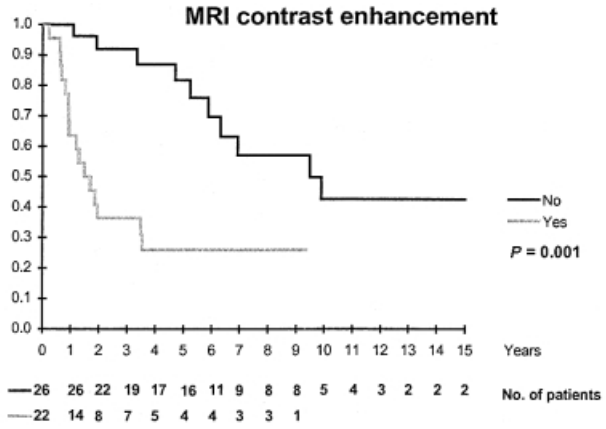
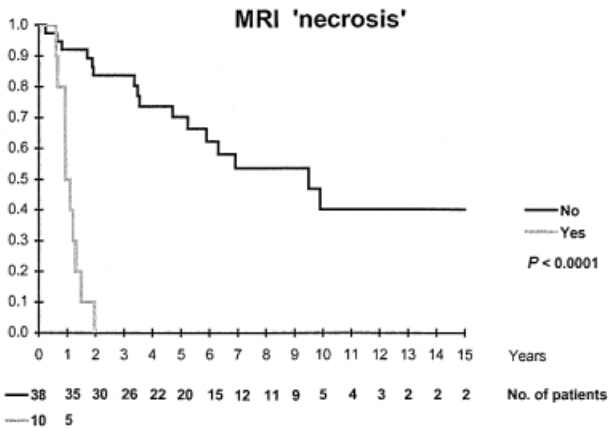


Fig. 5 Axial T_1-weighted MRI of a patient with focal tectal brainstem glioma.





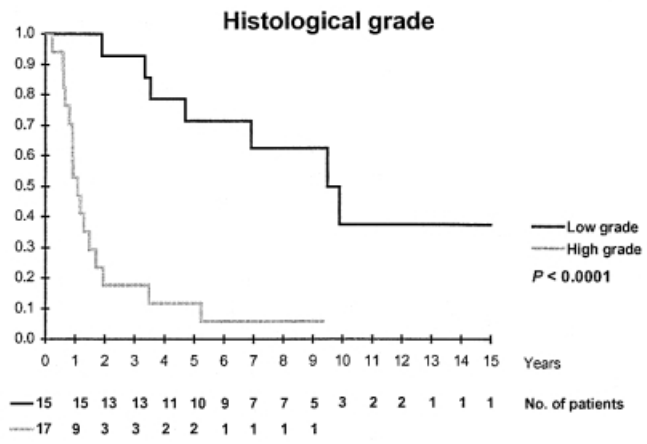


Fig. 6 Comparison of Kaplan–Meier survival curves according to radiological and histological prognostic factors. Absence of contrast enhancement and 'necrosis' on MRI and low-grade histology were significantly associated with longer survival (log-rank test).

Radiotherapy and chemotherapy

Forty-five patients out of 48 (94%) received radiotherapy. Two patients were not treated because they had minor symptoms and non-progressive tumours during 3 and 6 years of follow-up, and one patient died before starting radiotherapy. Irradiation consisted of conventional focal radiotherapy in 35 patients (mean dose 52 Gy, using fractions of 1.8–2 Gy) and hyperfractionated focal radiotherapy for 10 patients (mean dose 68 Gy, using fractions of 1–1.2 Gy twice daily). Survival did not seem to be affected by the radiation schedule (conventional versus hyperfractionated) ($P = 0.671$). Durable symptomatic clinical improvement (defined as regression of cranial nerve palsies or weakness of the limbs or cerebellar syndrome for >6 months) was observed in 40% of patients after radiotherapy. After radiotherapy, a partial radiological response was noted in eight patients (18%), stable disease in 27 (64%) and progressive disease in eight (18%). The best response time was 14 ± 10 months (mean ± SD), with great variation between cases, ranging from 5 to 36 months after completion of the radiotherapy. Tolerance of radiotherapy was generally good, although two patients died before the end of treatment and eight others required increased doses of corticosteroids because of transient worsening of their symptoms during radiotherapy.

