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CLINICAL STUDY

WHO grade II meningioma: a retrospective study for outcome and prognostic factor assessment

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Abstract To analyse the outcome of patients with WHO grade II meningioma and identify factors that may influence recurrence and survival. Between January 2007 and September 2015, a retrospective search identified 194 WHO grade II meningiomas at the National Hospital for Neurology and Neurosurgery, London. Survival methods were implemented. 31 patients (16 %) had a previous history of grade I meningioma. The patients underwent a total of 344 surgical resections and 43.3 % received radiotherapy. 55 patients (28.4 %) had been re-operated on for a WHO grade II meningioma relapse. Median follow-up was 4.4 years. At the end of the study, 75 patients (40.1 %) had no residual tumour on the last scan. Surgical recurrence free survival at 5 years was 71.6, 95 % CI [63.5, 80.8]. Secondary grade II meningioma (HR = 2.29, $p = 0.010$), and, Simpson resection grade 1, 2 and 3 vs. 4 and 5 (HR = 0.57, $p = 0.050$) were associated with the surgical recurrence-free survival. 32 died from meningioma (16.5 %). Overall survival probability at 5 years was 83.2, 95 % CI [76.6, 90.4]. Age at diagnosis (HR = 0.22, $p < 0.001$), WHO grade I meningioma progressing into grade II (HR = 3.2, $p = 0.001$), tumour location (HR = 0.19, $p < 0.001$), and mitosis count (HR = 0.36, $p = 0.010$) were independently associated with the overall survival. Patients who received radiotherapy demonstrated neither a reduced risk of recurrence nor a longer overall survival ($p = 0.310$). In our series shorter survival correlated with older age, increased mitoses, progression from grade I to II and location. We were not able to demonstrate a significant improvement in any of the clinical outcomes after radiotherapy.

Keywords WHO grade II meningioma · Atypical meningioma · Radiotherapy · Recurrence · Prognostic factors

Abbreviations

CI	Confidence interval
MGTR	Macroscopic gross total resection
HPF	High power field
HR	Hazard ratio
IQR	Inter quartile range
MTOR	Mammalian target of rapamycin
WHO	World health organization
RT	Radiotherapy
STR	Sub total resection

Introduction

Meningiomas, which are thought to arise from arachnoidal cap cells, account for 13–26 % of intracranial tumours and are benign in about 90 % of cases [1]. The 2007 World Health Organisation (WHO) classification of tumours affecting the central nervous system recognizes three grades of meningioma. The chordoid, the clear cell and, the most common, atypical meningioma correspond to the WHO grade II.

WHO grade III meningiomas are associated with aggressive growth patterns reflecting their clinical and histopathological features of malignancy and can spread by metastatic dissemination [2]. WHO grade I meningioma occur most

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often in women and are associated with a relatively good outcome [3].

The behaviour and outcome of WHO grade II meningioma are intermediate. Atypical meningiomas are tumours with increased mitotic activity with four mitoses or more per ten high power fields (HPFs) and/or have at least three of the following characteristics: sheet-like growth, spontaneous necrosis, increased cellularity, prominent nucleoli, and small cells with high nuclear to cytoplasmic ratio. The proportion of grade II meningioma has increased since the 2007 classification, as brain infiltrating meningiomas should now be regarded as atypical [4]. No specific features on magnetic resonance imaging (MRI) or computed tomography (CT) scans can distinguish them from grade I or III.

Complete surgical excision is the treatment of choice in all types of meningioma. Further optimal management is difficult to establish, the role of post-operative radiotherapy as a standard adjuvant treatment remaining controversial [5].

The aim of this study was to investigate clinical and pathological prognostic factors associated with surgical recurrence and the survival of patients with WHO grade II meningioma, with an emphasis on the effect of post-operative radiotherapy in the prevention of recurrence and death.

Clinical material

A retrospective neuropathology database search was carried out between January 2007 and August 2015 at the National Hospital for Neurology and Neurosurgery, London. All patients with a diagnosis of WHO grade II/atypical/clear cell/chordoid meningioma were included in this study including patients with a recurrent meningioma whose grade had progressed from I to II. There was no specific inclusion criterion and no patient was excluded from the study.

