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Multicentric French study on adult intracranial ependymomas: prognostic factors analysis and therapeutic considerations from a cohort of 152 patients

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Ependymomas account for 2% of all intracranial tumours in adults. Considerable controversy continues to exist with regard to their prognostic factors and therapeutic management due to the rarity and the heterogeneity of series reported so far. The authors report a retrospective study of a homogenous population of 152 adult patients harbouring intracranial ependymomas from 24 French Neurosurgical Centres between 1990 and 2004. All clinico-radiological and follow-up data were analysed and a central pathologic review was performed by two confirmed neuropathologists. The 5- and 10-year overall survival rates were 84.8 and 76.5%, respectively; the 5- and 10-year progression-free survival rates were 63.5 and 52.8%, respectively. On multivariate analysis, overall survival rates were associated with histological grade ($P < 0.001$), extent of surgery ($P = 0.006$), patient age ($P = 0.004$) and patient Karnofski performance status ($P = 0.03$). The multivariate analysis also revealed that the risk of recurrence was associated with high histological grade ($P < 0.001$), incomplete resection ($P < 0.001$) and Karnofski performance status ≤ 80 ($P = 0.04$). The impact of radiotherapy was found to be beneficial for incompletely resected low-grade ependymomas and to a lesser extent for completely removed high-grade tumours. In association with Karnofski performance status and extent of surgery, histological grade is a major prognostic factor in adult intracranial ependymomas. The application of a simple and reproducible grading scheme using objective anaplastic criteria seems useful practically and clinically applicable. The role of adjuvant radiotherapy for patients with incompletely resected low-grade ependymomas seems to be beneficial but remains to be addressed for high-grade tumours.

Keywords: ependymoma; adult; prognostic factors; radiotherapy; classification

Abbreviations: CART = classification and regression tree; GTR (+) = gross total removal; GTR (−) = incomplete resection; KPS = Karnofski performance status; LV = lateral ventricle; Max = maximum; Min = minimum; OS = overall survival; P = parenchymal; PFS = progression-free survival; RPA = recursive partition analysis; RT = radiotherapy; V3 = third ventricle; WHO = World Health Organization

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Introduction

Adult intracranial ependymoma is a relatively rare brain tumour entity, accounting for 2–5% of all intracranial neoplasms (Rawlings *et al.*, 1988; Ernestus *et al.*, 1997; Guyotat *et al.*, 2002; Korshunov *et al.*, 2004; Reni *et al.*, 2004). A considerable number of retrospective studies have been reported in the last decade on ependymomas (Rawlings *et al.*, 1988; Lyons and Kelly, 1991; Schiffer *et al.*, 1991; Vanuytsel *et al.*, 1992; Rezai *et al.*, 1996; Ernestus *et al.*, 1997; Stuben *et al.*, 1997; McLaughlin *et al.*, 1998; Robertson *et al.*, 1998; Schild *et al.*, 1998; Schwartz *et al.*, 1999; Figarella-Branger *et al.*, 2000; Spagnoli *et al.*, 2000; Guyotat *et al.*, 2002; Korshunov *et al.*, 2004; Reni *et al.*, 2004). However, the pertinent prognostic factors as well as the pattern of recurrence remain to be elucidated. According to several recent reports, the prognostic value of Karnofski performance status, tumour location, the extent of surgical removal, histological grade and even post-operative radiotherapy remain controversial. Actually, the small number of patients included in the studies reported, the heterogeneity of the population of patients in terms of age (adult, children) and location (intracranial, spinal) as well as the very long period in which the patients were treated (1960 to 2000) probably explain the lack of significant prognostic parameters validated in this pathological entity. As a consequence, optimal therapeutic management of adult intracranial ependymomas remains an ongoing debate.

We report herein the results of the first and largest multi-institutional retrospective analysis of intracranial ependymomas in 152 adult patients diagnosed in 24 French Neurosurgical University Hospital Centres after 1990. This cohort study was conducted by the French Neurosurgical Society (Société Française de Neurochirurgie, SFNC), the French Speaking Association of Neurologist and Neuro-Oncolgists (Association des Neurologues et Neuro-Oncologues de Langue Française, ANOCEF) and the French Neuropathological Society (Société Française de Neuropathologie, SFNP) to determine whether age, pre-operative clinical status, tumour location, extent of surgery, histological features and post-operative radiotherapy affect overall survival and progression-free survival.

Material and methods

Patient population

A multi-institutional database search on adult intracranial ependymomas including 24 French Neurosurgical University Hospital Centres was conducted by the SFNC, the ANOCEF and the SFNP. Inclusion criteria were: confirmation by two independent neuropathologists (DFB, AJ) of intracranial ependymoma in patients of both sexes, aged 18 years or older, operated after 1990, and with no previous brain irradiation for any intracranial pathology (Table 1). After central pathological review of 258 cases, 152 patients with confirmed diagnosis of ependymoma were eligible for this multicentric retrospective study. The clinical and radiological treatment and follow-up data were collected by a senior neurosurgeon (PM) and a senior neuro-oncologist (MB).

Table 1 Inclusion/Exclusion criteria

Inclusion criteria	Exclusion criteria
Both sex	
Age >18 years	Age <18 years
Diagnosis made after 1990	Diagnosis made before 1990
Diagnosis made before 2004	Diagnosis made after 2004
Confirmed histological diagnosis of ependymoma after central pathological review	Excluded diagnosis of ependymoma after central pathological review
Absence of previous cerebral radiotherapy for brain lesion	Previous cerebral radiotherapy for brain lesion

Clinico-radiological data

The following clinical data were collected: patient's age at surgery, sex, presenting symptoms and pre- and post-operative Karnofski performance status (KPS) score. Tumour location was divided into two groups: supratentorial and infratentorial ependymomas. Among supratentorial ependymomas, three subgroups were identified: intraparenchymal tumours, tumours arising in the lateral ventricles and tumours of the third ventricle. In the infratentorial tumour group, the invasion of the floor of the IVth ventricle and lateral extension into the foramen of Lushka were always notified. Contrast enhancement as well as associated hydrocephalus was also analysed. Patients were considered metastatic if MRI scans demonstrated intracranial or spinal tumour dissemination and/or if CSF analysis revealed abnormal cells.

Treatment modalities

Except for patients who died in the peri-operative period, the extent of surgery was evaluated by post-operative MRI scans. Peri-operative mortality was defined as death occurring within 3 months post-surgery and included neurosurgical complications and systemic complications such as pulmonary embolism, sepsis or cardiac failure. For these patients, extent of surgery was evaluated by a single neurosurgeon (PM) according to an extensive review of all operative protocols. Surgical resection was classified as complete (patients with no residual tumour on MRI scans or considered with total tumour removal based on operative protocol examination) or incomplete for all patients.