Chemotherapy was given to 27 patients (56%) at the time of relapse or if radiotherapy failed. Regimens included nitrosourea-based chemotherapy for 12 patients BCNU [1,2-bis(2-chloroethyl)-1-nitrosourea], three patients; BCNU-procarbazine, one patient; CCNU [1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea]-procarbazine-vincristine, eight patients, platin-based chemotherapy for 12 patients (carboplatin, five patients; carboplatin-VP16, four patients; carboplatin-VP16-ifosfamide, three patients) and miscellaneous for three patients (ifosfamide, one patient; procarbazine-VP16, one patient; temozolomide, one patient). The mean duration of treatment was 4.5 months (range 1–24 months). Symptomatic clinical improvement lasting >6 months was observed in four (15%) patients after chemotherapy. Three months after the onset of chemotherapy, a partial radiological response was seen in two patients (7%) (one of them had an anaplastic oligodendroglioma), stable disease in nine (33%) and progressive disease in 16 (60%). Two patients

Table 3 *Histology of the tumours biopsied (*n = *32)*

Histological type (WHO classification)	(*n*)	(%)
Astrocytic gliomas		56%
High-grade astrocytoma (III and IV)	11	
Anaplastic astrocytoma (III)	7	
Glioblastoma (IV)	4	
Low-grade astrocytoma (II)	6	
Pilocytic astrocytoma (I)	1	
Oligodendrocytic or mixed gliomas		25%
Anaplastic oligodendroglioma (III)	3	
Low-grade oligodendroglioma (II)	1	
Low-grade oligo-astrocytoma (II)	4	
Unspecified gliomas		19%
High-grade glioma (⩾III)	3	
Low-grade glioma (II)	3	

Table 4 *Multivariate analyses of prognostic factors*

Factor	Relative risk	95% CI
Clinical factors (*n* = 40)		
Duration of symptoms <3 months	9.3	2.9–29.4*
Age at onset >40 years	2.0	0.7–5.8
Karnofski performance status ⩽70	1.3	0.4–3.7
Laboratory investigations (*n* = 32)		
Histologically high grade	5.1	1.4–18.2*
Necrosis on MRI	3.5	1.01–12.4*
Contrast enhancement	1.1	0.4–3.4
Laboratory investigations and clinical factors (*n* = 27)		
Necrosis on MRI	3.8	1.01–14.7*
Histologically high grade	3.4	0.7–17.5
Duration of symptoms <3 months	2.7	0.6–11.8

*$P < 0.05$.

died of chemotherapy-related causes (one patient died of sepsis during aplasia and one of gastrointestinal bleeding during thombocytopenia).

Evolution and complications

During the follow-up, hydrocephalus occurred in eight patients (16%); it required a shunt placement in six patients (13%). Tumour progression was characterized either by steady deterioration or by rapid clinical worsening following a long period of stable disease, a finding that we observed in six patients (13%), associated with the appearance of an enlarging, contrast-enhancing lesion on MRI suggestive of anaplastic transformation.

Tumour extension was either intra- or extra-parenchymatous. Intra-axial progression (particularly in the medulla oblongata, with swallowing difficulties in 42% of patients leading to severe aspiration pneumonia in 15%) eventually extended outside the brainstem in 12 (24%) patients, involving the diencephalon and the cerebral hemispheres (five patients), the cerebellum (four patients) and the cervical spinal cord (three patients). Extra-parenchymatous dissemination was due to leptomeningeal dissemination, a finding observed in six (13%) patients and characterized on MRI by multiple disseminated contrast-enhancing nodules in the ventricles and subarachnoid spaces. Two patients had spontaneous intra-tumoral haemorrhage that was rapidly fatal in both cases. These tumours were anaplastic oligodendrogliomas.