Histology slides were not systematically reviewed, only in cases of recurrence, however, all pathology reports were carefully examined. Meningioma sub-type, mitosis count per 10 HPFs (mitotic index), Ki-67 index (MIB-1), presence of necrosis, brain invasion, architectural sheeting, small cell change, increased cellularity, prominent nucleoli, sheet-like growth and presence of psammoma bodies were separately extracted. In cases of recurrence, histology reports were compared with those from previous resections.

Patient demographic and medical data were collected retrospectively. We used radiographic and surgical reports, and all available in- and out- patient records. Patients' CT and MRI images were studied pre and post operatively. Tumour location was initially divided into ten categories. However, some locations e.g. spinal or petroclival had only a few cases making them unsuitable for statistical analysis. These cases were placed in a new category named "other locations".

Age at diagnosis was defined according to the date of first surgery for a grade II meningioma. Surgical resection was evaluated according to the Simpson grading scale using the operative records [6]. We defined macroscopic gross total resection (MGTR) as Simpson grade 1, 2 and 3 and, incomplete resection or subtotal resection (STR) as Simpson grade 4 and 5. If radiotherapy was given, data on the technique, overall dose and time of completion were collected.

We defined two types of recurrence. The first type was defined as a "surgical relapse", characterizing the patients who underwent a second surgical procedure for a WHO grade II meningioma recurrence (local control). The second type as a "radiological relapse" corresponded to radiological evidence of tumour regrowth in cases of total resection, or to residual tumour progression in cases of incomplete resection (progression-free survival). For each case, we compared the surgical impression with the early post-operative gadolinium contrasted scan.

For deaths, the cause was searched and quoted differently if related or not to the surgery or the progressing meningioma disease.

Patient outcome and clinical status were assessed through medical records, the patient database and information obtained from the general practitioners. A patient who became lost by being unreachable 2 years after the surgery was considered as lost to follow-up and right-censored in the survival analysis.

This retrospective study was conducted according to the ethical guidelines for epidemiological research in accordance with the ethical standards of the Helsinki Declaration (2008).

Statistical methods

Survival statistics were based on two different events: redo surgery for meningioma recurrence and death. Both time to event were calculated from the date of diagnosis i.e. the date of the first surgery for a WHO grade II meningioma. Survival function was assessed by the Kaplan–Meier method and, the Mantel Cox log-rank test was used to compare different survival functions according to clinical and therapeutic factors (cause-specific or corrected survival; individuals who died of other causes were censored) [7, 8]. Because death was the most untoward event, mortality was the primary outcome of interest and surgical recurrence the secondary. Independent prognostic factors with a p value <0.20 were selected in an adjusted regression by a backward elimination. A p value <0.05 was considered as statistically significant.

Results

Population description

Median follow-up was 4.4 years, IQR [1.8–7.9], range (0, 30). 36 patients (18.6%), mostly from overseas, were lost

to follow-up. Of the 194 cases collected, 93 patients were male (47.9 %). Median age at diagnosis was 54.2 years, IQR [44.4–66.7]. Seizure was the most frequent presenting symptom in 20.6 %, generally associated with other clinical signs at presentation. The most common location was parafalcine in 36.6 % (Table 1). 119 patients (63 %) had MGTR.

Radiotherapy

77 patients (39.7 %) received conventional external beam radiotherapy (median dose = 50.4 Gy, IQR [50.4, 54], range (30, 60)).

11 patients (5.7 %) received stereotactic radiotherapy, mostly by Gamma knife® (median dose = 15 Gy), of which four had already had conventional radiotherapy. For the analysis, we considered equally any form of radiation therapy (RT) (n = 84).

A precise date of radiotherapy end was not available for 48 patients (57.1 %). RT was delivered before the WHO grade II meningioma surgery in 2 cases for a recurrent grade I. RT was given in 11 cases within the 6 post-operative months, in 16 cases within the post-operative year, after the post-operative year in 19 cases and after a 3-year time in 14 cases. The median delay between the WHO grade II meningioma surgery and the end of the RT was 1.2 years, IQR [0.5–4.3].

41 patients (21.1 %) had RT upon radiological relapse but were not re-operated on and 43 patients (22.2 %) had RT and redo surgery.

30.3 % of the patients (n = 36) who had a MGTR also underwent RT, compared to 65.7 % (n = 46) in the incomplete resection group. In case of MGTR, median time between the surgery and the RT was 4.3 years, IQR [2.5, 4.6].

