J Neurooncol (2009) 95:367–375
DOI 10.1007/s11060-009-9934-0

CLINICAL STUDY - PATIENT STUDY

WHO grade II and III meningiomas: a study of prognostic factors

Anne Durand · François Labrousse · Anne Jouvet · Luc Bauchet · Michel Kalamaridès · Philippe Menei · Robert Deruty · Jean Jacques Moreau · Michelle Fèvre-Montange · Jacques Guyotat

Received: 17 January 2009 / Accepted: 1 June 2009 / Published online: 27 June 2009

Abstract Meningiomas represent one of the largest subgroups of intracranial tumors. They are generally benign, but may show a histological progression to malignancy. Grades II and III meningiomas have been less well studied and are not well controlled because of their aggressive behaviour and recurrences. There is no consensus on therapeutic strategies and no prognostic factors are known. In order to determine these parameters, a multi-institutional retrospective analysis was performed in France with the support of the Neuro-Oncology Club of the French Neurosurgical Society. This study was performed on 199 adults treated for WHO grade II (166 patients) or grade III (33 patients) meningiomas between 1990 and 2004 in the Neurosurgery Departments of five French University Hospitals. Data on epidemiology, clinical behaviour and therapy were collected. Overall survival and progression-free survival were analysed as a function of each possible prognostic factor. For patients with grade II meningiomas, the 5- and 10-year OS rates were 78.4 and 53.3%, respectively, while, for patients with grade III meningiomas, the corresponding values were 44.0 and 14.2%. For patients with grade II meningiomas, the 5- and 10-year PFS rates were 48.4 and 22.6%, respectively, the corresponding values for patients with grade III meningiomas being 8.4 and 0%. For the grade II meningiomas, univariate analysis showed that age < 60 years ($P < 0.0001$) and Simpson 1 resection ($P = 0.055$) were associated with a longer OS. For the grade III meningiomas, univariate analysis showed that age < 60 years ($P < 0.0001$) and RT ($P = 0.036$) were associated with a longer OS. Histological grade II was found to be associated with a longer PFS ($P = 0.0032$) and RT reduced the PFS in grade II meningiomas ($P = 0.0006$) There were no other prognostic factors in terms of PFS for grades II and III meningiomas in univariate analysis. Multivariate analysis confirmed that age (< 60 years), Simpson 1 and histological grade II were independent prognostic factors for survival. This retrospective study might improve the management of grades II and III meningiomas. Prospective trials should delineate strong therapeutic guidelines for high-grade meningiomas.

Keywords Malignancy · Meningiomas · Prognostic factors · Survival · Treatment

A. Durand (✉) · R. Deruty · J. Guyotat
Department of Neurosurgery D, Groupement Hospitalier Est, Hôpital Neurologique Wertheimer, 69677 Bron, France
e-mail: anne.durand2@orange.fr

F. Labrousse
Department of Neuropathology, CHU Dupuytren, 87000 Limoges, France

A. Jouvet
Department of Neuropathology, Groupement Hospitalier Est, Hôpital Neurologique Wertheimer, 69677 Bron, France

L. Bauchet
Department of Neurosurgery, Hôpital G. Chauliac, 34295 Montpellier, France

M. Kalamaridès
Department of Neurosurgery, Hôpital Beaujon, 92118 Clichy, France

P. Menei
Department of Neurosurgery, CHU, 49933 Angers, France

J. J. Moreau
Department of Neurosurgery, CHU Dupuytren, 87000 Limoges, France

A. Jouvet · M. Fèvre-Montange
Inserm U482, Université de Lyon, Lyon1, UMR-S842, 69372 Lyon, France

Introduction

Malignant meningioma subtypes were clearly defined in 1938 by Cushing and Eisenhardt [1], and later recognised by the World Health Organization (WHO). The 2000 and 2007 WHO classifications defined the most frequent subtype as grade I meningioma and atypical and anaplastic neoplasms as grades II and III meningiomas, respectively [2, 3]. Grade II meningiomas, which represented only 5–7% of meningiomas before the 2007 WHO classification [3], now account for more than 20% of all meningiomas [3–5]. Because of their aggressive behaviour, grades II and III meningiomas have an unpredictable outcome [4, 6, 7]. Reported series have consisted of only a few patients [8–13]. As a consequence, prognostic factors and therapeutic strategy are not clear and considerable controversy remains.

There is no consensus on the management of grades II and III meningiomas. Surgical resection is recognised as a determinant prognostic factor in all meningiomas [14, 15]. There is no consensus for the role of radiotherapy (RT) in therapeutic management [5, 16]. Concerning WHO grade III meningiomas, RT is considered necessary because of their potential for recurrence and aggressive behaviour [17]. This adjuvant treatment is more controversial in the treatment of WHO grade II meningiomas. Some surgeons favour repeated surgical resections. Chemotherapy (CT) has not shown any convincing effect on atypical and anaplastic meningiomas and should be reserved for recurrent meningiomas when all standard therapies have failed [15, 16, 18].

In order to analyse the prognostic factors, the effect of different treatments and the behaviour of grades II and III meningiomas, a multi-institutional retrospective analysis was performed in France with the support of the Neuro-Oncology Club of the French Neurosurgical Society (Société Française de Neurochirurgie, SFNC). This study included adults treated for WHO grades II and III meningiomas between 1990 and 2004 in the Neurosurgery Departments of five French University Hospitals.

