

Prognostic factors of CNS tumours in Neurofibromatosis 1 (NF1)

A retrospective study of 104 patients

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Summary

In addition to multiple peripheral neurofibromas, Neurofibromatosis 1 (NF1) predisposes to CNS tumours. Most of them are pilocytic astrocytomas, arise in children and are located in the optic pathways or in the brainstem. The majority are indolent, but factors predictive of poor prognosis have yet to be identified. Furthermore, the incidence and natural history of gliomas of a higher grade, arising in adults or involving other locations are largely unknown in NF1. In order to address these issues, we performed a retrospective study of 104 patients followed in seven French centres between 1982 and 2000. Inclusion criteria were a diagnosis of NF1, according to the National Institutes of Health criteria, and the presence of a CNS tumour, regardless of type, location or age of onset. The series included 88 children (age range 3 months to 17 years) and 16 adults (age range 19–52 years). The median follow-up was 5.6 years. One hundred and twenty-seven CNS tumours were observed in the 104 patients. Eighty-four (66%) were optic pathway tumours (OPT)

and 43 (34%) extra-optic pathway tumours (extra-OPT) (brainstem: $n = 21$; other locations: $n = 22$). Twenty-one patients (20%) had multiple CNS tumours. OPT were symptomatic in 50 patients and extra-OPT in 19. Main clinical findings at presentation included visual loss ($n = 29$; 58%) and precocious puberty ($n = 5$; 10%) for OPT, increased intracranial pressure ($n = 9$; 48%) for extra-OPT. Fourteen out of the 27 symptomatic tumours with histology were pilocytic astrocytomas. The overall survival rate was 90% at 5 years (95% confidence interval 82–95%). Extra-optic location, tumour diagnosis in adulthood and symptomatic tumours were independent factors associated with shorter survival time ($P < 0.05$, Cox model). Radiotherapy for OPT was associated with vascular complications (ischaemic strokes) and growth hormone deficiency in 32 and 46% of patients, respectively. In conclusion, mortality is high in extra-OPT, particularly in adults, whereas OPT are only exceptionally life-threatening. Radiotherapy of OPT is associated with an important morbidity in NF1.

Keywords: brainstem glioma; Neurofibromatosis 1; optic pathway glioma

Abbreviations: NF1 = Neurofibromatosis 1; OPT = optic pathway tumour; UBO = unidentified bright object

Introduction

Neurofibromatosis 1 (NF1) is a common genetic disorder, with an incidence of one per ~3500 births (Riccardi, 1991; Friedman, 1999). The *NF1* gene, a tumour-suppressor gene

located on chromosome 17q11.2, encodes neurofibromin, a negative regulator of the *Ras* oncogene, the inactivation of which leads to cell proliferation and tumour development

(Seizinger, 1993; Rasmussen and Friedman, 2000). NF1 predisposes mainly to tumours developed from peripheral or central nerve tissue (Sorensen *et al.*, 1986; Huson *et al.*, 1988; Friedman and Birch, 1997; Gutmann *et al.*, 1997; McGaughan *et al.*, 1999). Tumours of the peripheral nervous system are the most frequent tumours of NF1, and malignant peripheral nerve sheath tumours are the major cause of mortality in adult patients (Créange *et al.*, 1999). Although less frequent than peripheral nervous system tumours, CNS tumours are important because they may lead to major morbidity and mortality, despite the fact that most of them are grade I pilocytic astrocytomas (Sorensen *et al.*, 1986; Matsui *et al.*, 1993; Listernick *et al.*, 1999a).

Optic pathway (Listernick *et al.*, 1994) and brainstem (Pollack *et al.*, 1996) gliomas are prevalent CNS tumours in NF1. Most of the studies, carried out in children, showed that these tumours were less aggressive than their counterparts in non-NF1 patients (Listernick *et al.*, 1995; Molloy *et al.*, 1995; Deliganis *et al.*, 1996; Pollack and Mulvihill, 1996). However, few data are available for tumours located outside optic pathways and brainstem, and for tumours arising in adults, even though we have recently suggested that brainstem gliomas could lead to an unusual mortality in NF1 adults (Guillamo *et al.*, 2001). Moreover, asymptomatic or low symptomatic tumours are increasingly revealed by systematic MRI, raising new prognostic queries and difficulties in patient management (Aoki *et al.*, 1989; Bonawitz *et al.*, 1998; DiMario and Ramsby, 1998).