Of the 36 patients who had a MGTR and RT, 24 were re-operated on and 12 not. This difference is significant (Fisher test p value <0.001). However, there is no statistical interaction between RT and completeness of resection (Wald test p value = 0.220). Therefore, RT is an independent predictor of the surgical recurrence-free risk.

Table 1 Patients' characteristics

Characteristics	n (%)
Gender male	93 (47.9)
Median age at surgery	54.2 years, IQR [44.4–66.7]
Symptoms and clinical signs	
Motor and walking impairment	25 (12.9)
Seizure	40 (20.6)
Cognitive disorders	21 (10.8)
Visual disorders	29 (14.9)
Others	66 (34)
Location	
Convexity	55 (28.4)
Para sagittal/falx	71 (36.6)
Skull base	56 (28.9)
Others	21 (10.8)
Tumour volume	35.6 cm^3, IQR [15.4–68.2]
Pre-operative embolisation	45 (23.2)
Resection status	
MGTR (Simpson 1, 2 and 3)	119 (63)
STR (Simpson 4 and 5)	70 (36.1)
Venous sinus invasion	101 (52.1)
Histological sub-types	
Atypical meningioma	158 (83.2)
Clear cell meningioma	4 (2.1)
Chordoid meningioma	21 (11.1)
Median mitoses count per 10 HPFs	4 per 10 HPFs, IQR [2–5]
Presence of a brain invasion	80 (46)
Radiotherapy	77 (39.7)
Stereotactic radiotherapy	11 (5.7)

Surgical recurrence-free outcome

A total of 344 surgical resections were performed. 55 patients (28.4 %) had been re-operated on, at least once, for a WHO grade II meningioma relapse. 37 patients (19.1 %) had three or more craniotomies. The median time between the first and the second surgery was 3.7 years, IQR [1.6, 7.6]. 11 patients (61.1 %) demonstrated malignant transformation into WHO grade III meningiomas.

At data analysis, only 75 patients (40.1 %) had no residual tumour on the last scan, of which 71 (94.7 %) had a MGTR. Among those who underwent a redo surgery, only 7 patients (9.3 %) showed no residual on the last scan of which six had a redo MGTR. The median surgical recurrence-free survival was 9.3 years. 95 % CI [7.65, 10.4]. Surgical recurrence-free survival at 1, 2, 5 and 8 years were respectively: 93.5, 95 % CI [89.8, 97.3], 90.1, 95 % CI [85.6, 94.8], 71.6, 95 % CI [63.5, 80.8] and, 55.6, 95 % CI [44.2, 70] (Fig. 1a).

The univariate Cox regression identified that previous history of grade I meningioma, venous sinus invasion, completeness of resection, presence of brain invasion and RT were associated with the surgical recurrence risk (Table 2). It suggested an association between the age at diagnosis, mitoses count and the surgical relapse that did not reach the significance but did warrant inclusion in the subsequent multivariate analysis (Table 3).

Progressing WHO grade I meningioma into grade II (secondary grade II meningioma) (HR = 2.29, 95 % CI [1.18, 4.41], p value = 0.010) and, Simpson resection grade 1, 2 and 3 (MGTR) vs. (STR) (HR = 0.57, 95 % CI [0.33, 1], p value = 0.050), were independently associated with the surgical recurrence-free survival.