Clinical materials and methods

Patient population

A retrospective multi-institutional database search was carried out. Data were collected in the Neurosurgery Departments of five French teaching hospitals (Angers $n = 37$, Limoges $n = 53$, Lyon $n = 47$, Montpellier $n = 29$ and Paris Beaujon $n = 33$) with the support of the SFNC.

The criteria for inclusion were adult patients (>18 years) presenting with intracranial grades II and III meningiomas between 1990 and 2004. Each case included was followed up for more than 3 years. The patients included in the cohort were operated on the first time. Cases were included when initial diagnosis of grade II or III meningioma was retained.

Clinico-radiological data

Once the histopathological diagnosis had been confirmed, data were collected including patient's age at surgery, gender and symptoms. Initial imaging was a computed tomography scan or magnetic resonance imaging (MRI) with contrast, depending on the centre. MRI was not always available. Data on location and contrast were obtained from the imaging. Tumour location was divided into the six groups of convexity, falx, parasagittal, posterior fossa, cranial base and others. Contrast was classified into two groups: homogeneous or heterogeneous (suggested necrosis in the tumour).

Treatment modalities

Surgical resection was graded according to the Simpson grade [14], which was determined from the operation notes for all cases by the same neurosurgeon. In the case of RT, the data collected were dose and delay to surgery (adjuvant, on recurrence). Recurrences were confirmed by the radiological data. The diagnosis of metastasis was retained when confirmed by pathologists. The outcome for each patient was assessed after contacting the referring physician after 2004. Date of death was obtained by consulting the registry office.

Pathological examination

For all patients, the slides used for diagnosis were reviewed by two senior neuropathologists. The tumours were classified according to the 2000 WHO grading system criteria [2]. Atypical meningioma can be diagnosed if the tumour has four or more mitoses per HPF, or if three of the following five features are present: high cellularity, high nuclear/cytoplasmic ratio, prominent nucleoli, loss of architectural pattern, and necrosis not due to embolisation. Anaplastic meningioma is defined by either 20 or greater mitoses per 10 HPF, or malignant cytologic features (i.e. resembling sarcoma, carcinoma, melanoma) [2]. The cellular proliferation index was assessed using the Ki 67 when immunohistochemistry was available and feasible. The Ki 67 analysis, an index of proliferation, was not performed systematically in some centres before 2000, as the fixative used at that time in these centres was not compatible with Ki 67 immunolabeling. The quantification of the Ki 67 immunolabelling was performed by the authors. Brain invasion was noted, but was not considered as a criterion of malignancy on the basis of the 2000 WHO classification.

Statistical analysis

A descriptive analysis of the population was performed using the software STAVIEW 5.0 (SAS Institute, Cary, CA, USA). Comparisons between overall survival (OS) and progression-free survival (PFS) rates at 5 and 10 years were based on chi-square tests. Statistical analysis of OS and PFS was performed by comparing computer-generated curves estimated by the Kaplan–Meier method. Differences in OS and progression-free survival (PFS) curves were assessed using the log-rank test (Mantel-Cox). When the difference almost reached statistical significance, other tests (Breslow, Tarone-Ware) were used. The threshold for statistical significance was $P = 0.05$. Multivariate forward stepwise linear regression analysis was based on Cox's forward function. The factors studied were age, gender, tumour location, WHO grade II or III, Ki 67, surgery (Simpson), RT and CT.

Results

Population

The characteristics of the patient population are summarised in Table 1. Our study included 199 patients, 42.2% of which were male and 57.8% female. The mean age was 57.4 ± 13.9 years. The convexity location was predominant (93 cases, 46%). Clinical signs were unspecific and depended on the location of the tumour. A neurological deficit was present in 107 cases (53.8%). The diagnosis was fortuitous in 14 cases with atypical meningiomas (8.4% of all grade II tumours). In two cases presenting with grade III meningiomas, the tumour was acutely diagnosed after brain haemorrhage and coma. There was no difference between grades II and III meningiomas in terms of gender and age. However, meningiomas that were initially grade II, but recurred as grade III, were more frequent in males (12 males, 63.2% of such cases). No statistical correlation was observed between histological grading and location.

On MRI, homogeneous contrast was observed in 183 tumors (92% of all tumors) and heterogeneous contrast in 16 (8% of all tumors), of which 9 were grade II meningiomas (5.4% of the grade II meningiomas) and 7 grade III (21% of the grade III meningiomas).

Pathological data

Of the 199 meningiomas studied, 166 were grade II tumours (6 clear cell, 11 chordoid and 149 atypical meningiomas) and 33 grade III (1 papillary, 2 rhabdoid and 30 anaplastic meningiomas). Of the 105 cases presenting with grade II meningiomas with recurrence, 19 (11.5%) showed an increase in malignancy from grades II to III. These tumours were classified as grade II, based on the initial tumour. As brain invasion was not recognised as a criterion of malignancy in the 2000 WHO grading system, this aspect was not systematically reported by the pathologists. Ki 67 immunolabelling was performed in 93 cases (46.7% of all tumours), consisting of 81 cases with grade II (48.8%) and 12 with grade III (64.4%) meningiomas, with a mean of 9.9% for grade II and 28.8% for grade III.