Regarding irradiation, the following data were collected: doses, time to surgery (adjuvant, at recurrence or progression) and location—cranial (focal or panencephalic) or cranio-spinal. For patients who received chemotherapy or radiosurgery treatments, no precision was collected concerning protocol or doses but precise time to surgery was noted.

Pathological examination

For all patients, slides used for diagnosis, coloured by hematein eosin and/or paraffin-embedded blocks, were sent to the same neuropathologist. Pathological examination was conducted centrally by two senior neuropathologists (DFB, AJ). Subependymomas and ependymoblastomas were excluded according to the WHO classification (2000). Ependymomas were

first classified as WHO grade II or WHO grade III (anaplastic) (Bouvier *et al.*, 2003). Secondarily, ependymomas were graded according to the Marseille neograding system based on objective anaplastic features. The following criteria were assessed and quantified as follows: necrosis (present versus absent), microvascular proliferation (presence versus absence) and mitotic count in 10 consecutive high-power fields (<5 versus ≥5). An ependymoma was considered low grade if 0 or 1 of the criterion was present and high grade if 2 or 3 criteria were present. Ki67-labelling index was performed in 108 cases (paraffin-embedded blocks and specimen fixed in formalin).

In doubtful cases, immunohistochemistry (immunoperoxydase with avidin biotin complex after antigen retrieval on Ventana Devices®) was performed to reach diagnosis. Expression of the following antigens was searched for with appropriate antibodies: GFAP (polyclonal Dakopatts), EMA (clone E29), synaptophysin (polyclonal Dakopatts), keratin (clone AE1/AE3/PCK26 and KL1) and vimentin (clone V9).

Statistical analysis

Categorical variables are expressed as percentage. Survivals were estimated by using the Kaplan–Meier method and curves were compared by using the log-rank test. The effect of potential risk factors on the disease-free and overall survival were evaluated with Cox proportional hazards models. Recursive partitioning analysis (RPA) using classification and regression trees (CART) algorithm was applied to establish prognostic groups (Breinman *et al.*, 1984). This is a method of building decision trees to model predictors. RPA using CART algorithm was performed using the variables significantly correlated to survival in both uni- and multivariate analysis. These variables were examined for the best split in a given population. A restriction was imposed on the tree construction such that terminal subgroups resulting from any given split must contain at least 10 patients. Terminal node populations were tested by log-rank test to determine whether any two groups were similar enough in survival to be merged. All statistical tests were two-sided, and the threshold for statistical significance was $P = 0.05$. Analyses were performed with SPSS for Windows version 11.5 (SPSS Inc, Chicago, Illinois, USA).

Results

Clinical data

Demographic data are summarized in Table 2. Mean age was 45.2 years (±16.3 yr) and the age range was 16 to 82 years. Impairment of cranial nerves as well as cerebello-vestibular symptoms were predominantly seen in infratentorial tumours, intracranial hypertension was more frequent in tumours of the third ventricle (V3) but also in tumours located infratentorially and in the lateral ventricle (LV). Hydrocephalus requiring shunting or endoscopic ventriculostomy was present in the intraventricular location only. Supratentorial parenchymal tumours were more likely to be associated with epilepsy, motor deficit and behavioural changes. No correlation was found between age, sex, clinical status and location, grade or extent of surgery (not shown).

Table 2 Population characteristics

Age (years)	
Min–max	18–82
Mean (years ± DS)	46.4 ± 16
Sex	
Male	76 (50%)
Female	76 (50%)
KPS score (pre-operative)	
≤80	71 (46.7%)
>80	81 (53.3%)
Location	
Supratentorial	46 (30.3%)
Parenchymal	22 (14.5%)
V3	16 (10.5%)
Lateral ventricle	8 (5.3%)
Infratentorial	106 (69.7%)
Lateral extension	20 (18.9%)
Floor extension	30 (28.2%)
Extension (lateral + floor)	31 (29.2%)
No extension	25 (23.6%)
Extent of surgery (MRI based)	
Gross total resection (GTR+)	89 (58.6%)
Gross total resection (GTR–)	63 (41.4%)
Operative mortality	12 (7.9%)
Histology	
WHO	
Grade II	109 (71.7%)
Infratentorial	88 (57.9%)
Supratentorial	21 (13.8%)
Grade III	43 (28.3%)
Infratentorial	18 (11.8%)
Supratentorial	25 (16.5%)
Marseille grading system	
Low grade	112 (73.7%)
Infratentorial	90 (59.2%)
Supratentorial	22 (14.5%)
High grade	40 (26.3%)
Infratentorial	16 (10.5%)
Supratentorial	24 (15.8%)
Complementary treatment	
RT	79 (52%)
Cranial RT alone	63 (41.4%)
Craniospinal RT	16 (10.5%)
Radiosurgery	2 (1.3%)
Chemotherapy	23 (15.1%)
Recurrence/progression	51 (33.6%)
Local isolated	41 (27%)
Metastasis	10 (6.6%)

Note: KPS = Karnofski preformance status; Max = maximum; Min = minimum; RT = radiotherapy; SD = standard deviation; V3 = third ventricle; WHO = World Health Organization.

Pathological data

Of the 258 cases sent for central pathological review, only 152 fulfilled diagnostic criteria of ependymomas. On both pathological and immunohistochemical features, the following diagnoses were excluded: glioblastomas, oligodendrogliomas and mixed oligoastrocytomas, pilocytic astrocytomas, subependymomas, papillary tumours of the pineal gland, central neurocytomas, papillary neuroglial tumours, oligodendroglioma with

neurocytic differentiation, medulloblastomas, metastases and papillary meningiomas (Table 3).

Tumours were graded in two different manners according to WHO classification and the Marseille grading system.