Death was related to glioma in 92% of patients (24 of 26 deaths) if we include tumour progression, intra-tumoral haemorrhages and one patient who died of status epilepticus secondary to temporal extension of the tumour. Toxicity of chemotherapy accounted for two deaths, as reported above.

Classification of adult brainstem gliomas

Using univariate analysis, six favourable prognostic factors were identified: young age (<40 years); duration of symptoms >3 months; Karnofski performance status >70; absence of contrast enhancement or 'necrosis' on MRI; and low-grade histology. It is important to note that the prognostic value of these factors remained significant when patients without histology were removed from the analysis.

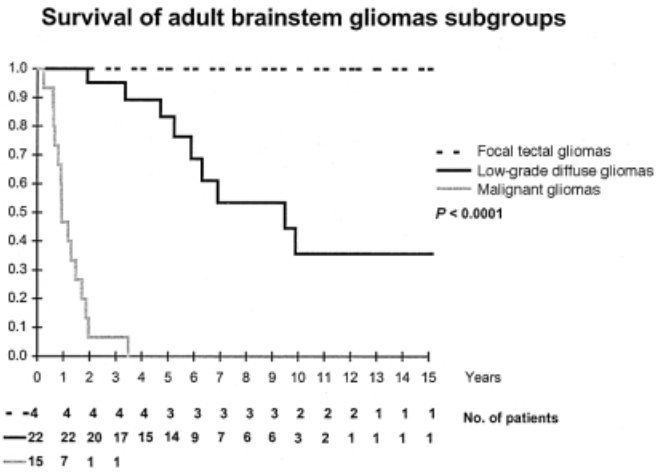


Fig. 7 Comparison of Kaplan–Meier survival curves of the three main subgroups of adult brainstem gliomas (log-rank test).

The main results of the multivariate analysis are shown in Table 4. Of the three clinical factors, duration of symptoms was the only one to be significant on multivariate analysis ($P < 0.001$). Of the three paraclinical factors, histological grade and MRI 'necrosis' were significant prognostic factors ($P < 0.05$) but contrast enhancement was not. When the duration of symptoms, histological grade and MRI 'necrosis' were introduced into multivariate analysis, the relative risks of these factors were similar (Table 4) but MRI 'necrosis' was the only one to be significant ($P < 0.05$).

According to these variables and to the clinical and radiological patterns, we classified *a posteriori* 85% of cases ($n = 41$) in three main categories with significant survival differences between them ($P < 0.0001$; Fig. 7).

Adult diffuse intrinsic low-grade brainstem glioma

This group comprised 22 patients (46%). Onset occurred in young adults in their third decade (19 out of 22 were aged <40 years). Symptom duration was >3 months (18 out of 22) and symptoms sometimes appeared several years before diagnosis. In seven cases the presentation was remarkable and was characterized by prolonged isolated facial palsy with facial hemispasm in five cases. Most of the gliomas appeared as infiltrative, diffuse, pontomedullary (18 out of 22) tumours without contrast enhancement (22 out of 22) and without necrosis (22 out of 22) on MRI. Pathological examination showed a low-grade glioma (nine out of 11) (two tumours had one or a few mitoses and discrete cytonuclear atypia without vascular proliferation and necrosis and were classified as grade III, but grading was probably overestimated because both patients had a long survival time (61 and 107 months). Radiation therapy significantly improved the clinical neurological status in 13 out of 21 cases (one patient was not irradiated) and there were four partial radiological responses (19%). A presumed anaplastic transformation, characterized by contrast enhancement after a long period of stable disease, occurred in 27% of patients. The overall median survival time of this group was 7.3 years.

Adult malignant brainstem glioma

Fifteen cases (31%) were in this group, whose results contrasted with those for the previous group in most respects. The majority of patients were aged >40 years (10 out of 15). Onset was rapidly progressive (14 out of 15) and there was altered performance status (11 out of 15). At diagnosis, contrast enhancement (15 out of 15) and necrosis (10 out of 15) were found on MRI. Pathological examination revealed astrocytic tumours (12 out of 14) or oligodendrocytic tumours (two out of 14), with evidence of anaplasia (14 out of 14) (one patient with NF1 was not biopsied). These tumours were highly resistant to treatment (after radiotherapy, only two patients had clinical and radiological improvement). Evolution was always rapidly fatal, with a median survival time of 11.2 months.