Table 1 Characteristics of the 199 patients

	Grade II *n* (%)	Grade III *n* (%)
Number	166	33
Age (years)	57.5 ± 14.1	57.0 ± 13.2
Gender		
Male	69 (41.6)	15 (45.5)
Female	97 (58.4)	18 (54.5)
Clinical signs		
ICH	46 (27.7)	12 (36.4)
Neurological deficits	88 (53.0)	19 (57.6)
Epilepsy	60 (36.1)	10 (30.3)
Asymptomatic	14 (8.4)	0
Location		
Convexity	74 (44.6)	19 (57.6)
Parasagittal	42 (25.3)	6 (18.2)
Falx	14 (8.4)	3 (9.0)
Cranial base	26 (15.7)	5 (15.2)
Posterior fossa	6 (3.6)	0
Other	4 (2.4)	0
Oedema	84 (50.6)	28 (48.5)
Heterogeneous contrast	9 (5.4)	7 (21.2)
Surgery		
Simpson 1	82 (49.4)	16 (48.5)
Simpson 2	63 (37.9)	13 (39.4)
Simpson 3	8 (4.8)	1 (3.0)
Simpson 4	12 (7.3)	3 (9.0)
Simpson 5	1 (0.6)	0
Radiotherapy	61 (36.7)	20 (60.6)
Chemotherapy	9 (5.4)	8 (24.2)
Recurrences	82 (49.4)	23 (69.7)
Death	57 (34.3)	24 (72.7)
Ki 67	9.9 ± 7.5	28.8 ± 24.3

Treatments

Surgery

Surgical resection was classified as Simpson 1 in 98 cases (49.2% of the entire series), Simpson 2 in 76 (38.2%), Simpson 3 in 9 (4.6%), Simpson 4 in 15 (7.5%) and Simpson 5 in 1 (0.5%). About the same percentage of each

Simpson score was found in the grades II and III meningiomas (Table 1). No correlation was found between the extent of resection and histological grading.

Radiotherapy

Conventional therapy was performed on 81 patients (40.7% of the entire series), of which 61 had grade II meningioma (36.7% of the grade II tumours) and 20 grade III meningioma (60.6% of the grade III tumours) (Table 1). In 16 cases (19.8% of all patients treated with RT), the patients were treated after initial surgery because of incomplete surgical resection or because of histological diagnosis. These cases consisted of 10 with grade II meningioma (16.4% of treated patients with grade II tumours) and 6 with grade III meningioma (30% of treated patients with grade III tumours). In the other 65 cases (80.2% of treated patients; 51 grade II and 14 grade III), RT was performed after recurrence. The mean radiation dose was 53.57 Gy (grays). Radiosurgery was carried out on 8 patients after recurrence, but each case had already received conventional RT.

Chemotherapy

Only a few patients were treated with CT (Table 1). Of the 166 patients with grade II meningioma, only 9 (5.4% of all grade II tumours) received CT, namely hydroxycarbamide (5 cases), doxorubicine (3 cases) or etoposide (1 case). All these cases presented with grade II meningioma with recurrence as grade III. Of the 33 patients with grade III meningioma, 8 were treated by CT (24.2% of all grade III tumours), using hydroxycarbamide (6 cases), temozolomide (1 case) or cyclophosphamide (1 case).

Recurrences

The proportion of recurrences is reported in Table 1. Recurrences occurred more frequently in grade III meningiomas than in grade II meningiomas (23 cases representing 69.7% of the grade III tumours and 82 cases representing 49.4% of the grade II tumours; $P = 0.0329$). The interval to recurrence was lower in the case of the high-grade meningiomas, with a median time of 31.9 months for grade II and of 21.0 months for grade III meningiomas ($P = 0.0245$). The number of recurrences as a function of the WHO grade and Simpson score is summarised in Table 2. Recurrences occurred more frequently in grade III meningiomas even if Simpson 1 surgery was performed. Recurrences were observed in 7 grade III meningiomas (100% of the grade III with heterogeneous contrast) and in 5 grade II meningiomas (71.4% of the grade II with heterogeneous contrast).

Five patients with a grade III tumour (15.2% of the grade III tumours) developed metastasis, which was proved by histopathological analysis. Three metastases were intradural, 1 cutaneous and 1 pulmonary.

Follow-up

The mean time of follow-up was 65.0 ± 46.9 months. At the end of follow-up, 81 patients had died, 57 with grade II meningioma (34.3% of the grade II tumours) and 24 with grade III meningioma (72.7% of the grade III tumours) (Table 1). The causes of death were: (1) complications within 3 months after surgery (peri-operative mortality) in 16 patients (19.7% of the dead patients, i.e. 8.0% of the entire series), (2) unrelated causes during a disease-free period (3 months after surgery) in 19 (23.4% of the dead patients, i.e. 9.5% of the series), and (3) tumoral progression