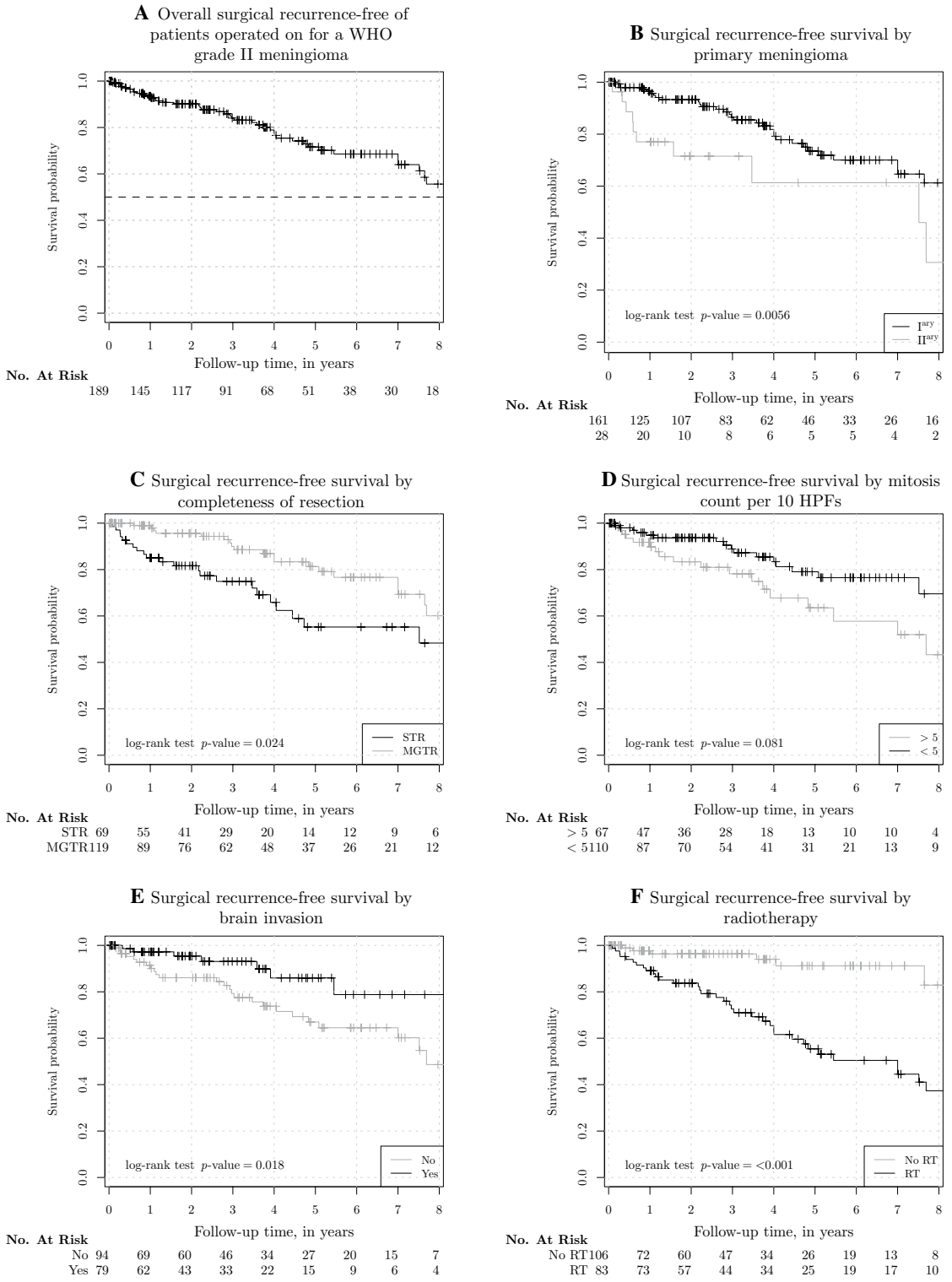

Fig. 1 Survival curves. **a** Overall recurrence-free survival. **b** Surgical recurrence-free survival by primary meningioma. **c** Surgical recurrence-free survival by completeness of resection. **d** Surgical recurrence-free survival by mitosis count. **e** Surgical recurrence-free survival by brain invasion. **f** Surgical recurrence-free survival by radiotherapy

Table 2 Univariate Cox regression for WHO grade II meningioma surgical recurrence

Variable	Recurrence			Overall survival		
	HR	[95 % CI]	*p* value	HR	[95 % CI]	*p* value
Gender male[a]	1.2	0.69, 2.06	0.52	1.12	0.57, 2.22	0.74
Age at diagnosis ≤54.2 years (median)[a]	0.66	0.38, 1.15	0.14	0.34	0.17, 0.68	<**0.001**
Previous history of GIM surgery[b]	2.44	1.27, 4.69	**0.01**	3.65	1.75, 7.6	<**0.001**
Motor and walking impairment	1.43	0.6, 3.41	0.42	1.23	0.43, 3.52	0.7
Convexity vs. others location	0.91	0.49, 1.66	0.75	0.46	0.19, 1.13	0.09
Convexity and parafalcine vs. others location[b]	1.05	0.54, 2.03	0.89	0.25	0.12, 0.53	<**0.001**
Side (right vs. left)[b]	1.18	0.68, 2.06	0.55	0.88	0.46, 1.7	0.7
Tumour volume ≤35.6 cm^3[b]	0.92	0.4, 2.15	0.85	0.41	0.17, 0.97	**0.04**
Venous sinus invasion (present vs. absent)[b]	1.64	0.94, 2.86	0.08	1.86	0.93, 3.74	0.08
Simpson resection grade 1, 2 and 3 (MGTR) vs. 4 and 5[b]	0.54	0.31, 0.93	**0.03**	0.39	0.2, 0.77	**0.01**
Mitoses count ≤4 (median)	0.58	0.31, 1.08	0.09	0.47	0.23, 0.97	**0.04**
Histological brain invasion	0.41	0.19, 0.88	**0.02**	1.42	0.69, 2.93	0.34
Radiotherapy or Radiosurgery[c]	3.82	1.91, 7.65	<**0.001**	1.05	0.53, 2.09	0.88
Redo surgery for recurrence	NA	NA	NA	0.56	0.25, 1.28	0.17