Table 3 Results of the French Study Central Pathological Review of 258 adult primary brain tumours initially diagnosed as ependymoma

	Number of patients (%)	Repartition among initial misdiagnosis
Confirmed ependymomas	152/258 (58.9%)	–
Misdiagnosis/differential diagnosis	106/258 (41.1%)	106 (100%)
Glioblastomas	*34 (13.2%)*	*32.1%*
Oligodendrogliomas and mixed oligoastrocytomas	*18 (7.0%)*	*17.0%*
Pilocytic astrocytomas	*4 (1.6%)*	*3.8%*
Subependymomas	*15 (5.8%)*	*14.1%*
Papillary tumors of the pineal gland	*12 (4.6%)*	*11.3%*
Central neurocytomas	*6 (2.3%)*	*5.7%*
Papillary glioneuronal tumors	*2 (0.8%)*	*1.9%*
Oligodendroglioma with neurocytic differentiation	*1 (0.4%)*	*0.8%*
Medulloblastomas	*6 (2.3%)*	*5.7%*
Metastasis	*6 (2.3%)*	*5.7%*
Papillary meningiomas	*2 (0.8%)*	*1.9%*

In WHO classification, 109 patients (88 infratentorial and 21 supratentorial tumours) harboured grade II ependymomas (71.7%) and 43 patients (18 infratentorial and 25 supratentorial tumours) grade III ependymomas (28.3%). In the Marseille grading system, 112 patients (90 infratentorial and 22 supratentorial) harboured low grade (0 or 1 anaplastic criterion) ependymomas (73.7%) and 40 patients (16 infratentorial and 24 supratentorial) high grade (2 or 3 anaplastic criterion) ependymomas (26.3%).

Location, grade and extent of surgery

These data are summarized in Table 4. Tumour location was supratentorial in 46 patients (30.3%) and infratentorial in 106 (69.7%). Among supratentorial tumours, parenchymal location was found in 22 patients (14.5%), V3 location in 16 (10.5%) and LV location in 8 (5.3%). Among patients with infratentorial tumours (106 patients), 30 patients (28.2%) presented with an extension into the floor of the IVth ventricle, 20 (18.9%) with a lateral extension through the foramen of Lushka, 31 (29.2%) with both extension and 25 (23.6%) with no extension. Supratentorial location was significantly associated with both grade III (WHO) and high grade (Marseille grading system) tumours compared to infratentorial tumours ($P<0.001$). Furthermore, within supratentorial tumours, parenchymal location was also

Table 4 Correlations between prognostic factors

Characteristics	Number of patients (%)	Number of patients (% of patients with specified characteristic)							
		Tumour location		Extent of surgery		Grade WHO		Marseille grading system	
		Infratentorial	Supratentorial	GTR (+)	GTR (−)	II	III	Low grade	High grade
Age (years)									
<55	99 (65.1)	69 (69.7)	30 (30.3)	59 (59.6)	40 (40.4)	71 (71.7)	28 (28.3)	72 (72.7)	27 (27.3)
≥55	53 (34.9)	37 (69.8)	16 (30.2)	30 (56.6)	23 (43.4)	38 (71.7)	15 (28.3)	40 (75.5)	13 (24.5)
Sex									
Male	76 (50)	58 (76.3)	18 (23.7)	43 (56.6)	33 (43.4)	53 (69.7)	23 (30.3)	55 (72.4)	21 (27.6)
Female	76 (50)	48 (63.1)	28 (36.9)	46 (60.5)	30 (39.5)	56 (73.7)	20 (26.3)	57 (75)	19 (25)
KPS score (pre-operative)									
≤80	75 (49.3)	48 (64)	27 (36)	35 (46.7)	40 (53.3)	50 (66.7)	25 (33.3)	54 (72)	21 (28)
>80	77 (50.7)	58 (75.3)	19 (24.7)	54 (70.1)	23 (29.9)	59 (76.6)	18 (23.4)	58 (75.3)	19 (24.7)
Tumour location									
Supratentorial	46 (30.3)	n.a.	n.a.	23 (50)	23 (50)	21 (45.7)*	25 (54.3)*	22 (47.8)*	24 (52.2)*
Infratentorial	106 (69.7)	n.a.	n.a.	66 (62.3)	40 (37.7)	88 (83)*	18 (17)*	90 (84.9)*	16 (15.1)*
Extent of surgery									
GTR (+)	89 (58.6)	66 (74.2)	23 (25.8)	n.a.	n.a.	64 (71.9)	25 (28.1)	66 (74.2)	23 (25.8)
GTR (–)	63 (41.4)	40 (63.5)	23 (46.5)	n.a.	n.a.	45 (71.4)	18 (28.6)	46 (73)	17 (27)
Grade (WHO)									
II	109 (71.7)	88 (80.7)	21 (19.3)	64 (58.7)	45 (41.3)	n.a.	n.a.	105 (96.3)	4 (3.7)
III	43 (28.3)	18 (41.9)	25 (58.1)	25 (58.1)	18 (41.9)	n.a.	n.a.	7 (16.3)	36 (83.7)
Marseille grading system									
Low grade	112 (73.7)	90 (80.4)	22 (19.6)	66 (58.9)	46 (41.1)	105 (93.8)	7 (6.2)	n.a.	n.a.
High grade	40 (26.3)	16 (40)	24 (60)	23 (57.5)	17 (42.5)	4 (10)	36 (90)	n.a.	n.a.
Adjuvant RT									
No	93 (61.2)	69 (74.2)	24 (25.8)	66 (71)	27 (29)	89 (95.7)*	4 (4.3)*	81 (87.1)*	12 (12.9)*
Yes	59 (38.8)	37 (62.7)	22 (37.3)	23 (39)	36 (61)	20 (33.9)*	39 (66.1)*	31 (52.5)*	28 (47.5)*

Note: GTR (+): gross total removal GTR (−): incomplete tumour resection.*$P<0.05$.