Table 2 Number of recurrences as a function of the WHO grade and Simpson score

Simpson score	No recurrence	1 recurrence	2 recurrences	3 recurrences	4 recurrences	5 recurrences	Total
Grade II							
1	44 (26.5%)	23 (13.9%)	13 (7.8%)	2 (1.2%)			82 (49.4%)
2	28 (16.9%)	20 (12%)	11 (6.6%)	2 (1.2%)	1 (0.6%)	1 (0.6%)	63 (37.9%)
3	1 (0.6%)	3 (1.8%)	3 (1.8%)	1 (0.6%)			8 (4.8%)
4	10 (6%)	2 (1.2%)					12 (7.2%)
5	1 (0.6%)						1 (0.6%)
Grade III							
1	4 (12.1%)	3 (9.1%)	6 (18.1%)	2 (6.0%)		1 (3.1%)	16 (48.4%)
2	4 (12.1%)	5 (15.2%)	2 (6.0%)	1 (3.1%)	1 (3.1%)		13 (39.4%)
3	1 (3.1%)						1 (3.1%)
4	1 (3.1%)		1 (3.1%)	1 (3.1%)			3 (9.1%)
5							0

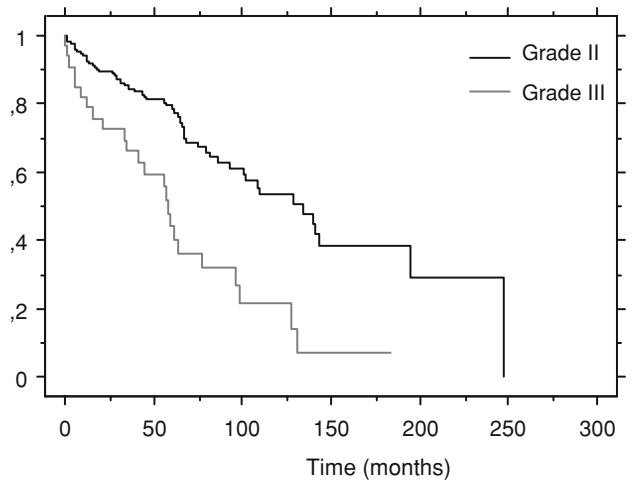

Fig. 1 Kaplan–Meier curve showing the overall survival for grades II and III meningiomas ($P < 0.0001$)

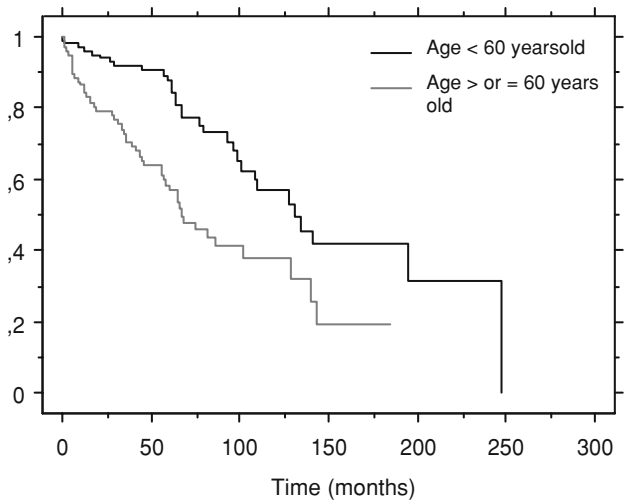

Fig. 2 Kaplan–Meier curve showing the overall survival relating to age in grades II and III meningiomas ($P < 0.0001$)

Table 3 Median overall survival rate in months for grades II and III meningiomas as a function of Possible prognostic factors

Possible prognostic factor	Grade II	Grade III
Location	$P < 0.209$	$P < 0.191$
Cranial base	140.5	127.7
Convexity	103.4	56.0
Falx/parasagittal	247.8	62.0
Ki 67	$P < 0.6079$	nd
<10%	194.6	nd
>10%	128.4	nd
Surgery	$P < 0.055$	$P < 0.80$
Simpson 1	140.1	63.8
Simpson 2, 3, 4, 5	109.5	56.0
Radiotherapy	$P < 0.4984$	$P < 0.036$
Yes	109.0	62.0
No	194.6	41.2
Chemotherapy	$P < 0.0187$	$P < 0.1083$
Yes	86.0	63.8
No	140.5	56.0

nd Not done

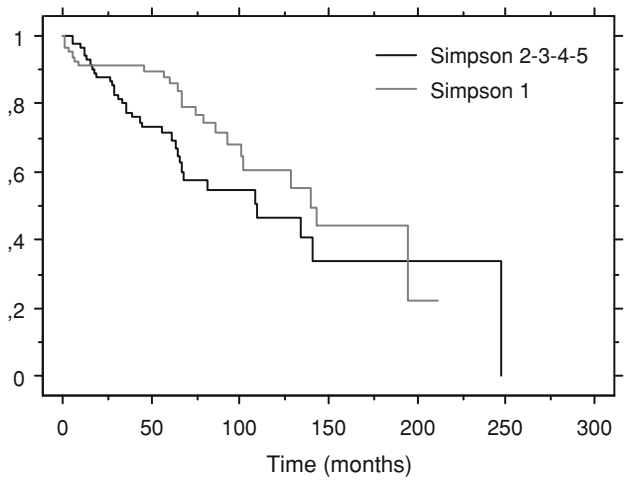

Fig. 3 Kaplan–Meier curve showing the overall survival relating to surgery in grade II meningiomas ($P = 0.055$)

in 46 (56.8% of the dead patients, i.e. 23.1% of the series). The last group consisted of 28 grade II meningiomas (16.9% of the grade II tumours) and 18 grade III (54.5% of the grade III tumours).