It therefore appears preferable to identify prognostic factors for patients with CNS tumours and NF1, in addition to, or, in most cases, as an alternative to histological criteria. The present multicentric retrospective study, based on a large NF1 population including both children and adults with CNS tumours, has been set up in order to address these issues.

Patients and methods

Patients

Records were collected for patients with NF1 according to the criteria of the National Institute of Health (National Institutes of Health Consensus Development Conference, 1988) and with CNS tumours referred to four Neurofibromatosis clinics: Henri Mondor ($n = 14$); Saint-Vincent de Paul ($n = 16$); Necker-Enfants Malades ($n = 14$); and Hôtel-Dieu de Nantes ($n = 13$); and three departments of oncology: Gustave-Roussy ($n = 33$); Curie ($n = 9$); and Pitié-Salpêtrière ($n = 5$), during the period from 1982 to 2000. Computed tomography (CT) scan at diagnosis was mandatory before 1987, and MRI after 1987. A list of 111 records was drawn up; 104 were available for the study (five records were not included because of incomplete clinical and/or radiological data, and two patients did not meet NF1 criteria). Patients aged >18 years at tumour diagnosis were defined as adults.

Tumour diagnosis

The diagnosis of CNS tumour was based on pathological confirmation except for infiltrating tumours of the optic pathways or the brainstem, in which diagnosis was based on radiological criteria (Listernick *et al.*, 1997). In the case of asymptomatic tumours, the diagnosis of CNS tumour was considered in presence of two or more of the following radiological features: expansive lesion, contrast enhancement or mass effect. The differential diagnosis, unidentified bright object (UBO), was considered in non-expansive T₂-weighted MRI lesions without contrast enhancement or mass effect (Ferner *et al.*, 1993; DeBella *et al.*, 2000). In the case of asymptomatic tumours, metastases were excluded on the basis of clinical history, absence of a known cancer, and clinical and radiological follow-up. Meningiomas that are not intrinsic tumours of the CNS and constitute a distinct entity in terms of embryological origin were excluded from the study.

Classification of tumours

Tumours were classified according to their location in two groups: optic pathway tumours (OPT) and extra-optic pathway tumours (extra-OPT). OPT included tumours of the optic nerves, chiasma and retrochiasmatic pathways. Extra-OPT included brainstem tumours and tumours of other locations (i.e. cerebral lobes, basal ganglia, cerebellum and spinal cord). Multiple tumours were defined as distinct lesions, i.e. lesions without an anatomical link. Histology of tumours was classified according to the World Health Organization (WHO) classification (Kleihues and Cavenee, 2000).

Record review and data collection

The medical record of each patient was reviewed by one of us (J.-S.G.). The following data were collected: demographic information (age, sex, familial history of NF1), date of tumour diagnosis, circumstances of diagnosis and age at onset, location and number of tumours, radiological features, histology when available, treatment, clinical and radiological course, and complications (including treatment complications).

Statistical analyses

Survival time was measured from the date of onset of symptoms or from the date of diagnosis for asymptomatic tumours, to the date of last follow-up visit or death. Survival time was estimated by the Kaplan–Meier method (Kaplan and Meier, 1958). The factors that may influence survival time (sex, age at tumour diagnosis, location of the tumour, symptoms at diagnosis, multiple tumours) were tested by comparing survival curves with the log rank test. Cox's proportional hazards model was used to take into account simultaneously all potential prognostic factors over time (Cox, 1972). Variables included in the final multivariate