Table 5 Overall survival rates

Variables	Nb of death/Nb of patients (%)	Univariate analysis			Multivariate analysis		
		5-yr (mo ± SE)	10 yr (mo ± SE)	Log rank	*P*	RR	CI 95%
Age (years)				0.07	**0.004**		
<55	21/99 (21.2)	88.7% ± 3.6	79.8% ± 5.0			1	–
≥55	17/53 (32.1)	75.8% ± 7.1	66.3% ± 10.8			3.8	1.5–9.3
Sex				0.55	0.85		
Male	24/76 (31.6)	81.2% ± 5.2	75.1% ± 6.3				
Female	14/76 (18.4)	88.2% ± 4.3	78.0% ± 6.1				
KPS score (preop)				0.002	**0.03**		
≤80	30/75 (40)	75.7% ± 5.8	65.0% ± 7.1			1	–
>80	8/77 (10.4)	93.4% ± 3.2	88.3% ± 4.7			0.3	0.1–0.9
Tumour location				<0.001	0.06		
Supratentorial	22/46 (47.8)	62.5% ± 9.1	45.8% ± 10.6				
Infratentorial	16/106 (15.1)	93.2% ± 2.7	87.1% ± 4.3				
Extent of surgery				0.03	**0.006**		
GTR (+)	15/89 (16.9)	89.0% ± 3.7	84.3% ± 4.8			1	–
GTR (−)	23/63 (36.5)	78.2% ± 6.2	64.0% ± 8.3			3.3	1.4–7.8
Grade (WHO)				<0.001	0.85		
II	14/109 (12.8)	93.8% ± 2.7	88.4% ± 4.0				
III	24/43 (55.8)	62.1% ± 8.5	46.7% ± 9.1				
Grade Marseille				<0.001	<**0.001**		
Low grade (0 or 1 crit./3)	13/112 (11.6)	94.0% ± 2.6	87.9% ± 4.2			1	–
High grade (2 or 3 crit./3)	25/40 (62.5)	59.5% ± 8.9	43.2% ± 10.3			10.0	3.5–28.2
Ki-67 index				0.001	–	–	–
<10%	6/70 (8.6)	94.3% ± 3.2	91.4% ±4.3				
≥10%	15/38 (39.5)	74.3% ± 8.0	55.3% ± 11.4				
Adjuvant RT				0.009	0.29		
No	13/93 (14)	93.1% ± 3.0	85% ± 5.4				
Yes	25/59 (42.4)	73.6% ± 6.4	64.9% ± 7.3				

Note: CI = confidence interval; Crit. = criteria; GTR = gross total removal; Nb = number; preop = pre-operative; RR = relative risk; RT = radiotherapy; yr = year; bold values are the values statistically significant (<0.05) in multivariate analysis.

significantly associated with grade III (WHO) tumours ($P = 0.02$) and high-grade (Marseille grading system) tumours ($P = 0.01$). Post-operative MRI scans were available for all patients alive 3 months post-operatively and constituted the reference method to evaluate the extent of surgery. There was neither significant correlation between location and extent of surgery nor between grade (WHO and Marseille grading system) and extent of surgery.

Follow-up data and patterns of failure

At the endpoint of the follow-up analysis, 114 patients (79 disease-free) (75%) were still alive after a median duration follow-up of 73 months (range, 14–159 months). Thirty-eight patients (25%) died during the follow-up period. Of these patients, causes of death included ependymoma progression in 25 patients (65.8%), complications within 3 months after surgery (operative mortality) in 12 patients (31.6% which represents 7.9% of the entire population) and unrelated cause during disease-free period (lung cancer) in 1 patient (2.6%). Fifty-one patients presented recurrence or progressive disease (33.6% of patients). Disease progressed as an isolated local recurrence in 46 patients (30% of patients; 82% of failures). Disseminated disease within the central nervous system was found in 10 patients (6.6% of patients; 18% of failures). Among these patients, five developed distant intracranial metastasis (3.3% of patients), four presented with spinal metastasis (2.6% of patients) and one patient combined distant intracranial and spinal metastasis (0.7% of patients). All of these patients presented associated focal progressive or recurrent disease. Of the 10 patients with central nervous system metastasis, eight were histological grade III and four had initially incomplete resection as assessed by post-operative MRI scans. Histology was significantly correlated to metastasis occurrence ($P = 0.03$) but not the extent of surgery ($P > 0.05$).

Survival analysis

Overall survival

The 5- and 10-year overall survival rates for the entire cohort were 84.8 and 76.5%, respectively. On univariate analysis (Table 5), infratentorial location ($P < 0.001$), pre-operative KPS score >80 ($P = 0.002$), GTR (+) ($P = 0.036$), low grade (Marseille grading system) ($P < 0.001$), WHO grade II ($P < 0.001$), the delivery of adjuvant RT ($P = 0.009$) and a Ki-67-labelling index <10% ($P = 0.001$) were

found to be associated with a longer survival (Fig. 1). On multivariate analysis (Table 5), age <55 years ($P = 0.004$), GTR ($P = 0.006$), pre-operative KPS score >80 ($P = 0.03$) and low (0 or 1 criterion/3) Marseille grade ($P < 0.001$) were confirmed as prognostic indicators while infratentorial location ($P = 0.06$) had borderline significance. Age, sex and adjuvant treatment exhibited no independent association with OS. Ki-67-labelling index was not considered a candidate variable because data was available for only 108/152 patients.

Progression-free survival

The 5- and 10-year progression-free survival rates for the entire cohort were of 65.3 and 52.8%, respectively. On univariate analysis (Table 6), infratentorial location ($P < 0.001$), pre-operative KPS score >80 ($P = 0.03$), GTR ($P = 0.004$), low grade (Marseille grading system) ($P < 0.001$), WHO grade II ($P < 0.001$) and a Ki-67-labelling index <10% ($P < 0.001$) were found to be associated with a longer progression-free survival (Fig. 2). On multivariate analysis (Table 6), only GTR ($P < 0.001$), pre-operative KPS >80 ($P = 0.04$) and low grade (Marseille grading system) ($P < 0.001$) were confirmed as significant independent prognostic indicators. For the same reason aforementioned, Ki-67-labelling index was not considered a candidate variable.

Adjuvant RT impact on OS and PFS

Among low-grade (Marseille grading system) ependymomas, GTR was achieved in 66 patients. Of these patients, 59 did not receive RT and 7 benefited from local irradiation. No significant difference was found in terms of PFS or OS in these subgroups. Among the 46 remaining patients in whom GTR was not achieved 24 benefited from post-operative RT. A significant statistical difference was found in PFS ($P = 0.05$) between patients who received post-operative RT compared to those without adjuvant treatment (Fig. 3) and a trend towards a better OS was also found (data not shown).

Among patients with high-grade (Marseille grading system) ependymomas, GTR was achieved in 23 patients. Of these patients, 11 did not receive adjuvant RT and 12 benefited from cranial or cranio-spinal RT. No significant difference was found in PFS or OS in these subgroups; however, a trend toward a better PFS ($P = 0.09$) was found in irradiated patients (data not shown). Among the 17 remaining patients with incomplete resection, 16 benefited from post-operative RT. No significant statistical difference was found in PFS or OS for patients who benefited from post-operative irradiation. However, due to the limited number of patients harbouring high-grade (Marseille grading system) ependymomas, statistical significance of the different tests remained weak.