Survival analysis

Overall survival For patients with grade II meningiomas, the 5- and 10-year OS rates were 78.4 and 53.3%, respectively, while, for patients with grade III meningiomas, the corresponding values were 44.0 and 14.2% (Fig. 1). On univariate analysis (Table 3), histological grade II was found to be associated with a longer OS ($P < 0.0001$). For the grade II meningiomas (Table 3), univariate analysis showed that age < 60 years ($P < 0.0001$) (Fig. 2) and Simpson 1 resection ($P = 0.055$) (Fig. 3) were associated with a longer OS. For this group, no significant statistical difference was found in OS between patients who received postoperative RT compared to those without RT adjuvant treatment. CT was associated with a lower OS ($P = 0.0187$), with a median duration of 86.0 versus 140.5 months without treatment. For the grade III meningiomas (Table 3), univariate analysis showed that age < 60 years ($P < 0.0001$) and RT ($P = 0.036$) were associated with a longer OS (Fig. 4). On multivariate analysis, age < 60 years ($P < 0.0001$), histological grade II ($P < 0.0001$) and Simpson 1 resection ($P = 0.0141$) were found to be associated with a longer OS (Table 4).

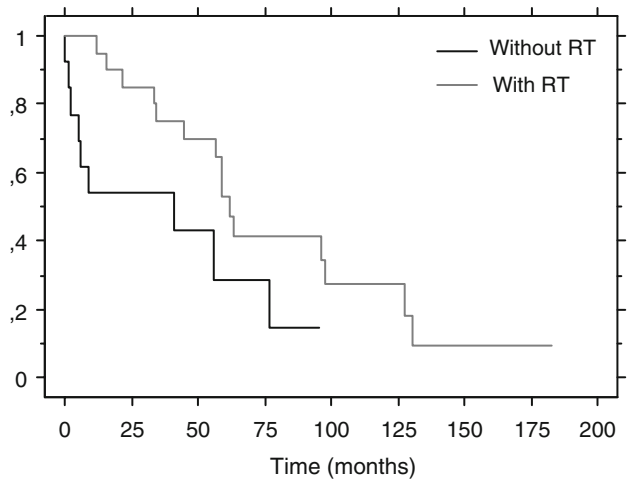

Fig. 4 Kaplan–Meier curve showing the overall survival relating to radiotherapy in grade III meningiomas ($P = 0.036$)

Table 4 Multivariate forward stepwise linear regression survival analysis, probability value and relative risk in patients with grades II and III meningiomas

Factor	Variable	*P*	Relative risk ± SEM
WHO grade	Grade II/III	<0.0001	0.269 ± 0.254
Age	<60/>60 years	<0.0001	1.063 ± 0.011
Surgery	Simpson 1/2, 3, 4, 5	=0.0141	1.752 ± 0.228

SEM Standard error of the mean

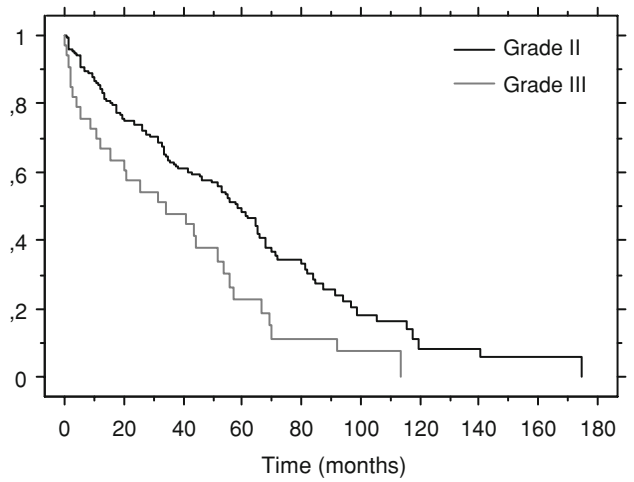

Fig. 5 Kaplan–Meier curve showing the progression free survival for grades II and III meningiomas ($P = 0.032$)

Progression-free survival For patients with grade II meningiomas, the 5- and 10-year PFS rates were 48.4 and 22.6%, respectively, the corresponding values for patients with grade III meningiomas being 8.4 and 0% (Fig. 5).

On univariate analysis (Table 5), histological grade II was found to be associated with a longer PFS ($P = 0.0032$).

Table 5 Median progression-free survival rate in months for grades II and III meningiomas as a function of possible prognostic factors

Possible prognostic factor	Grade II	Grade III
Location	nd	nd
Cranial base	37.7	57.0
Convexity	54.5	54.5
Falx/parasagittal	64.7	52.0
Ki 67	$P < 0.9256$	nd
<10%	45.5	nd
>10%	53.1	nd
Surgery	$P < 0.0763$	$P < 0.763$
Simpson 1	65.2	41.2
Simpson 2, 3, 4, 5	50.0	25.5
Radiotherapy	$P < 0.006$	$P < 0.1825$
Yes	35.2	43.6
No	65.7	5.6
Chemotherapy	$P < 0.1566$	$P < 0.4635$
Yes	52.0	31.8
No	59.4	34.0

nd Not done

RT reduced the PFS in grade II meningiomas ($P = 0.0006$), the median duration being 35.2 months with RT and 65.7 months without RT. For the grade III meningiomas, no significant statistical difference was found in term of PFS for patients who underwent postoperative irradiation. There were no other prognostic factors in terms of PFS for grades II and III meningiomas.