Bold values are statistically significant at $p < 0.05$

HR hazard ratio, *[95% CI]* 95 % confidence interval, *NA* not applicable

[a]Variable forced in the multivariate analysis

[b]Variable integrated in the multivariate analysis

[c]Statistical interaction

Overall survival outcome

At data analysis, 36 patients were deceased (18.6 %) however, only 32 died following the meningioma surgery or disease progression (16.5 %).

Overall survival probability at 1, 2, 5 and 8 years were respectively: 96.5, 95 % CI [93.8, 99.3], 92.3, 95 % CI [88.2, 96.6], 83.2, 95 % CI [76.6, 90.4] and 73.9, 95 % CI [65.1, 83.9] (Fig. 2a).

The univariate Cox regression identified that age at diagnosis, previous history of grade I meningioma, meningioma location, completeness of resection and mitosis index were associated with the overall survival (Table 2). It suggested an association between the venous sinus invasion, tumour volume and the overall survival that did not reach the significance but did warrant inclusion in the subsequent multivariate analysis (Table 4).

Age at diagnosis (HR = 0.22, 95 % CI [0.09, 0.5], *p* value <0.001), progressing WHO grade I meningioma into grade II (HR = 3.2, 95 % CI [1.44, 7.11], *p* value = 0.001), tumour location (HR = 0.19, 95 % CI [0.08, 0.41], *p* value <0.001), and mitosis count (HR = 0.36, 95 % CI [0.17, 0.76], *p* value = 0.010) were independently associated with the overall survival. The patients who received radiotherapy did not demonstrate a longer overall survival (log-rank test *p* value = 0.310) (Table 2; Figs. 2f, 3).

Table 3 Multivariate Cox regression for WHO grade II meningioma surgical recurrence-free survival

Variable	HR	[95 % CI]	*p* value
Progressing WHO grade I meningioma into grade II	2.29	1.18, 4.41	**0.01**
Simpson resection grade 1, 2 and 3 (MGTR) vs. 4 and 5 (STR)	0.57	0.33, 1	**0.05**

Bold values are statistically significant at $p < 0.05$

HR hazard ratio, *[95% CI]* 95 % confidence interval

Discussion

Despite its methodological limitations, including its retrospective nature and the number of lost to follow-up patients, this study is one of the largest series in the literature on outcome and prognostic factors affecting the survival of WHO grade II meningioma. A central neuropathology review was not possible due to limited study resources, however, our data represent the "real-world clinical scenario". This population has been heterogeneously treated. This is a fact that reflects the clinical situation we face in our everyday practice. We did not include any grade III meningiomas, as it is well recognized that those two types of tumour behave very differently. Therefore, they should not be grouped together when assessing outcome and predictors [9, 10].