Focal tectal brainstem glioma

We identified four cases (8%) of pure focal tectal tumours characterized by an indolent course. Hydrocephalus was the only presenting syndrome in two of them. Pathological examination was performed in two patients, both of whom were found to have a low-grade mixed glioma. One patient had partial resection of the tumour and all received radiation therapy. All the patients survived (>5 years in one case and 8 years in three cases).

Other tumours

Seven tumours (15%) could not be included in the three previous groups: one atypical extensively calcified oligodendroglioma, one radiation-induced oligodendroglioma, one glioma associated with an NF1 that had both diffuse infiltrative patterns and focal-enhancing nodule, one cystic pilocytic astrocytoma, one dorsal exophytic contrast-enhancing glioma and two diffuse non-enhancing gliomas that occurred in young patients (17 and 18 years old) and were rapidly progressive and fatal.

Discussion

This study confirms that adult brainstem gliomas are different from the childhood subtypes, identifies prognostic factors and proposes a classification of these tumours. Overall, brainstem gliomas are less aggressive in adults than in children. Our finding of a median survival time of 5.4 years is in agreement with previous reports (Table 5) (Linstadt *et al.*, 1991; Shrieve *et al.*, 1992; Guiney *et al.*, 1993; Landolfi *et al.*, 1998) and is clearly longer that the 10–12 months observed in children (Kaplan *et al.*, 1996; Mandell *et al.*, 1999). However, survival merely reflects the course of the most frequent subtype of tumours, as brainstem gliomas in adults, as in children (Albright *et al.*, 1986; Freeman and Farmer, 1998), do not constitute a homogeneous group. Analysis of this series indicates that brainstem gliomas in adults can be divided into at least three groups—diffuse, intrinsic, low-grade brainstem gliomas; malignant brainstem gliomas; and other gliomas (in particular tectal gliomas)—whose main characteristics are detailed below.

Diffuse intrinsic low-grade brainstem glioma

Interestingly, the most frequent type of of brainstem glioma in adults (representing 46% of the patients in this series) resembles the childhood diffuse gliomas of the pons in terms of clinical and radiological presentation but is radically different in course and survival. In both adults and children, the clinical picture is of a combination of cranial nerve and long tract signs (Tokuriki *et al.*, 1986; Maria *et al.*, 1993). However, while the onset is rapid in children, the duration of symptoms is often long in adults, as illustrated by our seven patients who experienced either long-lasting, isolated, discrete facial paresis or facial hemispasm. This finding has been reported previously (Westra and Drummond, 1991; Gutmann *et al.*, 1994) as the unique presenting symptom, and occurs up to 5 years before tumour recognition. Less frequent, and also reported previously (Dirr *et al.*, 1989; Ragge and Hoyt 1992), is a pseudomyasthenic presentation.

In both children and adults, MRI at presentation reveals a diffuse infiltration of the pons, often increasing the size of the brainstem considerably. There is high signal on T_2-weighted and low signal on T_1-weighted images, which usually do not show contrast enhancement (100% in adults at diagnosis) (Fischbein *et al*., 1996; Freeman and Farmer, 1998). It is worth noting that preferential location in the pons is less striking in adults than in children since the epicentre