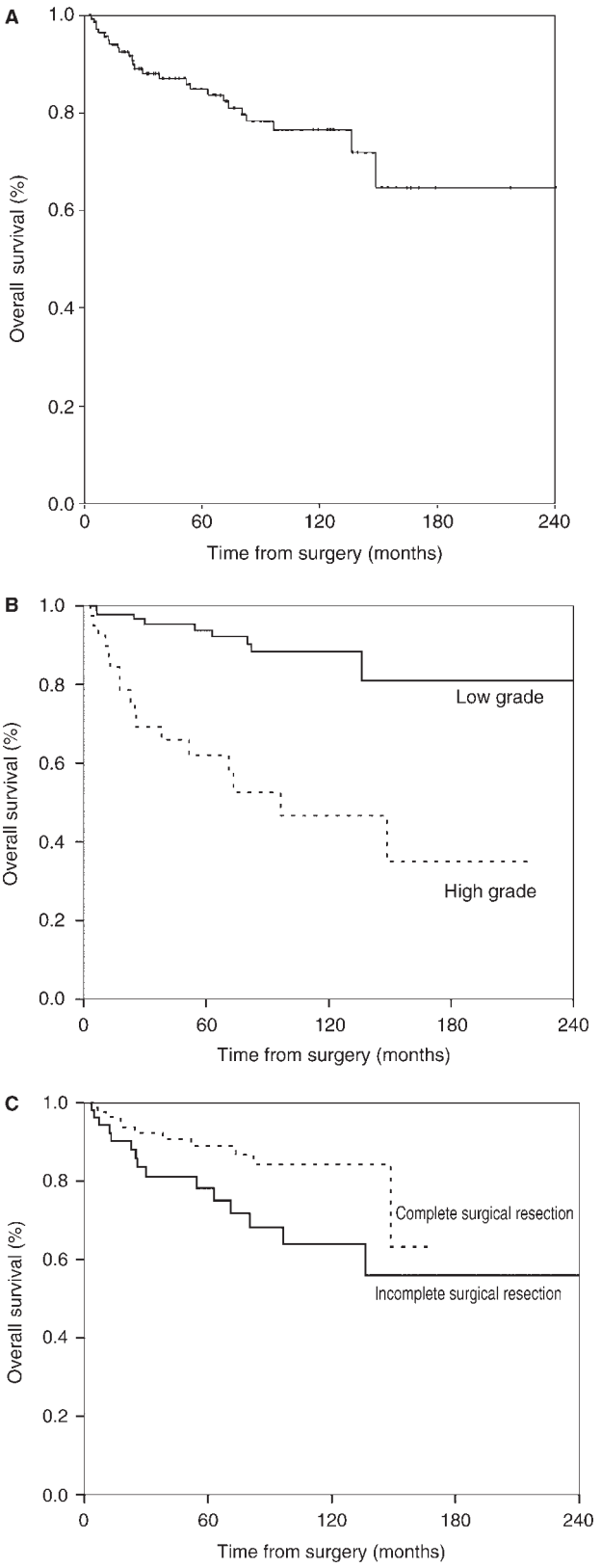

Fig. 1 (**A**) Kaplan–Meier overall survival curve for the entire population. (**B**) Comparison of Kaplan–Meier overall survival curves according to histological grade (log-rank test). (**C**) Comparison of Kaplan–Meier overall survival curves according to extent of surgery (log-rank test).

Table 6 Progression free-survival rates

Variables	Nb of disease progression/Nb of patients (%)	Univariate analysis			Multivariate analysis		
		5 yr (mo ± SE)	10 yr (mo ± SE)	Log rank	*P*	RR	CI 95%
Age (years)				0.373	0.11		
<55	40/99 (40.4)	67.1% ± 5.2	55.3 ± 5.9				
≥55	16/53 (30.2)	60.9% ± 8.4	43.8 ± 12.4				
Sex				0.777	0.35		
Male	29/76 (38.2)	65.8% ± 6.3	53.8% ± 7.6				
Female	27/76 (35.6)	64.8% ± 6.2	52.0% ± 7.2				
KPS score (preop)				0.003	**0.04**		
≤80	36/75 (48)	54.6% ± 6.6	41.6% ± 7.3			1	–
>80	20/77 (26)	75.3% ± 5.6	63.7% ± 7.2			0.5	0.3–0.9
Tumour location				<0.001	0.17		
Supratentorial	24/46 (52.2)	37.1% ± 8.7	27.8% ± 8.7				
Infratentorial	32/106 (30.2)	76.6% ± 4.6	62.4% ± 6.3				
Extent of surgery				0.004	**<0.001**		
GTR (+)	26/89 (29.2)	73.4% ± 5.3	59.7% ± 6.8			1	–
GTR (–)	30/63 (47.6)	52.6% ± 7.3	43.2% ± 7.8			2.9	1.6–5.3
Grade (WHO)				<0.001	0.14		
II	29/109 (26.6)	81.3% ± 4.3	64.2% ± 6.3				
III	27/43 (62.8)	25.7% ± 7.8	25.7% ± 7.8				
Grade Marseille				<0.001	**<0.001**		
0 or 1 crit./3	31/112 (27.7)	79.3% ± 4.4	62.6% ± 6.2			1	–
2 or 3 crit./3	25/40 (62.5)	27.6% ± 8.1	27.6% ± 8.1			5.1	2.8–9.4
Ki-67 index				<0.001	–		
<10%	17/70 (24.3)	86.0% ± 4.7	65.5% ± 7.9				
≥10%	24/38 (63.2)	32.1% ± 8.7	24.1% ± 9.5				
Adjuvant treatment				0.551	0.33		
No	32/93 (34.4)	66.4% ± 5.9	53.9% ± 7.1				
Yes	24/59 (40.7)	63.8% ± 6.7	52.3% ± 7.6				

Note: CI = confidence interval; Crit. = criteria; GTR = gross total removal; Nb = number; preop = pre-operative; RR = relative risk; RT = radiotherapy; yr = year; bold values are the values statistically significant (<0.05) in multivariate analysis.

Chemotherapy

In the entire population, 21 patients had chemotherapy (13.8%). All patients treated with chemotherapy have had concomitant or previous radiotherapy. According to Marseille grading system, 16 patients had high-grade and 5 had low-grade tumours. Among the 16 patients with high-grade tumours, 8 had gross total resection. Of these eight patients, all seven treated for recurrent disease died but one had adjuvant chemotherapy and is still alive after 36 months follow-up. Of the eight patients with incomplete resection, seven were treated at recurrence and five of them died. One patient benefited from adjuvant chemotherapy and is still alive.

Recursive partition analysis using CART algorithm

The most significant split for the first node was the histological grade evaluated by the Marseille grading system. Among the 40 patients with high-grade tumours, the most significant split was by the extent of surgery. Among the 112 patients with low-grade tumours the next significant split occurred between patients with KPS score ≤80 versus >80.

