

World Health Organization grade II meningiomas

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Abstract

Background We analyzed WHO grade II meningioma cases to identify factors influencing survival.

Materials and methods Between January 2000 and August 2015, 206 cases of World Health Organization (WHO) grade II meningioma were operated at our institution. This population underwent a total of 298 surgical resections and 55 patients received a radiotherapy. A Cox multivariate regression was conducted on clinical and histological criteria.

Results Sixty-four patients were deceased (31.1 %), of which 38 died following the disease progression (18.4 %). Overall survival probability at 1, 5, and 10 years were 95.4 %, 95 % CI [92.5, 98.4]; 84 %, 95 % CI [78.3, 90.2], and 72.9 %, 95 % CI [64.5, 82.4], respectively (Fig. 1a). At the end of the study, only 87 patients (42.2 %) were alive with no tumor residual or recurrence on the last scan. Age at diagnosis (hazard ratio (HR)=0.31, 95 % CI [0.15, 0.63], $p < 0.001$), extent of resection (HR=0.25, 95 % CI [0.12, 0.49], $p < 0.001$), and tumoral brain invasion (HR=0.49, 95 % CI [0.25, 0.98], $p=0.040$) were independent factors associated with the overall survival. The patients who received radiotherapy did not demonstrate a longer overall survival ($p=0.540$).

Conclusions WHO grade II meningioma significantly impaired the survival of the patients. In the adjusted Cox regression, a macroscopic gross total resection (Simpson grades 1, 2, and 3), an age below 62 years at diagnosis and the absence of brain invasion were independent factors associated with a

longer survival. Radiotherapy may not increase the overall survival after complete or incomplete resection.

Keywords WHO grade II meningioma · Atypical meningioma · Radiotherapy · Survival · Outcome · Prognostic factors

Introduction

Meningiomas that are thought to arise from arachnoidal cap cells account for 13–26 % of intracranial tumors and are benign in about 90 % of cases [19]. The 2000 and revised 2007 WHO classification of tumors affecting the central nervous system recognizes three grades of meningiomas. The chordoid, the clear cell, and the most common atypical meningioma correspond to a WHO grade II classification. WHO grade III meningiomas are associated with aggressive growth patterns reflecting their clinical and histopathological features of malignancy and can spread by metastatic dissemination [5]. WHO grade I meningiomas occur most often in women and are associated with a relatively good outcome. The behavior and outcome of WHO grade II meningiomas are intermediate. Histopathologically, atypical meningiomas are tumors with increased mitotic activity with four mitoses or more per ten high power fields (HPF) and/or have at least three of the following characteristics: sheet-like growth, spontaneous necrosis, increased cellularity, prominent nucleoli, and small cells with a high nuclear-to-cytoplasmic ratio. The number of grade II meningiomas increased when using the WHO 2007 classification (30 %) compared to previous editions, mainly due to the definition of brain infiltrating meningiomas as atypical (grade II) [3]. Complete surgical excision is the treatment of choice in all types of meningiomas. Further optimal

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management in the case of grade II meningioma is difficult to establish.

Several studies addressed the usefulness of radiotherapy in the management of WHO grade II meningiomas but none were able to demonstrate a significant improvement in any of the clinical outcomes [14]. The aim of this study was to investigate the clinical and histological prognostic factors that may be associated with overall survival and outcome of patients operated on for a WHO grade II meningioma.

Materials and methods

Clinical material

A retrospective neuropathology database search for meningioma was carried out at the Southern General Hospital, Glasgow. All patients with a diagnosis of WHO grade II/atypical/clear cell/chordoid meningioma were included in this population-based series.

Inclusion criteria were: newly diagnosed meningioma between January 2000 and August 2015; a pathology diagnosis of grade II meningioma according to WHO 2000 or 2007 in use at time of surgery, including secondary WHO grade II meningioma that progressed from grade I. Exclusion criteria were inconclusive reports or ambiguous histology such as hemangiopericytoma.

Histology slides were not reviewed but all pathology reports were carefully examined. Cases diagnosed before 2007 were reclassified according to the last WHO grading system if necessary. Meningioma sub-type, mitoses count per ten high power fields (HPFs) also called mitotic index, Ki-67 index (MIB-1), presence of necrosis, brain invasion, architectural sheeting, and presence of psammoma bodies were separately extracted. In case of recurrence, histology reports were compared to 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 postoperatively. Tumor location was divided into ten categories.