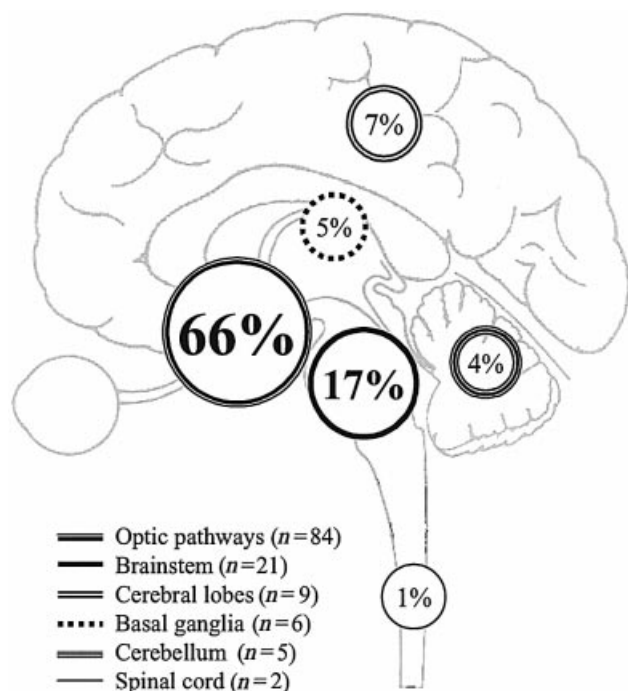


Fig. 1 Schematic distribution of 127 tumours in 104 patients.

model were those emerging from univariate models with a P value <0.15 . Hazard ratios and their two-sided 95% confidence interval (CI) were estimated. All tests were two-tailed, a P value of <0.05 indicated statistical significance. Data were analysed using the Biomedical Statistical Package (BMDP) software (University of California, Berkeley). Percentages were compared with the Fisher's exact test.

Results

Patients and tumours

One hundred and four patients were included in the study (male : female, 54 : 50). Fifty-nine patients had sporadic NF1, 38 patients had a familial form; familial status was not available in seven. Eighty-eight patients were children (median age 5.2 years; range 3 months to 17 years) and 16 were adults (median age 28.8 years; range 19–52 years). The median follow-up was 5.6 years (range 4.5 months to 18 years; mean 6.3 years).

One hundred and twenty-seven tumours were observed in the 104 patients included in the study. Their locations are summarized in Fig. 1. Twenty-one (20%) patients had either two ($n = 19$) or three ($n = 2$) CNS tumours. Nine patients had both an OPT and a brainstem tumour.

Characteristics of OPT

Age and clinical features at diagnosis

OPT were diagnosed in 84 patients (74 children and 10 adults; Fig. 2A). Thirty-four tumours were asymptomatic and were

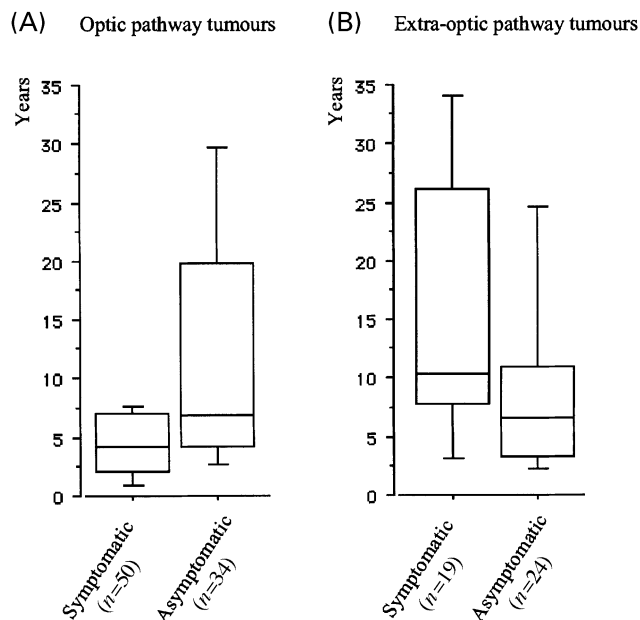


Fig. 2 Age distribution of patients according to the presence of symptoms. (A) OPT; (B) extra-OPT. Boxes represent the median, 25th and 75th percentile, and bars the 10th and 90th percentile. Symptomatic optic pathway tumours were observed only in children aged under 9 years.