Discussion

Grades II and III meningiomas are considered rare CNS tumors. Due to their rarity and the heterogeneity of series reported so far, controversy exists with regard to their prognostic factors and therapeutic management. Previous studies were based on only 49 cases [15], 28 cases [19] or 71 cases [9], and comparisons are difficult because of the change in the histopathological guidelines in 2000. A large range of prevalence data for these aggressive forms has been reported, owing to the use of various grading systems since 2000 [4, 5]. These findings confirm the necessity for a consensus on management.

In our multi-institutional study, a statistical analysis was performed on a large and homogeneous population of adults with intracranial grades II and III meningiomas diagnosed between 1990 and 2004 to determine whether age, pre-operative clinical status, tumour location, extent of surgery, histological features or post-operative RT affected OS or PFS. Patients were treated according to the usual medical practice at each centre.

A predominance of males in patients presenting with atypical or anaplastic meningiomas [4] was not confirmed by our study, in which 57.8% of the patients were female. However, in our study, male patients were predominant in those patients with grade II meningiomas progressing to grade III when recurrence.

Analysis of the patient's age showed that grades II and III meningiomas were diagnosed at around 55 years of age. Age < 60 years was a prognostic factor, with a better outcome when the patient was under 60 years of age. Other authors have defined 65 years as the cut-off for a poor prognosis [4, 20].

In our series, the location of intracranial meningiomas was not linked to the clinical outcome. The results of reported series are consistent with our findings [1, 4, 21], but it seems that meningiomas located in the skull base and spine are less often grades II and III meningiomas [22].

The prognostic value of histological findings is well established, with a worse prognosis for WHO grade III meningiomas [2]. Palma et al. [9] reported a series of grade III meningiomas with an OS of 64.3 and 34.5% at 5 and 10 years, respectively, the corresponding values for PFS being 45 and 15%, whereas, in grade II meningiomas, the OS was 95 and 79% at 5 and 10 years, respectively, and the PFS 77 and 55%. Our findings are in general agreement with these data, but the survival rates were lower. For grade III meningiomas, the OS was 44.0 and 14.2% and the PFS 8.4 and 0% at 5 and 10 years, respectively, while, for grade II meningiomas, the OS was 78.4 and 53.3% and the PFS 48.4 and 22.6%. However, comparisons between published series are not easy because of the different histological grading systems used by the WHO before and after 2000.

Brain invasion was not retained as a malignant criterion in the 2000 WHO grading system. The significance of brain invasion has been widely debated and is nowadays one of the criteria used for grading tumors [3, 23]. The mechanisms of invasion have not been clearly defined and molecular biological approaches have not shown any particular gene alterations in these invasive tumors [24, 25].

As regards Ki 67 immunolabelling, there is controversy in the literature and considerable variation in Ki 67 immunolabelling of meningiomas has been reported [12, 19, 26–28]. For instance, Bruna et al. [19], in a review of 28 patients, reported that a Ki 67 value of 9.9% was a prognostic factor for grades II and III meningiomas, and others have quoted 10% as a prognostic factor for tumoral progression [10, 26]. In contrast, Baser [29] did not find any relationship between Ki 67 immunolabelling and evolution. Our study did not validate Ki 67 immunolabelling as a prognostic factor. However, Ki 67 was not performed in every centre, as the fixative used in some centres at that time was not compatible with Ki 67 immunolabelling. The lack of correlation between the Ki 67 proliferation index and survival may be due to the relatively small number of cases, especially grade III meningiomas. Although it is undeniable that the Ki 67 index helps neuropathologists to determine the aggressiveness of the tumour, no therapeutic decision is proposed on the basis of the Ki 67 index alone.

Heterogeneous contrast has been quoted as a prognostic factor and has been correlated with frequent recurrences [30], in agreement with our results. The presence of heterogeneous contrast seems to be predictive of an aggressive behaviour for high-grade meningiomas.

Extent of surgery has been reported as one of the most significant predictors of outcome in patients with meningiomas. Surgery should be performed with as large a resection as possible and can reduce both mortality and recurrences [2, 4, 10, 14, 31, 32]. In our study, there was no difference between grades II and III meningiomas in terms of the Simpson score. Palma et al. [9] showed that survival rates are significantly better after Simpson 1 resection than after Simpson 2–3 resection for atypical meningiomas. In our study, for grade II meningiomas, we confirmed that surgery was a prognostic factor and that the Simpson score was linked to recurrences. However, in a recent study, Pasquier et al. [4] reported that the extent of surgical resection was not a significant prognostic factor for grades II and III meningiomas, but their statistical analysis was performed on the whole group, with no distinction between the grades. In addition, in their retrospective study, the extent of surgery was not checked by post-operative imaging, as was the case in our series.

The role of surgery is less clear in grade III meningiomas presenting with more frequent recurrences. Surgery is sometimes impracticable when recurrences are multifocal or when the interval to recurrence is short, which is common in anaplastic meningiomas. In grade III meningiomas, our univariate analysis of OS and PFS showed that surgery was not a prognostic factor. Similar results have been reported by Palma et al. [9]. Moreover, the extent of surgical resection was not correlated with the onset of recurrences. After surgery, the rate of recurrence in grade III meningiomas is high, being 69.8% in our study, 75% in Kim et al. [20], 78% in Jääskeläinen et al. [33] and 72% in Maier et al. [7]. Multivariate analysis in our study confirmed the independent prognostic role of surgery for the whole series (grades II and III meningiomas), as was also demonstrated by Kim et al. [20]. However, as the group of grade III meningiomas was limited in number, multivariate analysis was not performed on each grade separately.