Invasion of a venous sinus or its wall was separately noted for the four major sinuses. Volumes from the diameter method were calculated using the following formula to measure volumes of an ovoid object.

Methods

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 and post-operative images [22]. We defined total resection (TR) as Simpson grades 1 and 2, gross total

resection (MGTR) as Simpson grades 1, 2, and 3, and incomplete resection or subtotal resection (STR) as Simpson grades 4 and 5. If radiotherapy was given, data on the technique, overall dose, and time of completion after surgery 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 of recurrence was defined as a "radiological relapse" corresponding to radiological evidence of tumor regrowth in case of total resection, or to a residual tumor progressing or not, in case of incomplete resection (progression-free survival).

In case of death, the cause was searched and quoted differently if related or not to the surgery or the progressing meningioma disease.

A patient with no record for more than 2 years was considered as lost to follow-up. Patient outcome and clinical status were assessed through medical records, the patient database, and information obtained from general practitioners.

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

Statistical analysis

Prior to modeling, the data were summarized with descriptive analysis including medians and inter-quartile ranges (IQR) for non-Gaussian distributed variables and frequencies for categorical variables. For exploratory purposes, an initial analysis of the data was performed using the Mann–Whitney–Wilcoxon test, χ^2 and Fisher's exact tests to compare alive to dead patients, regardless of follow-up time. This allowed identification of potential prognostic factors. Survival statistics were based on time to death, which was measured from the age at diagnosis to the date of last follow-up or decease only if related to the meningioma surgery or progression. 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. A univariate Cox regression was subsequently run. Independent prognostic factors with a p value < 0.20 were assessed with a multivariate stepwise Cox proportional regression model. We used Walds test, analysis of deviance, Akaike and Bayesian information criteria in the search of the best fitted model. Proportional hazard assumption was tested with Schoenfeld residuals. A p value < 0.05 was considered as statistically significant. In the survival analysis, some observations were automatically deleted due to missing of data, which were not imputed. For the analysis, we considered equally as radiotherapy any form of radiation therapy. Analyses were performed with the R programming language and software environment for statistical computing and graphics (R version 3.2.3 (2015-12-10)), the survival, the rms packages among others. The statistical

program and workflow was written in R Markdown v2 with RStudio® for dynamic and reproducible research.

Results

Population description

Of the 206 cases collected, 95 patients were male (46.1 %). Median age at diagnosis was 57.2 years, IQR [45.5–67.9]. Seizures were the most frequent revealing symptom and the most common location was parafalcine meningioma, in 63 cases (34.1 %) (Table 1). There were four cases (1.9 %) of spinal grade II meningiomas. Seventeen patients (8.3 %) had initially a grade I meningioma that progressed to a grade II in a median time 5.7 years, IQR [2.7–8.5].

Concerning the past medical history, five patients had a type II neurofibromatosis and nine patients (6.5 %) had a presumed radiation-induced meningioma of whom four had had previous cranio-spinal radiotherapy for leukemia and five for radiation therapy for other types of previous brain tumors. Median follow-up was 4.1 years, IQR [1.6–7.3]. Only two patients were lost to follow-up.

Surgery

A total of 298 surgical resections was performed. Twenty-eight patients (13.6 %) had two surgical procedures and 24 (11.7 %) three or more; 156 patients (76.8 %) had a macroscopic gross total resection (MGTR). Forty-three patients (21.5 %) were re-operated for a relapse of their grade II meningioma. The median time between the first and second surgery was 4.2 years, IQR [1.4, 5.7]; 11.4 % of the patients experienced a postoperative infection, usually requiring a re-intervention for surgical site cleansing and infected bone flat removal; 7.1 % had a (titanium) cranioplasty inserted, mainly following an deep postoperative infection. Fourteen patients demonstrated a malignant transformation into a WHO grade III meningioma.