Table 1 Clinical presentation and circumstances of diagnosis in 69 symptomatic patients

		% (n)
OPT ($n = 50$)	Visual loss	58 (29)
	Precocious puberty	10 (5)
	Obesity	6 (3)
	Increased intracranial pressure	6 (3)
	Exophthalmia	6 (3)
	Strabismus	6 (3)
	Miscellaneous	
	Eye pain	2 (1)
	Epilepsy	2 (1)
	Macrocrania	2 (1)
Extra-OPT ($n = 19$)	Russell–Silver syndrome	2 (1)
	Increased intracranial pressure	48 (9)
	Hemiplegia	16 (3)
	Unspecified headache	11 (2)
	Ataxia	5 (1)
	Paraplegia	5 (1)
	Epilepsy	5 (1)
	Aphasia	5 (1)
	Bilateral ptosis	5 (1)

diagnosed on systematic imaging (24 out of 74 in children, and 10 out of 10 in adults). Fifty tumours were symptomatic (50 out of 74 in children, and zero out of 10 in adults). Symptoms at diagnosis are summarized in Table 1. Visual loss (58%) and precocious puberty (10%) were the most frequent symptoms. Fifteen children out of 50 with symp-

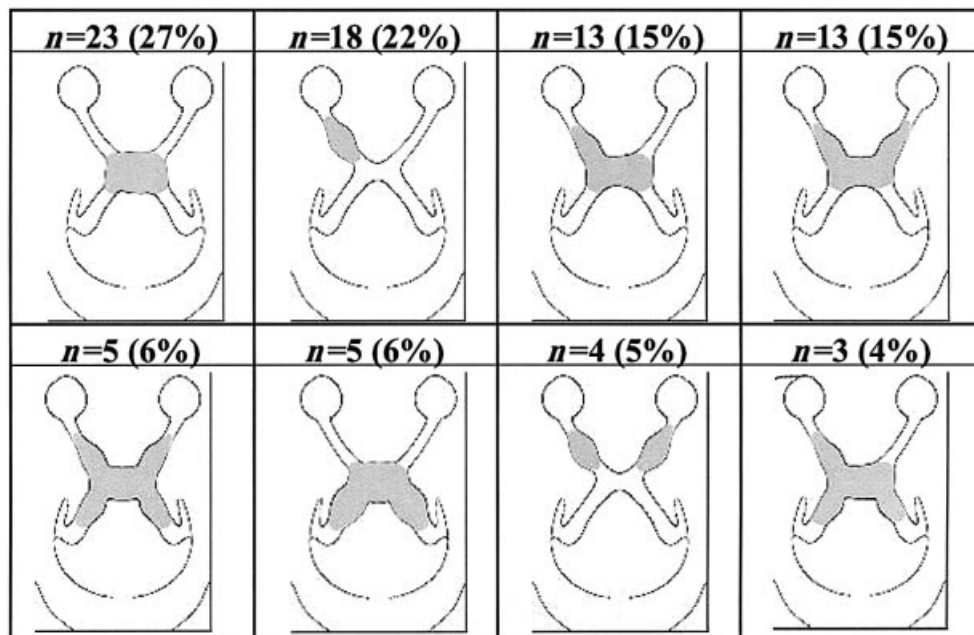


Fig. 3 Schematic representation of tumour location in the optic pathways ($n = 84$). Eighty-four per cent of tumours were located in the anterior optic pathways.

tomatic OPT were diagnosed after the age of 6 years. All were under 9 years of age. Of these 15 OPT in older children, four progressed after diagnosis and required specific treatment.

Location

OPT represented 66% of CNS tumours. OPT locations are summarized in Fig. 3. Anterior OPT were the most frequent tumours (84% of OPT).

Radiological features

Radiological examinations of OPT, based either on CT scans ($n = 21$) or MRI ($n = 63$), showed a mass effect on adjacent structures in 23 (27%) tumours and a cystic component in four (5%). Thirty-six (56%) of the 64 tumours with contrast infusion showed contrast enhancement.

Pathological features

Pathological examination was available in eight progressive OPT (all in children). Five were pilocytic astrocytomas (grade I) and three were low-grade astrocytomas (grade II).