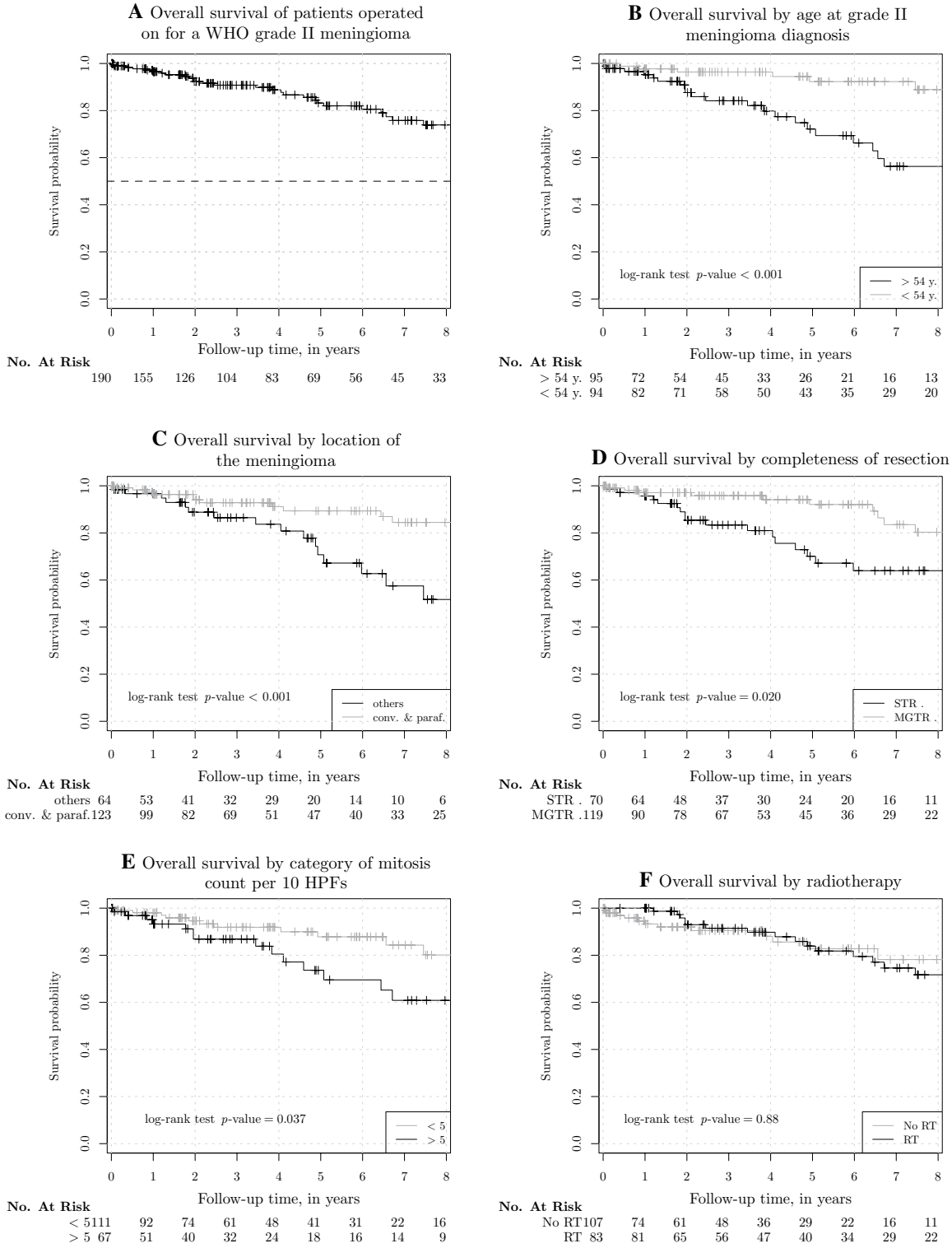

Fig. 2 Survival curves. **a** Overall survival. **b** Overall survival by age at diagnosis. **c** Overall survival by location. **d** Overall survival by completeness of resection. **e** Overall survival by mitosis count. **f** Overall survival by radiotherapy

Age at diagnosis

We found that patients aged under 54.2 years at WHO grade II surgery (median) are less likely to die of their meningioma. This finding is consistent with previous reports [9, 11–13]. Some authors have defined 65 years as the cut-off for a poor prognosis [9, 11]. Moreover, Aghi et al. also found that an older age was predictive of recurrence [14].

Progressing meningioma

In common with other tumours such as gliomas, the histological features of meningiomas are not fixed and can evolve. 31 grade I meningiomas progressed to a grade II and 11 transformed into a malignancy (grade III). Primary and secondary grade II meningioma may behave differently in addition to the fact that patients with progressing meningioma are likely different from those with a primary grade II, as they have already undergone surgery at least once and, for some, have received RT.