Radiotherapy

Fifty-one patients (26.6 %) received conventional radiotherapy. Twenty-two patients (11.2 %) had radiotherapy but were not re-operated on. The median delay between the WHO grade II meningioma surgery and the end of radiotherapy was 1 year, IQR [0.3–2.6]. Nine patients (4.7 %) received a stereotactic radiotherapy, mostly by Gamma Knife (median

Table 1 Univariate Cox regression for grade II meningioma overall survival

Variable	n, % or median, IQR ^d	HR ^a	[95 % CI] ^b	p value
Gender male	95 (46.1 %)	1.28	0.67, 2.47	0.45
Age at diagnosis ≤ 57.2*	57.2 years, IQR [45.5–67.9]	0.49	0.25, 0.96	0.04
Age at diagnosis ≤ 62 years*	125 (61.9 %)	0.3	0.15, 0.61	<0.001
Previous history of GIM surgery*	17 (8.3 %)	2.22	0.92, 5.36	0.08
Motor and walking impairment	28 (20.4 %)	0.63	0.14, 2.8	0.54
Convexity vs. others location	59 (31.9 %)	0.73	0.31, 1.73	0.48
Convexity & parafalcine vs. others location*	122 (59.2 %)	0.51	0.24, 1.1	0.09
Side (right vs. left)	93 (48.9 %)	0.79	0.38, 1.63	0.53
Tumor volume ≤ 48.6 cm ³ *	48.6 cm ³ , IQR [25.5–80.2]	0.26	0.08, 0.8	0.02
Venous sinus invasion (present vs. absent)*	76 (41.1 %)	2.95	1.33, 6.57	0.01
Simpson resection grade 1 and 2 (TR) vs. 3, 4 and 5*	140 (69 %)	0.27	0.14, 0.52	<0.001
Simpson resection grade 1, 2, and 3 (MGTR) vs. 4 and 5*	156 (76.8 %)	0.28	0.15, 0.55	<0.001
Mitoses count ≤ 5 (median)*	5 per 10 HPFs, IQR [2–6]	1.91	0.97, 3.74	0.06
Ki-67 index ≤ 15 % (median)	15, IQR [10–20]	1.09	0.46, 2.58	0.84
Presence of a brain invasion*	68 (34 %)	2.13	1.1, 4.11	0.03
Radiotherapy or radiosurgery	55 (26.7 %)	1.25	0.62, 2.52	0.54
Chemotherapy ^c	9 (4.8 %)	3.19	1.38, 7.4	0.01
Re-intervention for grade II meningioma recurrence *	43 (21.5 %)	2.04	1.05, 3.98	0.04

p values in bold are statistically significant

* Variable integrated in the multivariate analysis

^a Hazard ratio

^b 95 % confidence interval

^c Statistical interaction

^d Interquartile ranges

dose = 16 Gy), of which five had already had conventional radiotherapy. In the survival analysis, we considered as radiotherapy, whether conventional or stereotactic method ($n = 55$). Seventeen patients (36.2 %) had early adjuvant radiotherapy within the six postoperative months and 24 patients (31.9 %) received a late radiotherapy i.e., after the postoperative year; 21.8 % of the patients ($n = 34$) who had a MGTR underwent also radiotherapy compared to 42.6 % ($n = 20$) in the incomplete resection group. However, there is no statistical interaction between radiotherapy and completeness of resection (Wald test p value = 0.566). Therefore, radiotherapy is an independent predictor of overall survival.

Chemotherapy

Nine patients received conventional chemotherapy by hydroxycarbamide or somatostatin as palliative treatment without any remarkable efficiency. No one received newer targeted agents, such as MTOR inhibitors, bevacizumab, or sunitinib. Only the patient with tumor progression out of control received chemotherapy. Thus, chemotherapy is an independent predictor neither of the recurrence nor of the survival.

Outcome and survival analysis

Sixty-four patients were deceased (31.1 %), of which 38 died following the meningioma surgery or disease progression (18.4 %) (Fig. 1a). Overall survival probability at 1, 5, and 10 years were 95.4 %, 95 % CI [92.5, 98.4]; 91.09 %, 95 % CI [87, 95.39], 84 %, 95 % CI [78.3, 90.2] and 72.9 %, 95 % CI [64.5, 82.4], respectively (Figs. 1a and 2).

At the end of the study, only 87 patients (42.2 %) were alive with no tumor residual or recurrence on the last scan.

Univariate (unadjusted) Cox regression analysis performed on clinical and pathological criteria identified age at diagnosis, tumor volume, venous sinus invasion, completeness of resection, brain invasion and re-intervention for WHO grade II recurrence as predictive of the survival (Table 1). It suggested an association between previous surgery for a grade I meningioma, tumor location, and mitoses count that did not reach significance but did warrant inclusion in the subsequent multivariate analysis (Table 2). Age at diagnosis (HR = 0.31, 95 % CI [0.15, 0.63], $p < 0.001$), extent of resection (HR = 0.25, 95 % CI [0.12, 0.49], $p < 0.001$), and tumoral brain invasion (HR = 0.49, 95 % CI [0.25, 0.98], $p = 0.040$) were independent factors associated with the overall survival.