Treatment and complications

Twenty-eight asymptomatic and 13 symptomatic OPT were not treated. One patient had spontaneous regression of the tumour during follow-up. Six asymptomatic (three of them progressed after diagnosis) and 37 symptomatic OPT had treatment. Treatment consisted of surgical resection ($n = 9$),

cerebrospinal fluid shunt ($n = 7$), radiotherapy ($n = 28$) and chemotherapy ($n = 11$). Among the 28 OPT treated with radiotherapy, 17 tumours enlarged on radiological examinations before treatment. Of these 17 OPT, four had partial responses, 11 stable diseases and two progressive diseases after radiotherapy. Only one out of nine severely affected patients (visual acuity <2 out of 10) improved after radiotherapy.

Twenty-four patients had precocious puberty: five at the time of tumour diagnosis, 19 during the follow-up and among them, nine after radiotherapy ($P = 0.17$; Fisher's exact test). Fourteen patients had growth hormone deficiency and among them, 13 after radiotherapy within a median interval of 23 months (46% of OPT with radiotherapy) compared with only one who had no radiotherapy ($P < 0.001$; Fisher's exact test). Nine patients (32% of OPT with radiotherapy) had presumed radiation related ischaemic strokes within a median interval of 28 months.

Characteristics of extra-OPT

Age and clinical features at diagnosis

Extra-OPT were diagnosed in 43 patients (33 children and 10 adults; Fig. 2B). Twenty-four tumours were asymptomatic and diagnosed on systematic imaging (20 out of 33 in children and four out of 10 in adults). Nineteen tumours were symptomatic (13 out of 33 in children and six out of 10 in adults). Symptoms at diagnosis are summarized in Table 1. Increased intracranial pressure (48%) was the most frequent clinical presentation.

Location

Extra-OPT locations are summarized in Fig. 1. Brainstem tumours were the most frequent tumours (49% of extra-OPT).

Radiological features

Radiological examinations of extra-OPT based either on CT scans ($n = 4$) or MRI ($n = 39$) showed a mass effect on adjacent structures in 19 (44%) tumours and a cystic component in nine (21%). Twenty-seven (82%) tumours out of the 33 with contrast infusion showed contrast enhancement.

Pathological features

Pathological examination was available in 19 progressive extra-OPT. Nine were pilocytic astrocytomas (grade I; eight children, one adult), five were low-grade astrocytomas (grade II; four children, one adult), two were anaplastic astrocytomas (grade III; one child, one adult), two were glioblastomas (grade IV; one child, one adult) and one was a dysplastic neuroepithelial tumour (one child).

Treatment and complications

Nineteen asymptomatic and one symptomatic extra-OPT were not treated. Five asymptomatic (four in children and one in an adult that progressed after diagnosis) and 18 symptomatic extra-OPT had treatment. Treatment consisted of surgical resection ($n = 14$), cerebrospinal fluid shunt ($n = 4$), radiotherapy ($n = 15$) and chemotherapy ($n = 13$).

There was no endocrinological complication or radiation-induced stroke in patients with extra-OPT in this series. Leptomeningeal dissemination was observed for three tumours.

Other associated tumours and UBOs

Other associated tumours included multiple meningiomas ($n = 2$), malignant peripheral nerve sheath tumour (sarcoma) ($n = 1$), rhabdomyosarcoma of the bladder ($n = 1$), compressive spinal cord neurofibroma ($n = 3$) and plexiform neurofibroma ($n = 3$). UBOs were observed in 73% of patients with MRI, all in children, except for the youngest adult (aged 19 years).

Survival analysis

Twelve (11%) out of the 104 patients died during follow-up. Causes of death are presented in Table 2. Death was related to glioma progression in 10 patients and to another tumour (sarcoma) in two patients with stable OPT. The survival curve of the population is shown in Fig. 4. The survival rate was 90% at 5 years (95% CI 82–95%) and 82% at 10 years (95% CI 70–90%).

Table 2 Cause of the death in 12 patients

		<i>n</i>
Children	Brainstem glioma	3
	Diencephalic glioma	1
	Optic pathway glioma	1*
	Sarcoma	2†
Adults	Brainstem glioma	2
	Cerebral hemispheric glioma	2
	Cerebellar glioma	1

*Death related to intra-tumoural haemorrhage.

†Sarcoma located outside the CNS in two patients with stable OPT.