There is no consensus on the use of RT in meningiomas [5]. Hug et al. [31] reported a local control of 38% in grade II and 52% in grade III meningiomas at 5 years and of 19 and 17% at 8 years. Our study suggests that RT is a valuable weapon in the treatment of grade III meningiomas, with a significantly improved OS. There seems to be a

consensus that patients with grade III meningiomas should be treated with RT whatever the extent of surgery. However, its use in grade II meningiomas is not clear. For grade II meningioma, Marcus et al. [32] reported that most neurosurgeons who responded to a questionnaire would not advocate adjuvant RT if the tumour was completely excised, but the majority would recommend it in cases of subtotal resection. These medical practices are in agreement with those in our retrospective study. No patient was treated with RT when surgical resection was complete. The most usual attitude in our retrospective study was to treat patients with RT after the first recurrence. Survival analysis in our study showed that RT was associated with a poorer prognosis than no RT. This analysis must be treated with caution because the grade II meningiomas treated by RT were often difficult cases (recurrences, aggressiveness). A major question was to determine whether patients with incomplete tumoral resection should be treated with RT or not. Ten patients were treated after incomplete surgery but, as few cases were involved, the statistical power was not high enough to compare these patients with those without RT. Recently, an informal study involving the neurosurgeons of the Neuro-Oncology Club of the French Neurosurgical Society revealed that, when surgery was not complete, only 45.5% of neurosurgeons treat patients with RT. A review of the literature provided few details for the modalities of treatment. Only a few patients have been studied, and radiation dose was the parameter most often assessed [31, 32]. Finally, the question of whether to give this treatment after initial surgical resection or at recurrence remains unanswered. In our opinion, there is not sufficient evidence supporting the effect of RT in completely resected grade II meningioma to recommend, or not to recommend, adjuvant treatment in this situation. Only a prospective randomised study will make it possible to clearly define the place of RT in the management of grades II meningiomas. A number of issues remain, the most important being whether immediate postoperative RT provides any long-term advantage over RT on recurrence.

Radiation dose was also an important point in the analysis. As reported in the literature, radiation dose is important in the treatment of meningiomas, 60 Gy being the optimal dose [5, 31, 32]. In our study, the mean dose was 53.67 Gy. This parameter should be analysed more precisely. The role of radiosurgery and CT was not analysed in our study because few cases received this adjuvant treatment.

Conclusion

To our knowledge, the present series represents one of the largest reported on grades II and III meningiomas. This study highlights the fact that complete tumour removal is a main prognostic factor in grade II meningiomas. On univariate analysis, we found that age (<60 years) and surgical resection (Simpson 1) were prognostic factors for grade II meningiomas, while, for grade III meningiomas, age (<60 years) and RT were prognostic factors.

Multivariate analysis confirmed that age (<60 years), surgical resection (Simpson 1 versus 2–5) and WHO histological grading were independent prognostic factors for survival. Prospective trials would probably delineate strong therapeutic guidelines for grades II and III meningiomas.

Acknowledgments We would like to thank the Neuro-Oncology Club of the French Neurosurgical Society for its support, the Neurosurgical Departments of Angers, Lyon, Montpellier, Limoges and Paris Beaujon for the use of their patients' data, the "Unité Fonctionnelle de Recherche Clinique et Biostatistiques" CHU Limoges for help with the statistics, Jacques Champier for reviewing the manuscript and Dr Tom Barkas for linguistic help.

References

1. Cushing HW, Eisenhardt LC (1938) Serial enumeration of meningiomas. In: Thomas CC (ed) Meningiomas their classification regional behavior, life history, and surgical end results. Thomas CC, Springfield, pp 56–73
2. Louis DN, Scheithauer BW, Budka H, Von Deimling A, Kepes JJ (2000) Meningiomas. In: Khleihues P, Cavenee WK (eds) WHO Classification of tumours pathology and genetics tumours of the nervous system. IARC, Lyon, pp 176–184
3. Perry A, Louis DN, Scheithauer BW, Budka H, Von Deimling A (2007) Meningiomas. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds) WHO Classification of tumours of the central nervous system, 4th edn. IARC, Lyon, pp 164–172
4. Pasquier D, Bijmolt S, Veninga T, Rezvoy N, Villa S, Krengli M, Weber DC, Baumert BG, Canyilmaz E, Yalman D, Szutowicz E, Tzuk-Shina T, Mirimanoff RO (2008) Atypical and malignant meningioma: outcome and prognostic factors in 119 irradiated patients a multicenter, retrospective study of the rare cancer network. Int J Radiat Oncol Biol Phys 71:1388–1393
5. Pearson BE, Markert JM, Fisher WS, Guthrie BL, Fiveash JB, Palmer CA, Riley K (2008) Hitting a moving target: evolution of a treatment paradigm for atypical meningiomas amid changing diagnostic criteria. Neurosurg Focus 24:E3
6. Yamasaki F, Yoshioka H, Hama S, Sugiyama K, Arita K, Kurisu K (2000) Recurrence of meningiomas. Cancer 89:1102–1110
7. Maier H, Ofner D, Hittmair A, Kitz K, Budka H (1992) Classic, atypical, and anaplastic meningioma: three histopathological subtypes of clinical relevance. J Neurosurg 77:616–623
8. Mahmood A, Caccamo DV, Tomecek FJ, Malik GM (1993) Atypical and malignant meningiomas: a clinicopathological review. Neurosurgery 33:955–963
9. Palma L, Celli P, Franco C, Cervoni L, Cantore G (1997) Long-term prognosis for atypical and malignant meningiomas: a study of 71 surgical cases. Neurosurg Focus 2:e3
10. Perry A, Scheithauer BW, Stafford SL, Lohse CM, Wollan PC (1999) "Malignancy" in meningiomas: a clinicopathologic study of 116 patients, with grading implications. Cancer 85:2046–2056
11. Lusis E, Gutmann DH (2004) Meningioma: an update. Curr Opin Neurol 17:687–692
12. Whittle IR, Smith C, Navoo P, Collie D (2004) Meningiomas. Lancet 363:1535–1543