The classification tree resulting from the CART modelling process exhibited three final groups of ependymoma patients with distinctly different survival (Fig. 4). According to the CART tree, the patients with the worst survival (group III) are those with high-grade tumours and incomplete resection. The best survival was in patients with low-grade tumours and KPS score >80 (group I). All other patients had minor differences in survival and form a middle stage (group II). Median survival time was not estimable for groups I and II and was of 25.7 months for group III (95% CI, 7.2–44.1%) (Table 7).

Discussion

Adult intracranial ependymomas are rare CNS tumours that continue to generate considerable controversy with regard to their clinical management. The lack of widely accepted and recognized prognostic factors leads to the absence of standardized therapeutic guidelines. In this study we analysed potential clinical and pathological prognostic factors in the most important and homogenous population of adult patients harbouring intracranial ependymomas treated in the microsurgical era.

The extent of surgery has emerged as one of the most significant predictors of outcome in patients with intracranial ependymomas (Ernestus *et al.*, 1997;

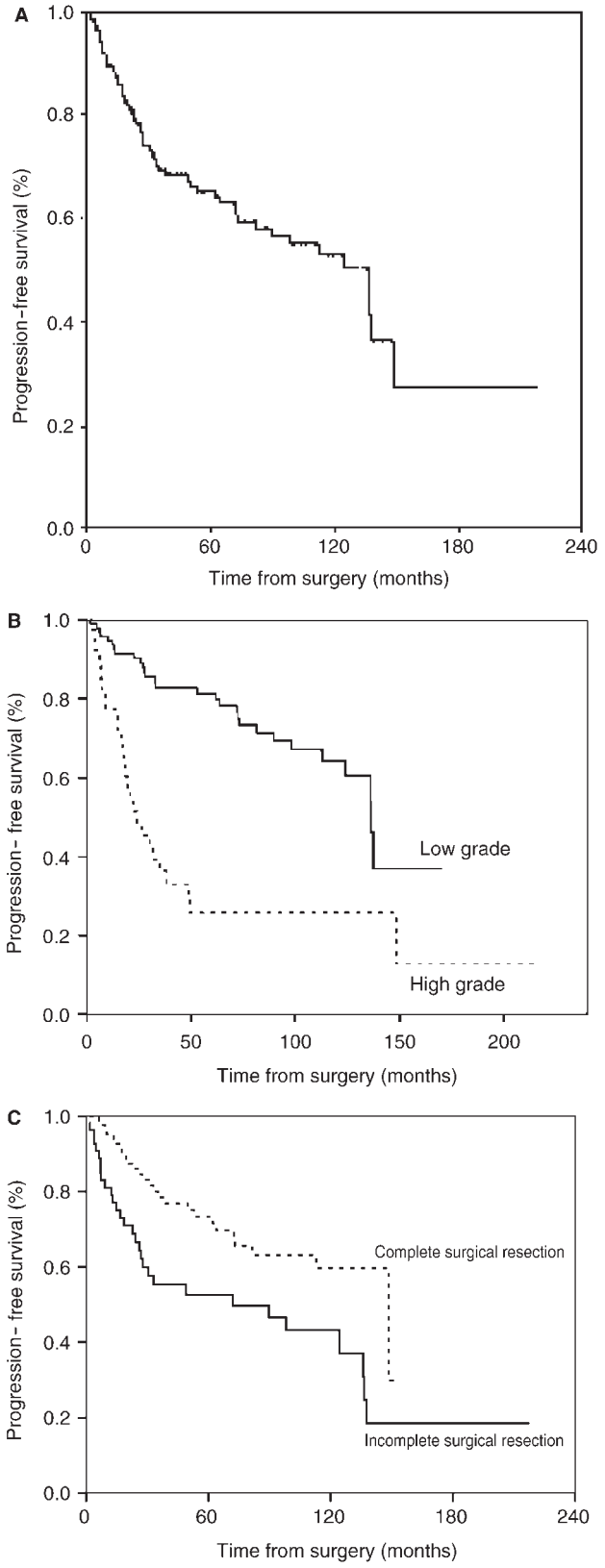

Fig. 2 **(A)** Kaplan–Meier progression-free survival curve for the entire population. (**B**) Comparison of Kaplan–Meier progression-free survival curves according to histological grade (log-rank test). (**C**) Comparison of Kaplan–Meier progression survival curves according to extent of surgery (log-rank test).

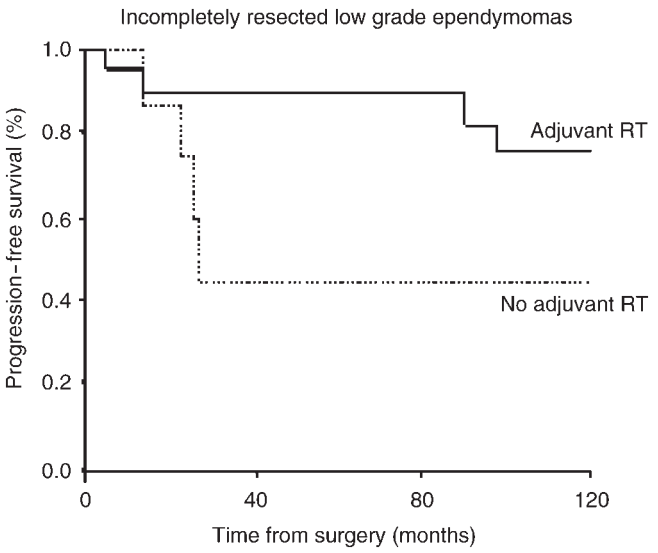

Fig. 3 Impact of radiotherapy in incompletely resected low-grade ependymomas.

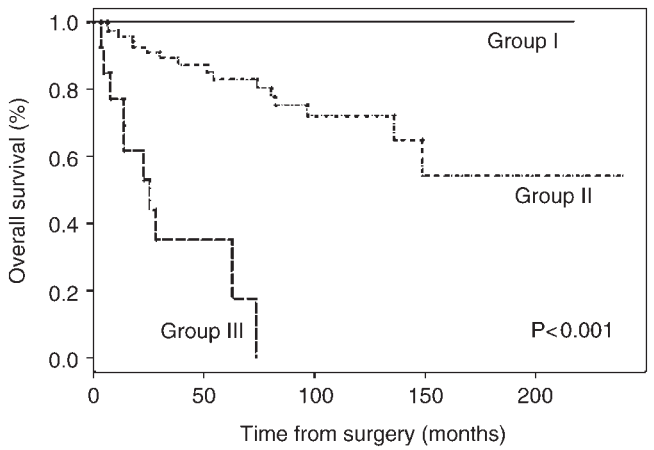

Fig. 4 Comparison of Kaplan–Meier overall survival curves of the three groups generated by RPA using CART modelling process.