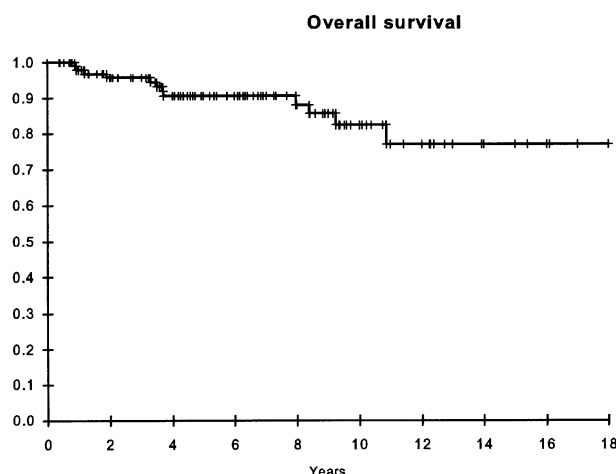


Fig. 4 Kaplan–Meier survival curve for the 104 patients. The survival rate was 90% at 5 years (95% CI 82–95%) and 82% at 10 years (95% CI 70–90%).

Survival according to the location of the tumour, age at diagnosis and the presence of symptoms at diagnosis is shown in Fig. 5. Survival time of patients with extra-OPT was significantly shorter than patients with OPT ($P < 0.0001$). Adult patients had a significantly worse prognosis than children ($P < 0.0001$), even for extra-OPT only ($P = 0.002$). Asymptomatic patients tended to have a better survival than symptomatic patients, but the difference did not reach significance in univariate analysis ($P = 0.08$). There was no difference in survival between patients with a single tumour and patients with multiple CNS tumours ($P = 0.66$) or between males and females ($P = 0.77$).

In multivariate analyses, extra-optic location, tumour diagnosis at adulthood and symptoms at diagnosis were independently associated with a higher mortality ($P < 0.05$; Cox's proportional hazards model; Table 3).

Discussion

This study included CNS tumours in NF1, whatever their location or histological type, or the age of the patient. The use of definite criteria of NF1, the median follow-up of 5.6 years