Table 5 *Recent series of adult brainstem gliomas*

Series	ANOCEF, this paper	Landolfi *et al.*, 1998	Linstadt *et al.*, 1991	Grigsby *et al.*, 1989	Selvapandian *et al.*, 1999	Guiney *et al.*, 1993	Shrieve *et al.*, 1992
Period of observation	1985–1999	1989–1997	1984–1989	1950–1984	1987–1995	1980–1989	1984–1990
Population studied	Adult	Adult	Adult	Adult	Paediatric and adult*	Paediatric and adult*	Paediatric and adult*
No. of adults	48	19	14	32	30	21	19
Median survival time (years)	5.4	4.5	>5	–	–	–	3.6
Median age (years)	29	40	37	48	–	–	–
Median symptom duration (months)	4	3	5	2	10	–	–
Signs and symptoms (%)							
Cranial nerve	87	84	–	53	87	75	68
Gait disturbance	61	11	–	57	44	57	–
Diplopia	40	58	–	–	44	27	–
Focal weakness	42	32	–	48	50	41	–
Radiology	MRI	MRI	CT or MRI	CT after 1975	CT or MRI	CT or MRI	MRI
Contrast enhancement (%)	46	37	–	–	52	–	–
Location (%)							
Midbrain	15	10	–	16	4	10	26
Pons	60	68	–	75	15	43	–
Medulla	25	22	–	9	–	–	–
Pons and medulla	57	–	–	–	44	47	74
Surgery (%)							
Stereotactic biopsy	46	16	36	7	83	33	58
Direct surgery	25	5	7	15	17	–	–
Shunt	20	10	–	18	–	–	–
Radiological response to radiotherapy (%)							
Stable disease	64	58	–	–	–	–	–
Partial response	18	–	–	–	–	–	–
Histology (*n*)							
Low grade	15	1	5	1	24	–	5
High grade	17	2	1	4	6	–	6
Prognostic factors (univariate analysis)	Age, duration of symptoms, KPS, contrast enhancement, MRI 'necrosis', histology	Trend for KPS	–	Location in the pons and medulla	Histology	Location in the pons Duration of symptoms	–
Prognostic factors (multivariate analysis)	Duration of symptoms, MRI 'necrosis', histology	–	–	–	–	–	
Comments		MRI for all patients	Hyper-fractionated radiotherapy	Series including brainstem and thalamic tumours	Better prognosis for adults, surgical series		Hyper-fractionated radiotherapy

*For mixed series of paediatric and adult brainstem gliomas, results are given for the adult group. KPS = Karnofski performance status.

of the tumour was located in the pons in 15 out of 22 patients and in the medulla in seven out of 22 patients in this study.

When a biopsy is performed, which is far from routine practice in these diffuse intrinsic forms, a malignant glioma (grades III–IV) is found in many children (Albright *et al.*, 1986, Franzini *et al.*, 1988), whereas we found a benign histology in 82% (nine out of 11) of the adults. It is likely that lower grades of the tumours in the adult population explain, at least in part, their much better prognosis compared with children. Indeed, median survival was 7.3 years in our adult group, which is similar to the survival of patients with low-grade supratentorial gliomas (Mason and Macdonald, 1997) but strikingly different from the survival of <1 year in children with intrinsic brainstem gliomas. In addition, intrinsic diffuse glioma seems to be more responsive to radiotherapy in adults than in children since 62% (13 out of 21) of adults improved for a long period after radiotherapy, although clinical improvement was often not correlated with a radiological response (19%). In this group, the optimal date of radiotherapy remains unknown since several of our patients did well for many years without treatment.

We suggest that this subgroup of tumours be designated in adults as 'diffuse intrinsic low-grade brainstem gliomas'. Nevertheless, it is important to underline the possibility of exceptions since the tumours of two of our youngest patients (aged 17 and 18 years), who had rapidly progressive cranial nerve deficits and a typical aspect of non-enhancing diffuse intrinsic glioma, behaved like the childhood subtype, and the patients' survival time was very short (14 and 16 months) despite vigorous treatment with radiotherapy and chemotherapy. These exceptions in adults seem to indicate overlaps among tumour subtypes between the two age groups.

Malignant brainstem gliomas

The other common tumour type identified in this adult series is clearly different from those discussed above. It occurs later than the diffuse, intrinsic, low-grade type and affects mainly older adults (most of them in their sixth decade). The clinical picture is characterized by the rapid onset of cranial nerve palsies and long tract signs leading to an early alteration in performance status. MRI reveals a brainstem mass that enhances after gadolinium infusion, often in a ring-like fashion. In our series, contrast enhancement was a pejorative factor (particularly when the area of enhancement surrounded a low-signal area suggestive of necrosis) in contrast with children, in whom the prognostic value of contrast enhancement remains controversial (Albright *et al.*, 1986; Fischbein *et al.*, 1996). Pathologically, these tumours correspond to high-grade gliomas (grades III–IV) and median survival time is short (11.2 months) despite treatment with radiotherapy and chemotherapy. Thus, the clinical–radiological pattern, pathology and course closely resemble the common malignant supratentorial gliomas in adults and we suggest that this group be designated 'malignant brainstem gliomas'.