Paulino and Wen, 2000; Oya *et al.*, 2002; Paulino *et al.*, 2002; Korshunov *et al.*, 2004; Reni *et al.*, 2004; Kawabata *et al.*, 2005; Rogers *et al.*, 2005). Note, however, that some authors have found no correlation between extent of surgery and prognosis (Vanuytsel *et al.*, 1992; McLaughlin *et al.*, 1998; Robertson *et al.*, 1998; Guyotat *et al.*, 2002). In our series, the extent of resection was a major prognostic factor in terms of survival and recurrence. Actually, gross total removal was significantly associated with better OS and PFS in our population both in univariate and multivariate analysis. These results are strengthened by the fact that almost all of our patient population benefited from post-operative MRI examination. Thus, we recommend performing a second surgery in patients with incomplete resection when technically feasible. In some

Table 7 Differences in outcome for the final adult intracranial ependymoma subsets generated by RPA using CART algorithm

Final ependymoma subset	Nb of patients (%)	Death Nb of patients (%)	Median OS (months)	5-year OS	10-year OS
Group I [low-grade (Grade Marseille 0 or 1 crit./3), KPS score (preop) ≤80]	60	60 (0%)	NA	100%	100%
Group II (others)	77	23 (29.9%)	NA	83%	71%
Group III [high-grade (Grade Marseille (2 or 3 crit./3), GTR (−)]	15	15 (100%)	25 (95%CI, 7.2–44.1%)	27%	0%

Note: CI = confidence interval; Crit. = criteria; GTR = gross total removal; Nb = number; OS = overall survival; preop = pre-operative.

reports, extent of surgery also correlated with CSF dissemination and metastatic rate (Rezai *et al.*, 1996; Korshunov *et al.*, 2004; Kawabata *et al.*, 2005). This was not the case in our study but histological grade as reported in other studies was strongly correlated with CSF dissemination and metastasis (Rezai *et al.*, 1996; Korshunov *et al.*, 2004; Kawabata *et al.*, 2005).

The prognostic value of histological findings remains a controversial issue probably attributable to sample size, variability in the definition of anaplasia, discrepancies in histological diagnoses and the inclusion in some series of ependymoblastomas and subependymomas which exhibit different biological behaviour and should be analysed separately (Lyons and Kelly, 1991; Schiffer *et al.*, 1991; Ernestus *et al.*, 1997; Schild *et al.*, 1998; Spagnoli *et al.*, 2000; Korshunov *et al.*, 2004; Reni *et al.*, 2004; Kawabata *et al.*, 2005). As emphasized by this study, in 106/258 (41.1%) cases an initial incorrect diagnosis of ependymoma was made. Four classes of pathological misdiagnoses can be distinguished. The first concerns erroneous diagnosis which would be avoided by a trained pathologist aware of the peculiar histological and immunohistochemical features. This category includes central neurocytomas, medulloblastomas, metastatic carcinomas and papillary meningiomas. The second concerns confusion between subependymomas and ependymomas. The third class results from the emergence of new pathological entities such as papillary tumours of the pineal region, glioneuronal tumours and oligodendrogliomas with neurocytic differentiation. The fourth and last class corresponds to gliomas which are frequently misdiagnosed as ependymomas. In our study, except for pilocytic ependymomas which were located in the posterior fossa, the other gliomas were all in supratentorial parenchymal location. Therefore, in the authors' opinion, in the case of supratentorial parenchymal location, the pathologist should carefully exclude oligodendrogliomas, mixed oligoastrocytomas or glioblastomas before assessing the diagnosis of ependymoma. Because *olig2* staining is usually lacking in ependymomas, it might be useful to differentiate true ependymomas from others gliomas based on this molecular marker expression (Bouvier *et al.*, 2003). In a recent series, Reni *et al.* (2004) did not find histological grade to be correlated to survival. However, in their study, no central pathological review was planned and the role of histology in predicting outcome may have been masked by the varying definitions of anaplasia used by pathologists involved in the diagnostic process. The lack of impact of tumour grade on survival in their report may be also attributable to the relatively small number of anaplastic ependymomas. Some other reports have denied the prognostic value of histology (Schiffer *et al.*, 1991; Gerszten *et al.*, 1996; Robertson *et al.*, 1998). However, most recent series have demonstrated a significant increase in overall and progression-free survival in low-grade ependymomas (Ernestus *et al.*, 1997; McLaughlin *et al.*, 1998; Figarella-Branger *et al.*, 2000; Korshunov *et al.*, 2004; Wolfsberger *et al.*, 2004; Kawabata *et al.*, 2005; Kurt *et al.*, 2006). Korshunov *et al.* (2004), in a recent single institution study of 258 intracranial ependymomas including 143 adults treated in the microsurgical era, found the grade of tumour malignancy to be a cornerstone for the prognosis. The lack of consensus regarding ependymomas anaplastic criteria may explain the conflicting data concerning histological grade and prognosis. For this reason we have elucidated the Marseille grading system, a simple and more reproducible grading scheme to classify ependymomas. Only three criteria were taken into account, necrosis, microvascular proliferation (present/absent) and mitotic count (threshold 5). We observed that ependymomas exhibiting 0 or 1 criterion had a significantly better prognosis than ependymomas showing 2 or 3 criterion. Although WHO grade was also significantly correlated to a better OS and PFS in univariate analysis, in our study, only the Marseille grading system was significantly correlated to OS and PFS in multivariate analysis. These criteria were already used for prognostic significance in paediatric ependymomas but in this particular population only ependymomas showing the presence of three criteria differed statistically from others. Our results are consistent with those of Korshunov *et al.* (2004). In the present study, histological grade was significantly and strongly correlated with OS and PFS both on univariate and multivariate analysis. These results are strengthened by the fact that a central pathological review was planned and conducted by two confirmed neuropathologists (D.F.B and A.J.). The results of the RPA using CART modelling process reinforces the importance of the prognostic value of histological grading which correspond to the first split in the entire population. The fact that tumour grade influences outcome for patients with ependymoma, independently of