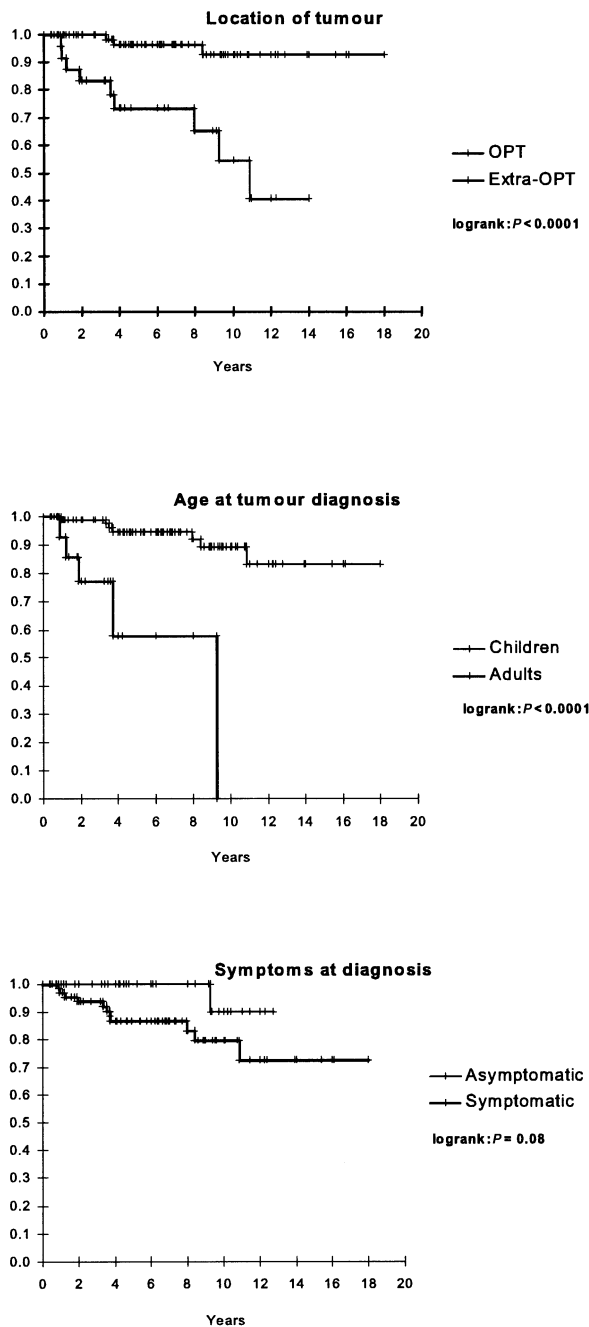


Fig. 5 Comparison of Kaplan–Meier survival curves according to the location of the tumour, age at diagnosis and the presence of symptoms at diagnosis. Extra-optic tumours and adult patients were significantly associated with shorter survival time in univariate analysis.

and the large proportion of MRI examinations allowed a good overview of the spectrum of CNS tumours in NF1. This population included a high proportion of tumours located outside the optic pathways (34%) and a high proportion of patients with multiple CNS tumours (20%). The overall prognosis was good, with a 5-year survival rate of 90% and a 10-year survival rate of 82%. However, this study also

Table 3 Multivariate analyses of predictive factors for death (Cox's model)

Factor	Hazard ratio	95% CI	P value
Extra-optic location	5.84	1.36–25.13	0.018
Diagnosis at adulthood	12.59	2.75–57.64	0.001
Symptoms at diagnosis	12.23	2.84–52.62	0.025

showed that mortality was independently associated with extra-optic location, symptomatic tumours and adult patients.

Astrocytomas are the major type of CNS tumours in NF1, and pilocytic astrocytoma (WHO grade I) the main histological subtype (Stern *et al.*, 1980; Listernick *et al.*, 1997). Pilocytic astrocytomas are usually characterized by a stable or a very slow progressive course that may account for the overall good prognosis of CNS tumours in NF1. Interestingly, a high proportion of progressive tumours in our series were not pilocytic astrocytomas but higher grade astrocytomas (grade II, III and IV), an observation consistent with previous data from NF1 brainstem gliomas (Molloy *et al.*, 1995; Pollack *et al.*, 1996) suggesting that symptomatic/progressive tumours may be associated with a more aggressive histological subtype. Therefore, in cases of symptomatic and progressive tumours, particularly when located outside the optic pathways, histological specification can be useful for treatment adjustment and prognosis. Although other rare types of CNS tumours have been reported in NF1, including ependymomas (Es *et al.*, 1996), medulloblastomas (Matsui *et al.*, 1993) and dysplastic neuroepithelial tumours (Lellouch-Tubiana *et al.*, 1995), only one of these rare tumours was observed in the present series, suggesting that either the incidence of these tumours in NF1 is very low or that they should not be considered as NF1 associated tumours.

Not surprisingly, the majority of tumours were OPT (66%). In large population-based studies or in studies with systematic radiological evaluation, OPT are observed in 5–20% of NF1 patients, most being asymptomatic (Lewis *et al.*, 1984; Sorensen *et al.*, 1986; Listernick *et al.*, 1994; Friedman and Birch, 1997). Previous studies have shown that the age distribution and location of optic pathway gliomas are different in patients with NF1 and without NF1, and that optic pathway gliomas are associated with a better prognosis in patients with NF1 (Listernick *et al.*, 1995; Deliganis *et al.*, 1996; Kornreich *et al.*, 2001). However, in the present series, the age limit for symptomatic and progressive OPT was 9 years, a slightly older limit than previously considered (Listernick *et al.*, 1997). Secondly, our data showed that although OPT were exceptionally life threatening in NF1, they were associated with a significant morbidity related either to the tumour itself (visual loss, precocious puberty) or to the treatment. Although the high proportion of symptomatic OPT (58%) in our study was probably related to inclusion bias of patients from NF clinics and oncological departments, it is a real concern in the overall population of NF1 patients.