Table 4 Multivariate Cox regression for WHO grade II meningioma overall survival

Variable	HR	[95 % CI]	*p* value
Age at diagnosis ≤54.2 years	0.22	0.09, 0.5	<**0.001**
Progressing WHO grade I meningioma into grade II	3.2	1.44, 7.11	<**0.001**
Convexity and parafalcine vs. others location	0.19	0.08, 0.41	<**0.001**
Mitoses count ≤4 (median)	0.36	0.17, 0.76	**0.01**

Bold values are statistically significant at $p < 0.05$

HR hazard ratio, *[95 % CI]* 95 % confidence interval

However, we decided not to exclude the secondary grade II meningiomas in order to prevent any bias of selection and present the data as they are, in an intention to treat fashion.

Having a secondary grade II meningioma impaired both the surgical recurrence-free risk and the survival. Patients with secondary tumours had a much shorter progression-free survival than those with primary tumours, in both atypical and malignant groups according Zhao et al. [15]. As only certain meningiomas undergo malignant transformation, there might be genetic predispositions or other factors influencing this outcome, mediated by numerous processes interacting via a complex matrix of signals [16, 17]. A greater understanding of tumour cells' genetic mutations and molecular markers involved in critical signalling pathways may also aid in the identification of novel therapies targeted at distinct meningioma sub-types [18, 19].

Surgery and tumour location

Since the seminal publication of Simpson in 1957, there is a general agreement about the importance of resection completeness, and it is clear that sub-totally removed meningiomas may continue to grow [6]. The extent of resection (Simpson grading) is the most powerful prognostic factor for recurrence for all grades of meningioma including for

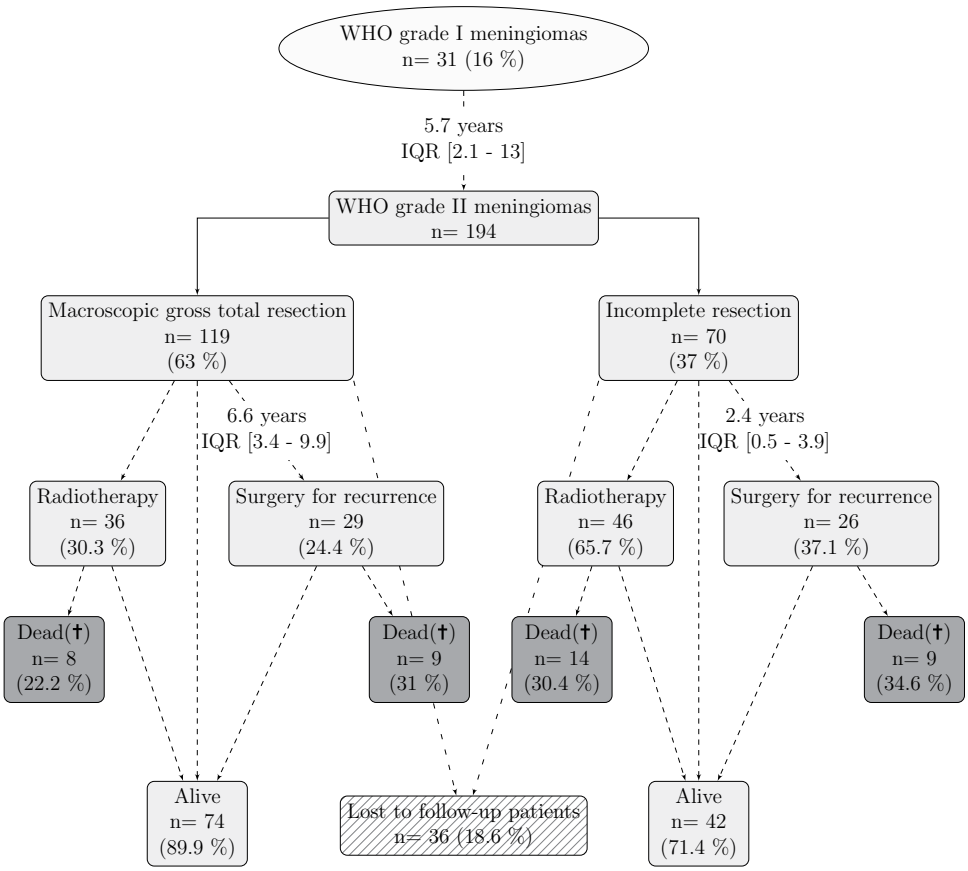

Fig. 3 Diagram of the WHO grade II meningiomas treatments and evolution

grade II. MGTR is associated with better local control than incomplete resection [11, 20–23].