Focal tectal gliomas

Focal tectal gliomas represent the third type of adult brainstem glioma and constitute a small subgroup (8%) that also exists in children (Squires *et al.*, 1994; Bowers *et al.*, 2000). The clinical picture is dominated by hydrocephalus. A diagnosis of mixed glioma was made in two of our patients after a pathological examination of the tumour. All our patients received radiotherapy and experienced long-term survival of good quality. Nevertheless, the benefit of radiotherapy can be questioned since paediatric patients with similar clinical and radiological features have been managed with ventricular shunt or observation alone for long periods (Squires *et al.*, 1994).

Other types

Other types of brainstem glioma can be observed in adults. Interestingly, we observed only one exophytic contrast-enhancing glioma arising from the floor of the fourth ventricle; this entity, which is associated with a good prognosis, is well described in children (representing up to 10% of brainstem gliomas) (Hoffman *et al.*, 1980; Pollack *et al.*, 1993). A likely explanation for this discrepancy between the two age-groups is that most of the exophytic gliomas correspond to pilocytic astrocytoma, a very rare type of tumour in adults.

Three of our patients had NF1. The brainstem is the second most frequent location of brain tumours after the optic pathways in patients with NF1 (Molloy *et al.*, 1995; Pollack *et al.*, 1996). In contrast with children, in whom the course is usually very long, the tumour behaviour that we observed in adults with NF1 was much more aggressive, but larger series will be necessary to draw any conclusion on this point.

Complications

Except for locoregional progression, two main complications were observed during the course of adult brainstem gliomas, namely hydrocephalus and leptomeningeal dissemination. Hydrocephalus was observed in 20% of cases. Whereas some pontine tumours may have an important mass effect on the fourth ventricle, hydrocephalus was always associated with mesencephalic involvement and blockage of the CSF at the level of the sylvian aqueduct. Leptomeningeal dissemination occurred in 13% of cases and was the cause of a quarter of the deaths in our series. This complication has also been reported with a high frequency in children (Packer *et al.*, 1983; Donahue *et al.*, 1998). Close proximity of the tumour and CSF pathways could explain such an increased trend for leptomeningeal dissemination, but this remains to be demonstrated.

The role of biopsy

Finally, this classification may help in the selection of patients for biopsy. In children, MRI has become the reference for

the diagnosis of brainstem glioma and is used for the current classification of these tumours (Barkovich *et al.*, 1990; Epstein and Farmer, 1993; Fischbein *et al.*, 1996). MRI has replaced biopsy in the diagnosis of paediatric diffuse brainstem gliomas, for which most authors agree that anticancer treatments can be administered without pathological confirmation if the clinical course is rapid, as is usual (Albright *et al.*, 1993; Bouffet *et al.*, 2000). In our study, 71% of patients underwent a surgical biopsy, which is nowadays considered a relatively safe (transitory worsening occurs in 12% of cases) and informative procedure (6% of specimens were non-contributory) (Franzini *et al.*, 1988). However, we believe that biopsy is not useful in the diagnosis of intrinsic, diffuse, low-grade brainstem gliomas in adults when the clinical and radiological criteria described above are met. The issue is different in contrast-enhancing lesions because several reports have underlined the limits of MRI in differentiating tumours from infectious (e.g. tuberculomas) (Del Brutto and Mosquera, 1999) and inflammatory (sarcoidosis, Behçet's disease) (Gizzi *et al.*, 1993; Akman-Demir G *et al.*, 1999) diseases. In this setting, a surgical approach is probably indicated in most cases.

Acknowledgement

We wish to thank François Doz for helpful criticism.