In the adjusted Cox regression, a gross total resection (Simpson grades 1, 2, and 3), an age below 62 years at WHO grade II meningioma diagnosis, and the absence of brain invasion were independent factors associated with a longer survival (Table 2 and Fig. 1b–d).

The patients who received radiotherapy did not demonstrate a longer overall survival (log-rank test p value = 0.540) (Table 2 and Fig. 1e, f).

Discussion

Despite its methodological limitations, this study on outcome and prognostic factors affecting the survival of WHO grade II meningioma is the largest series in the literature. We did not include any grade III meningiomas as it is well recognized that those two types of tumor behave very differently. Therefore, they should not be grouped together when assessing outcome and predictors [1, 7].

Predictors of survival

Age at diagnosis

The median age of 57.2 years at diagnosis is a prognostic factor of the survival (p value = 0.04). However, we found that the best statistical cut-off was 62 years ($p < 0.001$). Patients who are under 62 years old at WHO grade II surgery are less likely to die of their meningioma disease. This finding is consistent with previous reports where age at diagnosis has already been reported to be associated with the overall survival of grade II meningioma [7, 21, 27, 28]. Some authors have defined 65 years as the cut-off for a poor prognosis [7, 28]. Moreover, Aghi et al. found that older age was predictive of recurrence [2].

Surgery

Since the seminal publication of Simpson in 1957, there is general agreement about the importance of resection completeness, and it is clear that sub-totally removed meningiomas may continue to grow. The extent of resection (Simpson grading) is the most powerful prognostic factor for recurrence for all grades of meningiomas including grade II. GTR is associated with better local control than incomplete resection [8, 9, 12, 20, 28]. Surgical resection of grade II meningioma is not much 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 meningiomas (e.g., petro clival) or those deeply infiltrating a venous sinus (tentorium cerebelli), cannot generally be removed completely without high risks of severe postoperative disabilities or stroke.

Being re-operated on for a grade II meningioma relapse impaired the survival in univariate analysis (HR = 2.04, Wald test $p = 0.04$) but not in multivariate ($p = 0.27$).