13. Perry A (2006) Meningiomas. In: Mc Lendon RE, Rosenblum MK, Bigner DB (eds) Russell & Rubinstein's pathology of tumors of the nervous system, 7th edn. Hodder Arnold, London, pp 427–474
14. Simpson D (1957) The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 20:22–39
15. Ko KW, Nam DH, Kong DS, Lee JI, Park K, Kim JH (2007) Relationship between malignant subtypes of meningioma and clinical outcome. J Clin Neurosci 14:747–753
16. Modha A, Gutin PH (2005) Diagnosis and treatment of atypical and anaplastic meningiomas: a review. Neurosurgery 57:538–550
17. Dziuk TW, Woo S, Butler EB, Thornby J, Grossman R, Dennis WS, Lu H, Carpenter LS, Chiu JK (1998) Malignant meningioma: an indication for initial aggressive surgery and adjuvant radiotherapy. J Neurooncol 37:177–188
18. Sioka C, Kyritsis AP (2009) Chemotherapy, hormonal therapy, and immunotherapy for recurrent meningiomas. J Neurooncol 92:1–6
19. Bruna J, Brell M, Ferrer I, Gimenez-Bonafe P, Tortosa A (2007) Ki-67 proliferative index predicts clinical outcome in patients with atypical or anaplastic meningioma. Neuropathology 27:114–120
20. Kim YJ, Ketter R, Henn W, Zang KD, Steudel WI, Feiden W (2006) Histopathologic indicators of recurrence in meningiomas: correlation with clinical and genetic parameters. Virchows Arch 449:529–538
21. Claus EB, Bondy ML, Schildkraut JM, Wiemels JL, Wrensch M, Black PM (2005) Epidemiology of intracranial meningioma. Neurosurgery 57:1088–1095
22. Sade B, Chahlavi A, Krishnaney A, Nagel S, Choi E, Lee JH (2007) World Health Organization grades II and III meningiomas are rare in the cranial base and spine. Neurosurgery 61:1194–1198
23. Burger PC, Scheithauer BW (2007) Tumors of the central nervous system, vol 4. Fascicle 7, AFIP ARP, Washington, pp 331–362
24. Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, Cavenee WK (2002) The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol 61:215–225
25. Lamszus K (2004) Meningioma pathology, genetics, and biology. J Neuropathol Exp Neurol 63:275–286
26. Ho DM, Hsu CY, Ting LT, Chiang H (2002) Histopathology and MIB-1 labeling index predicted recurrence of meningiomas: a proposal of diagnostic criteria for patients with atypical meningioma. Cancer 94:1538–1547
27. Aguiar PH, Tsanaclis AM, Tella OI Jr, Plese JP (2003) Proliferation rate of intracranial meningiomas as defined by the monoclonal antibody MIB-1: correlation with peritumoural oedema and other clinicoradiological and histological characteristics. Neurosurg Rev 26:221–228
28. Roser F, Samii M, Ostertag H, Bellinzona M (2004) The Ki-67 proliferation antigen in meningiomas. Experience in 600 cases. Acta Neurochir (Wien) 146(3):7–44
29. Baser ME (2006) The distribution of constitutional and somatic mutations in the neurofibromatosis 2 gene. Hum Mutat 27:297–306
30. Ayerbe J, Lobato RD, de la Cruz J, Alday R, Rivas JJ, Gomez PA, Cabrera A (1999) Risk factors predicting recurrence in patients operated on for intracranial meningioma a multivariate analysis. Acta Neurochir (Wien) 141:921–932
31. Hug EB, Devries A, Thornton AF, Munzenride JE, Pardo FS, Hedley-Whyte ET, Bussiere MR, Ojemann R (2000) Management of atypical and malignant meningiomas: role of high-dose 3D-conformal radiation therapy. J Neurooncol 48:151–160
32. Marcus HJ, Price SJ, Wilby M, Santarius T, Kirollos RW (2008) Radiotherapy as an adjuvant in the management of intracranial meningiomas: are we practising evidence-based medicine? Br J Neurosurg 22:520–528
33. Jääskeläinen J, Haltia M, Servo A (1986) A typical and anaplastic meningiomas: radiology surgery radiotherapy and outcome. Surg Neurol 25:233–242