References

Akman-Demir G, Serdaroglu P, Tasci B. Clinical patterns of neurological involvement in Behcet's disease: evaluation of 200 patients. The Neuro-Behcet Study Group. Brain 1999; 122: 2171–82.

Albright AL, Guthkelch AN, Packer RJ, Price RA, Rourke LB. Prognostic factors in pediatric brain-stem gliomas. J Neurosurg 1986; 65: 751–5.

Albright AL, Packer RJ, Zimmerman R, Rorke LB, Boyett J, Hammond GD. Magnetic resonance scans should replace biopsies for the diagnosis of diffuse brain stem gliomas: a report from the Children's Cancer Group. Neurosurgery 1993; 33: 1026–30.

Barkovich AJ, Krischer J, Kun LE, Packer R, Zimmerman RA, Freeman CR, et al. Brain stem gliomas: a classification system based on magnetic resonance imaging. Pediatr Neurosurg 1990; 16: 73–83.

Bauman G, Pahapill P, Macdonald D, Fisher B, Leighton C, Caincross G. Low grade glioma: a measuring radiographic response to radiotherapy. Can J Neurol Sci 1999; 26: 18–22.

Bouffet E, Raquin M, Doz F, Gentet JC, Rodary C, Demeocq F, et al. Radiotherapy followed by high dose busulfan and thiotepa: a prospective assessment of high dose chemotherapy in children with diffuse pontine gliomas. Cancer 2000; 88: 685–92.

Bowers DC, Georgiades C, Aronson LJ, Carson BS, Weingart JD, Wharam MD, et al. Tectal gliomas: natural history of an indolent lesion in pediatric patients. Pediatr Neurosurg 2000; 32: 24–9.

Bricolo A, Turazzi S, Cristofori L, Talacchi A. Direct surgery for brainstem tumours. Acta Neurochir Suppl (Wien) 1991; 53: 148–58.

Constantini S, Epstein F. Surgical indication and technical considerations in the management of benign brain stem gliomas. [Review]. J Neurooncol 1996; 28: 193–205.

Del Brutto OH, Mosquera A. Brainstem tuberculoma mimicking glioma: the role of antituberculous drugs as a diagnostic tool. Neurology 1999; 52: 210–11.

Dirr LY, Donofrio PD, Patton JF, Troost BT. A false-positive edrophonium test in a patient with a brainstem glioma. Neurology 1989; 39: 865–7.

Donahue B, Allen J, Siffert J, Rosovsky M, Pinto R. Patterns of recurrence in brain stem gliomas: evidence for craniospinal dissemination. [Review]. Int J Radiat Oncol Biol Phys 1998; 40: 677–80.

Epstein FJ, Farmer JP. Brain-stem glioma growth patterns. J Neurosurg 1993; 78: 408–12.

Farwell JR, Dohrmann GJ, Flannery JT. Central nervous system tumors in children. Cancer 1977; 40: 3123–32.

Fischbein NJ, Prados MD, Wara W, Russo C, Edwards MS, Barkovich AJ. Radiologic classification of brain stem tumors: correlation of magnetic resonance imaging appearance with clinical outcome. Pediatr Neurosurg 1996; 24: 9–23.

Franzini A, Allegranza A, Melcarne A, Giorgi C, Ferraresi S, Broggi G. Serial stereotactic biopsy of brain stem expanding lesions. Considerations on 45 consecutive cases. Acta Neurochir Suppl (Wien) 1988; 42: 170–6.

Freeman CR, Farmer JP. Pediatric brain stem gliomas: a review. [Review]. Int J Radiat Oncol Biol Phys 1998; 40: 265–71.

Gizzi MS, Lidov M, Rosenbaum D. Neurosarcoidosis presenting as a tumour of the basal ganglia and brainstem: sequential MRI. Neurol Res 1993; 15: 93–6.

Grigsby PW, Garcia DM, Simpson JR, Fineberg BB, Schwartz HG. Prognostic factors and results of therapy for adult thalamic and brainstem tumors. Cancer 1989; 63: 2124–9.