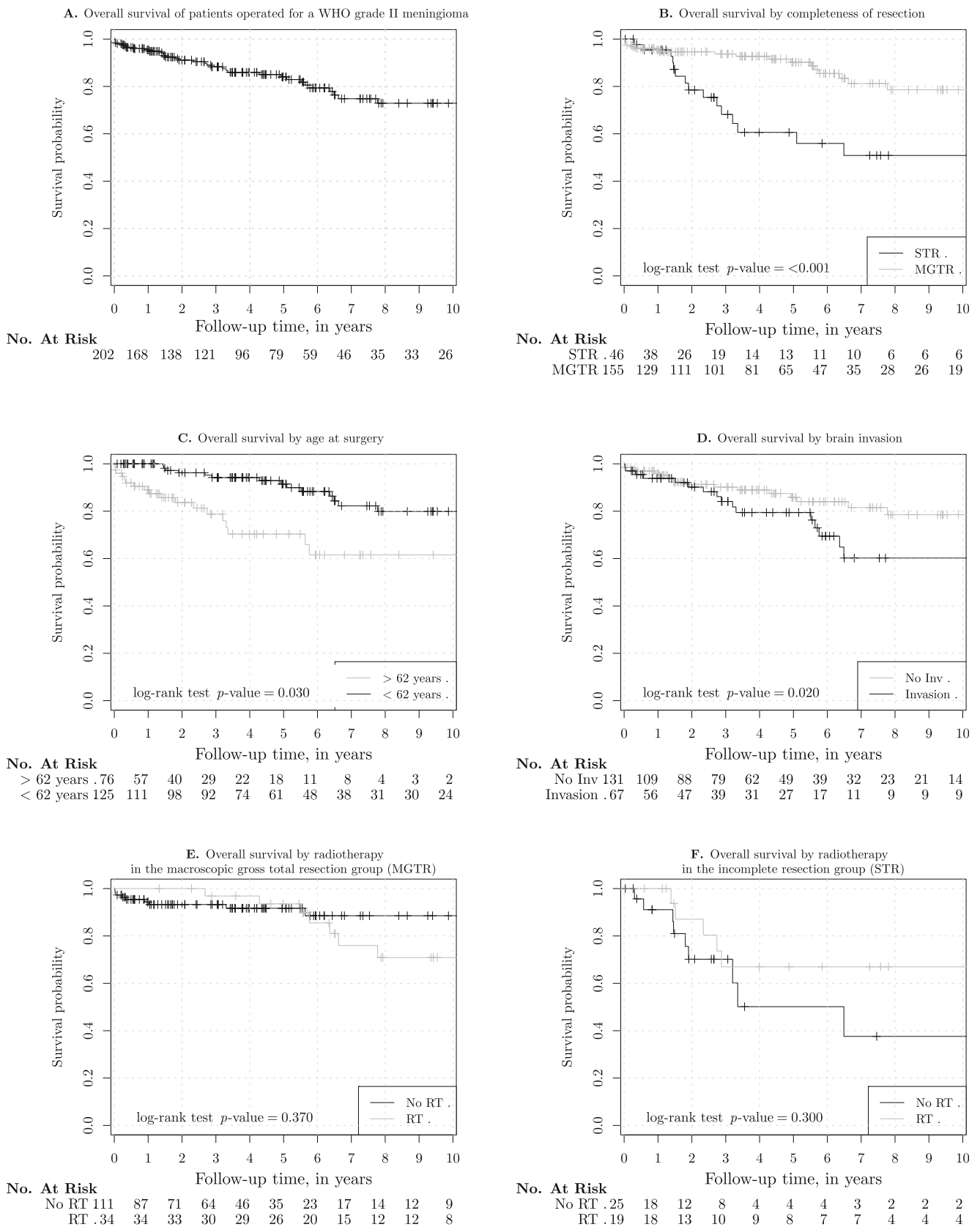


Fig. 1 Survival curves **a.** Overall survival **b.** Survival by completeness of resection **c.** Survival by age at WHO grade II meningioma diagnosis **d.** Survival by brain invasion **e.** Survival by radiotherapy in the GTR group **f.** Survival by radiotherapy in the STR group