The utility of screening neuroimaging for the improvement of clinical outcome of OPT has been questioned. Our data show that all the adults and a majority of children with OPT did not progress after detection. For those whose OPT progressed and required treatment, abnormal visual findings could be detected by ophthalmological examination. Consistent with the conclusions of the Neurofibromatosis Task Force on Optic Pathway Glioma (Listernick *et al.*, 1997), these results do not support recommendation of screening neuroimaging for detection of OPT in NF1. However, systematic annual eye examinations are highly recommended to detect OPT in NF1 children, particularly in very young children, in whom complaints of visual loss are rare (Listernick *et al.*, 1997; Pinson *et al.*, 2001).

In the past, various doses of radiotherapy have been used to treat OPT (Bataini *et al.*, 1991; Jenkin *et al.*, 1993; Grill *et al.*, 2000). Tumour control is obtained in up to 80–90% of NF1 patients (Bataini *et al.*, 1991; Jenkin *et al.*, 1993; Tao *et al.*, 1997). Despite this high rate of control, systematic use of radiotherapy has been questioned, since it has been associated with serious delayed toxicity in NF1 (Grill *et al.*, 1999). Main complications include radiation-induced stroke and growth hormone deficiency (32 and 46%, respectively, of patients in our series), although these two complications can be exceptionally observed in absence of radiotherapy. These data support the restricted use of treatment, the modalities of which should be carefully discussed, only in cases of symptomatic and progressive tumours. In this setting, given the high rate of delayed toxicity, there is virtually no role for radiotherapy in childhood OPT with NF1. Chemotherapy is currently a recommended alternative to radiotherapy, although there are few published data in NF1 to date (Packer *et al.*, 1997; Listernick *et al.*, 1999b).

The present series included a high proportion of extra-OPT. Extra-optic location was an independent prognostic factor for death. Brainstem gliomas are the second most frequent tumours in NF1 after OPT. As a rule, brainstem gliomas behave much less aggressively in NF1 patients than in other patients (Raffel *et al.*, 1989; Molloy *et al.*, 1995; Pollack *et al.*, 1996). Although most of them remained asymptomatic or did not progress clinically without treatment, our study clearly demonstrated that brainstem gliomas may also become life-threatening in NF1 patients, both in children (three out of seven deaths) and adults (two out of five deaths). Other symptomatic extra-OPT, including cerebral and cerebellar tumours, were associated with a poor prognosis. Extra-optic tumours were the only cause of death in adults.

Twenty per cent of patients in this series had multiple CNS tumours. This is in keeping with a previous study in which 18% of patients had multiple tumours (whatever the type and location) and 14% of patients had multiple CNS tumours (Sorensen *et al.*, 1986). In a recent neuroradiological series with MRI, 40% of patients with a brainstem glioma had a concurrent OPT (Bilaniuk *et al.*, 1997). Not surprisingly, the most frequent association was an OPT and a brainstem

tumour that usually combined one asymptomatic and one symptomatic tumour. The life prognosis of patients with multiple tumours was not different from the prognosis of patients with a single tumour. This result highlights the existence of tumours compatible with long survival, an assessment especially true when tumours are diagnosed in children, develop in the optic nerve and remain asymptomatic. Multiple tumours are therefore a core feature of NF1, even when only CNS tumours are considered.

Adulthood was an independent prognostic factor for shorter survival, and was associated with the development of malignant CNS tumours located outside the optic pathways. In a previous study, we had shown that life-threatening neurological complications were rare in adults, except malignant peripheral nerve sheath tumours (Créange *et al.*, 1999). Non-neoplastic neurological manifestations of NF1 are more severe in childhood than in adulthood (Créange *et al.*, 1999). This assessment is also true for OPT, but it cannot be extended to the other cerebral tumours. The increased risk for malignant tumours with ageing could well result from additional genetic alterations arising randomly over time. Although, malignant peripheral nerve sheath tumours in the peripheral nervous system arise from plexiform and subcutaneous neurofibromas (Leroy *et al.*, 2001), our study does not address the question of possible degeneration from asymptomatic benign CNS tumours. In our series, only one adult patient with an asymptomatic cerebral lesion experienced a rapid progression of the tumour, 9 years after detection.

In conclusion, survival of patients with CNS tumours and NF1 is dependent on age of onset, the presence of tumour related symptoms, and the presence of extra-optic tumours. Decision making for NF1 patients with CNS tumours should be facilitated by these results.

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