Guiney MJ, Smith JG, Hughes P, Yang C, Narayan K. Contemporary management of adult and pediatric brain stem gliomas. Int J Radiat Oncol Biol Phys 1993; 25: 235–41.

Gutmann L, Hopf HC. Facial myokymia and contraction persisting 20 years: a case of pontine glioma. Muscle Nerve 1994; 17: 1461–3.

Hoffman HJ, Becker L, Craven MA. A clinically and pathologically distinct group of benign brain stem gliomas. Neurosurgery 1980; 7: 243–8.

Kaplan AM, Albright AL, Zimmerman RA, Rorke LB, Li H, Boyett JM, et al. Brainstem gliomas in children. A Children's Cancer Group review of 119 cases. Pediatr Neurosurg 1996; 24: 185–92.

Landolfi JC, Thaler HT, DeAngelis LM. Adult brainstem gliomas. Neurology 1998; 51: 1136–9.

Linstadt DE, Edwards MS, Prados M, Larson DA, Wara WM. Hyperfractionated irradiation for adults with brainstem gliomas. Int J Radiat Oncol Biol Phys 1991; 20: 757–60.

Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 1990; 8: 1277–80.

Mandell LR, Kadota R, Freeman C, Douglass EC, Fontanesi J, Cohen ME, et al. There is no role for hyperfractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a Pediatric Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy. Int J Radiat Oncol Biol Phys 1999; 43: 959–64.

Maria BL, Rehder K, Eskin TA, Hamed LM, Fennell EB, Quisling RG, et al. Brainstem glioma: I. Pathology, clinical features, and therapy. [Review]. J Child Neurol 1993; 8: 112–28.

Mason WP, Macdonald DR. Low-grade gliomas. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology, Vol. 68. Amsterdam: Elsevier; 1997. p. 33–62.

Molloy PT, Bilaniuk LT, Vaughan SN, Needle MN, Liu GT, Zackai EH, et al. Brainstem tumors in patients with neurofibromatosis type 1: a distinct clinical entity. Neurology 1995; 45: 1897–902.

Packer RJ, Allen J, Nielsen S, Petito C, Deck M, Jereb B. Brainstem glioma: clinical manifestations of meningeal gliomatosis. Ann Neurol 1983; 14: 177–82.

Pollack IF, Hoffman HJ, Humphreys RP, Becker L. The long-term outcome after surgical treatment of dorsally exophytic brain-stem gliomas. J Neurosurg 1993; 78: 859–63.

Pollack IF, Shultz B, Mulvihill JJ. The management of brainstem gliomas in patients with neurofibromatosis 1. [Review]. Neurology 1996; 46: 1652–60.

Ragge NK, Hoyt WF. Midbrain myasthenia: fatigable ptosis, 'lid twitch' sign, and ophthalmoparesis from a dorsal midbrain glioma. Neurology 1992; 42: 917–19.

Selvapandian S, Rajshekhar V, Chandy MJ. Brainstem glioma: comparative study of clinico-radiological presentation, pathology and outcome in children and adults. Acta Neurochir (Wien) 1999; 141: 721–7.

Shrieve DC, Wara WM, Edwards MS, Sneed PK, Prados MD, Cogen PH, et al. Hyperfractionated radiation therapy for gliomas of the brainstem in children and in adults. Int J Radiat Oncol Biol Phys 1992; 24: 599–610.

Squires LA, Allen JC, Abbott R, Epstein FJ. Focal tectal tumors: management and prognosis. Neurology 1994; 44: 953–6.

Tokuriki Y, Handa H, Yamashita J, Okumura T, Paine JT. Brainstem glioma: an analysis of 85 cases. Acta Neurochir (Wien) 1986; 79: 67–73.

Walker DA, Punt JA, Sokal M. Clinical management of brain stem glioma. [Review]. Arch Dis Child 1999; 80: 558–64.

Westra I, Drummond GT. Occult pontine glioma in a patient with hemifacial spasm. Can J Ophthalmol 1991; 26: 148–51.

White HH. Brain stem tumors occurring in adults. Neurology 1963; 13: 292–300.

Received April 30, 2001. Revised July 5, 2001.
Accepted July 16, 2001