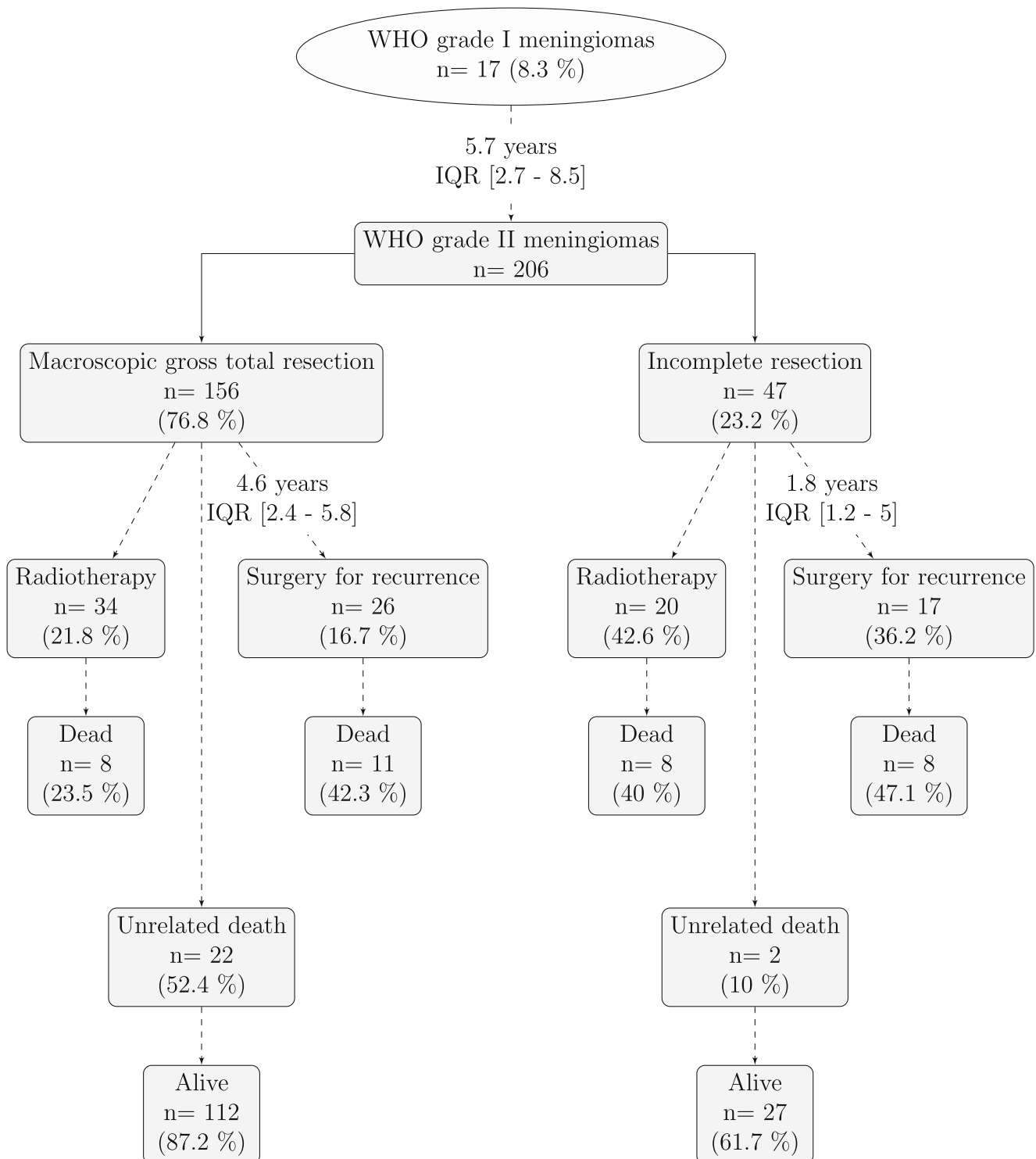


Fig. 2 Diagram of the WHO grade II meningiomas treatments and evolution

Histological brain invasion

The significance of brain invasion as a criterion of malignancy or determinant of poor survival has been controversial [25]. It has been traditionally considered to be indicative of malignancy but it was shown recently that brain-invasive meningiomas

without anaplasia pursue a less aggressive course than histologically malignant meningiomas. In 2007, the WHO criteria were further modified to remove the automatic classification of tumors with brain invasion into the grade 3 category, thereby further increasing the proportion of grade 2 [15]. In some studies, brain invasion has been found to be associated with

Table 2 Multivariate Cox regression for grade II meningiomas overall survival

Variable	HR ^a	[95 % CI] ^b	<i>p</i> value
Age at diagnosis ≤62 years	0.31	0.15, 0.63	< 0.001
Simpson resection grade 1, 2, and 3 (MGTR) vs. 4 and 5	0.25	0.12, 0.49	< 0.001
Absence of brain invasion	0.49	0.25, 0.98	0.04

p values in bold are statistically significant

^a Hazard ratio

^b 95 % confidence interval

the recurrence risk or the progression-free survival [25, 27]. Its role as an independent predictor of overall survival has never been reported before. Yang et al. demonstrated a survival benefit with adjuvant radiotherapy for patients with atypical meningiomas only in the presence of brain invasion. This was not the case in our study (log-rank test $p=0.550$).

Radiotherapy

Radiotherapy after surgical resection of WHO grade II meningiomas continues to be controversial. The studies addressing the usefulness of radiotherapy had a low level of evidence as no randomized clinical trials have been performed [9]. A particularly controversial management issue is the role of radiotherapy for WHO grade II meningioma treated with gross total resection. The treatment approach has largely been extrapolated from data on others meningioma grades, leading to non-uniform practices across institutions, adjuvant radiotherapy being used in many centers after subtotal resection of grade II meningioma [14, 17]. A total of 26.7 % of our patients received radiation therapy. This percentage is quite low compared to other series but still in previously reported ranges of 7.4–59.1 %. For grade II meningiomas, most neurosurgeons do not advocate adjuvant radiotherapy if the tumor is completely excised [16, 17]. However, the majority would recommend it in cases of incomplete resection [17, 28]. These practices are more or less in agreement with those in our department, which is to treat the

patients with radiotherapy after the first recurrence, operated or not. Our data shows that the patients who received radiotherapy did not have a different overall survival. Our findings are consistent with many previously reported results [14, 23]. Moreover, this absence of effect on the survival was not influenced by the resection status of the meningioma (Fig. 1e, f).