Surgical resection of grade II meningioma is not usually more difficult compared to grade I. A Simpson grade I can still be achieved when the meningioma is located on the convexity. This becomes more difficult with parasagittal meningiomas infiltrating a venous sinus wall. Invasive skull base meningioma (e.g. petroclival) or those infiltrating deeply into a venous sinus (tentorium cerebelli), cannot generally be removed completely without high risks of post-operative disabilities or stroke. Clark et al. showed that different mutations are found in meningiomas arising from different intracranial locations [18]. Non-NF2 meningiomas were nearly always benign, with chromosomal stability, and originating from the medial skull base. In contrast, meningiomas with mutant NF2 and/or chromosome 22 loss were more likely to be atypical along the convexity, showing genomic instability, and localizing to the cerebral and cerebellar hemispheres [18]. However, we found that the convexity and parafalcine meningiomas had a better outcome (HR = 0.19, 95 % CI [0.08, 0.41], $p < 0.001$). Currently most neurosurgeons prefer a safer but still useful brain decompression, leaving the patient in a reasonable functional state and the tumour remnant for the RT.

However, being re-operated on for a grade II meningioma relapse did not increase the survival (HR = 0.77, p value = 0.56).

Tumoral proliferation index

Mitosis count is a significant factor for both surgical recurrence-free and overall survival. When the mitosis count is closer to 20 per 10 HPFs, it may reflect more aggressive tumour biology compared to low mitosis in atypical meningiomas and high mitotic rate has been described to be associated with recurrence [24, 25]. The Ki-67 index is also a useful predictor of risk of recurrence and provides a potential means to circumvent the problems related to the mitosis count per 10 HPFs as a marker of proliferation [26]. We could not study these effects as this data was only available for less than of a quarter of our series.

Radiotherapy

RT after surgical resection of WHO grade II meningioma continues to be controversial. 43.3 % of our patients received RT. This percentage is within reported ranges of 7.4–59.1 %. For grade II meningioma, most neurosurgeons would not advocate adjuvant RT if the tumour was completely excised [27]. However, the majority would recommend it in cases of incomplete resection [11, 27]. These practices are generally in agreement with those in our department where patients receive RT after the first recurrence, whether re-operated on or not. In the radiotherapy group, surgical recurrence-free survival is significantly lower compared to the no RT group (Fig. 1d). Our findings are consistent with those of Yoon and Durand et al. [9, 13]. Kaur et al. reported a median 5-year progression-free survival after adjuvant RT of 54.2 % [28].

Our data shows that the patients who received RT are more likely to be re-operated on for a surgical recurrence (log-rank test p value <0.001) (Fig. 1f). This fact is possibly secondary to a selection bias or a complex interaction: the patients who underwent RT are those who recurred or had an incomplete resection. We could not conclude on its effectiveness contrary to few authors who found a modest impact of the RT on the recurrence rate [11, 29]. Our data shows that the patients who received RT did not have a different overall survival (Fig. 2f). Our findings are consistent with many previously reported results [5, 28]. Of these, none demonstrated a significant improvement in any of the clinical outcomes [28]. However, these studies had a low level of evidence as no randomized clinical trials have been performed [20]. A particularly controversial management issue is the role of RT for WHO grade II meningioma treated with MGTR. The treatment approach has largely been extrapolated from data on other meningioma grades, leading to non-uniform practices across institutions, adjuvant RT being used in many centres after subtotal resection of grade II meningioma [27, 28]. According to Kaur et al., the median 5-year survival of patients with atypical meningioma treated by RT was 67.5 % and ranged from 51 to 100 % [28]. No study was able to demonstrate a statistically significant improvement in any of the clinical outcomes with adjuvant RT for WHO grade II meningioma. Systematic postoperative RT irrespective of the resection extent failed to demonstrate its usefulness [25]. Therefore, we recommend careful consideration of the side effects and, if possible, application within research protocols.

The radiotherapy vs. observation following surgical resection of Atypical Meningioma (ROAM trial) may give information about the usefulness of radiotherapy in cases of MGTR in the future [30, 31].

Conclusion

Atypical meningiomas as defined by 2007 WHO classification are heterogeneous. Many biological, clinical and surgical factors may influence the recurrence and the survival, including tumour progression, location, completeness of resection and mitosis count. We were not able to demonstrate a significant improvement in any of the clinical outcomes after radiotherapy.

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Compliance with ethical standards

Conflict of interest None.

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