others factors, should be considered in the design and analysis of future prospective trials involving adult patients. In the present analysis, the Ki-67 immunolabelling index was available for 108 patients. On univariate analysis, a Ki-67 index <10 was significantly correlated to a better prognosis in PFS and OS. Due to lack of data for this prognostic factor, we did not use it in the Cox proportional hazards models construct. A review of the literature on tumour cells proliferation index in ependymomas shows a considerable variation of Ki-67 immunolabelling fractions (Rezai *et al.*, 1996; Prayson, 1998; Figarella-Branger *et al.*, 2000; Suzuki *et al.*, 2001; Verstegen *et al.*, 2002; Wolfsberger *et al.*, 2004). The variation is most likely attributable to tissue fixation, staining protocols and mode of quantification. For these reasons, in this multicentric study, Ki-67 immunolabelling index was measured from paraffin-embedded block of tumour in the same laboratory by the same neuropathologist (D.F.B). Our results are consistent with those of Wolfsberger *et al.* and others and underline the potential interest of assessing the Ki-67 index in adult intracranial ependymomas for outcome prediction in the routine diagnostic setting (Rezai *et al.*, 1996; Prayson, 1998; Figarella-Branger *et al.*, 2000; Wolfsberger *et al.*, 2004; Kurt *et al.*, 2006).

Another tumour-related prognostic factor is the tumour location whose predictive role is probably confounded essentially by patient age and histological grade (Figarella-Branger *et al.*, 2000; Korshunov *et al.*, 2004; Reni *et al.*, 2004; Kawabata *et al.*, 2005; Rogers *et al.*, 2005). The location of intracranial ependymomas has been found to be associated with clinical outcome, although conflicting results have been reported (Hamilton and Pollack, 1997). Since very few intracranial ependymoma studies have been conducted in adult patients, the role of tumour location in this population is not well-known. In the current series, tumour location was significantly correlated to OS and PFS in univariate analysis but not in multivariate analysis although infratentorial location was associated with a trend towards a more favourable prognosis in OS. This is consistent with earlier reports (McLaughlin *et al.*, 1998; Korshunov *et al.*, 2004; Reni *et al.*, 2004). A likely explanation is the prevalence of high-grade ependymoma in supratentorial location as found in our study. A recent report on intracranial ependymoma demonstrated site-related differences in the molecular biology of these neoplasms raising the question of whether infratentorial and supratentorial ependymomas represent a molecularly distinct entity (Korshunov *et al.*, 2003).

Among patient-related prognostic factors, age <55 years and KPS >80 had positive impact on survival. Age <55 years was associated with a better prognosis in multivariate analysis in terms of OS but not for PFS. These results are consistent with those of Reni *et al.* but differ from Guyotat *et al.* (Guyotat *et al.*, 2002; Reni *et al.*, 2004). These are the only two reports in the literature analysing survival in adult intracranial ependymomas with regard to different age groups. According to the median age of our population two cut-off values were chosen: 45 and 55 years. Only the latter exhibited a difference in survival analysis. KPS >80 was associated with a better prognosis in multivariate analysis both for OS and PFS. Few reports evaluated the influence of KPS in ependymomas. All these reports led to conflicting results (Rawlings *et al.*, 1988; Stuben *et al.*, 1997; Spagnoli *et al.*, 2000; Guyotat *et al.*, 2002).

There is a widespread opinion that post-operative irradiation should be included in standard care for patients with high-grade ependymomas (McLaughlin *et al.*, 1998; Oya *et al.*, 2002; Mansur *et al.*, 2005; Rogers *et al.*, 2005). This was the most usual attitude observed in our retrospective study. However, for patients with low-grade ependymomas, especially when complete tumour excision could be achieved, the role of RT remains controversial and this was observed in the current series. Recently, Rogers *et al.* reported the impact of RT in a series of 45 patients (25 irradiated) harbouring essentially grade II (96%) posterior fossa ependymomas (Rogers *et al.*, 2005). They concluded that adjuvant RT significantly improves tumour control but not overall survival and thus recommend the use of post-operative RT regardless of the extent of surgical resection. In our study we were unable to answer this question since almost all patients with low-grade ependymomas in whom complete resection of the tumour was achieved did not undergo RT. In the authors' opinion, there is not yet enough strong evidence that supports the benefit of RT in completely resected low-grade tumours to recommend adjuvant RT in this situation. A 'wait and see' policy could also be discussed for these cases reserving RT for recurrent disease. Only a prospective randomized study will be able to resolve this issue. In other respects, concerning incompletely resected low-grade ependymomas, in the current series adjuvant RT significantly improves the PFS rate and shows a trend towards a better OS. Although these data must be interpreted with caution, adjuvant RT in incompletely resected low-grade ependymomas might be of interest in this situation. Concerning high-grade tumours, we did not find significant differences in PFS and OS in completely resected tumours but a trend towards a better PFS and OS in patients with post-operative RT. However, the population subgroups involved were too small to draw any categorical conclusion. Finally, in patients with incompletely resected high-grade tumours, no significant difference could be found in terms of PFS and OS in patients who benefited from adjuvant RT or not but of these 17 patients 16 had adjuvant RT precluding any conclusion about impact of RT in this subgroup of patients. In these patients, 11 had chemotherapy, 10 at recurrence and 1 adjuvant to surgery associated with radiotherapy. Among these patients seven died during follow-up. Among the six patients who did not undergo chemotherapy regimen four died during follow-up. Again the small size of each sample precludes any conclusion on the optimal

therapeutic proposal in this grave outcome subgroup. It should be kept in mind that negative selection bias in the ependymomas series reported, which are almost all retrospective, cannot be ruled out and that prospective trials are warranted to delineate strong therapeutic guide lines.

To our knowledge, the present series represents the largest report on intracranial ependymomas in adults in the microneurosurgical era. This study and analysis of the literature further highlights that complete tumour removal is a main prognostic factor and the treatment of choice in adult intracranial ependymomas. Application of reproducible diagnostic criteria for ependymoma grading has highlighted the key role of histology in clinical outcome. These two issues are strengthened by the fact that in this multicentric study a central pathological review was conducted by two confirmed neuropathologists and that the post-surgical residual disease was evaluated on MRI in almost all cases. The three groups exhibited by the RPA using CART modelling process, with significantly different survival, could be considered in the design and analysis of future prospective trials involving adult ependymoma patients. Although no meaningful conclusion can be reached on the magnitude of impact of RT on clinical outcome, our results demonstrate a trend toward better PFS and OS in incompletely resected low-grade ependymomas and in completely resected high-grade ependymomas.

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