According Kaur et al., the median 5-year overall survival of patients with atypical meningioma treated by radiotherapy was 67.5 %, and ranged from 51 to 100 % [14]. No study was able to demonstrate a statistically significant improvement in any of the clinical outcomes with adjuvant radiotherapy for WHO grade II meningioma. Systematic postoperative radiotherapy irrespectively of the resection extent failed to demonstrate its usefulness [24]. Therefore we think that it should be carefully considered regarding the side effects and, if possible, applied within research protocols. The relatively divergent results in the literature are most likely explained by bias of selection. Randomized clinical trials to adequately address this question are clearly necessary.

The “Radiotherapy versus Observation following surgical resection of Atypical Meningioma” (ROAM trial) may give us in 10 years time more clues about the usefulness of radiotherapy in cases of GTR [10, 11].

Comparison of outcome with existing literature

We reviewed published surgical series of grade II meningiomas in the English literature, since 2000 (Table 3).

Table 3 Literature review of WHO grade II meningioma overall survival and associated predictors

Authors (year)	<i>N</i> ¹	Male (%)	Median age at diagnosis (years)	Radiotherapy (%)	Median OS ³ (years)	5-year OS (%)	Prognostic factors
Our series	206	46.1	55.9	26.7	NA ²	84	Age at diagnosis, GTR, brain invasion
Hammouche (2014) [9]	79	54	58	46	10.67	81	GTR
Zaher (2012) [28]	44	50	52	59.1	4.75	35	GTR, Age at diagnosis (<50)
Zhao (2012) [29]	89	47.2	53	44.9	8.05	89.1	KPS (< 80)
Durand (2009) [7]	166	41.6	57.5	36.7	11.2	78.4	GTR, Age at diagnosis (< 60)
Goyal (2000) [8]	22	63.6	55.5	36.4	10.6	91	GTR

¹ Number of subjects

² Not available

³ Overall survival

Among the several studies only dedicated to grade II meningiomas, there are noteworthy differences, especially in the number of irradiated patients, ranging from 12.7 to 59.1 %. Therefore it is difficult to compare the outcome results of median overall survival extending from 4.75 to 11.2 years and of 5-year overall survival expanding from 35 to 89.1 %.

Histological features of meningiomas are not fixed, and can evolve, like for gliomas. Fourteen progressed towards a WHO grade III meningioma. As only certain meningiomas undergo malignant transformation, there may be genetic predispositions or other factors influencing this outcome, mediated by numerous processes interacting via a complex matrix of signals [18, 26]. A greater understanding of tumor cells' genetic mutations and molecular markers involved in critical signaling pathways may also aid in the identification of novel therapies targeted at distinct meningioma sub-types [4, 6, 13, 26]. So far, no chemotherapeutic options have demonstrated their usefulness in meningioma treatment. Further larger studies are needed to establish prognostic factors that may allow greater accuracy in predicting tumor behavior and aid in selecting optimal treatment regimens. The implementation of a national registry or a multicenter study could help us to achieve these goals.

Conclusions

WHO grade II meningiomas significantly impaired the survival of the patients. In the adjusted Cox regression, a macroscopic gross total resection (Simpson grades 1, 2, and 3), an age below 62 years at diagnosis, and the absence of brain invasion were independent factors associated with longer survival. Radiotherapy may not increase the overall survival after complete or incomplete resection.

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Compliance with ethical standards

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Conflicts of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Comments

This is an important case series on atypical meningiomas. WHO grade II meningiomas have a somewhat unpredictable clinical behavior and studies with large cohorts do help in understanding disease characteristics. The authors have retrospectively reviewed 206 cases of WHO grade II meningiomas and have excluded anaplastic cases and other pathologies such as hemangiopericytomas. This is important, as most previous studies have analyzed grade II and III meningiomas as a single group. Some groups have also included hemangiopericytomas that have been established as a completely separate entity. Therefore, an analysis of this relatively more “purified” group is more desirable. Within the time frame of the reported cases from 2000 to 2015, the WHO pathological tumor classification has been revised twice and the authors indicate that they have reviewed the pathology records in detail to come to a definitive conclusion.

The low recurrence-free survival rate (42.2 %), despite exclusion of anaplastic cases, indicates that atypical meningiomas are high-risk pathologies and that they deserve the WHO grade II designation. The authors have found that an age above 62, extent of resection (Simpson 1 to 3), need for reoperation, and brain invasion as important variables influencing overall survival. Importantly, radiation therapy was not found to be a factor influencing patient survival. The conclusions of such a large cohort will certainly help clinicians to develop rational strategies in the management of atypical meningiomas.

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