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ORIGINAL ARTICLE - TUMOR - MENINGIOMA

Intracranial WHO grade I meningioma: a competing risk analysis of progression and disease-specific survival

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Abstract

Background Studies on meningioma are reported with inadequate allowance for competing causes of progression or death. The aim of this study was to describe the outcome of patients with intracranial WHO grade I meningioma and identify factors that may influence disease progression and cause-specific survival.

Methods Pathology reports and clinical data of 505 WHO grade I meningiomas treated between January 2003 and December 2017 were retrospectively reviewed at a single institution. We estimated a cumulative incidence function for progression and cause-specific mortality. A competing risk analysis was conducted on clinical and histological criteria. Median follow-up was 6.2 years.

Results A total of 530 surgical resections were performed on 505 cases. Forty-one patients received radiotherapy (RT). At data collection, 84 patients had died of their meningioma disease or demonstrated a recurrence eventually treated by redo surgery or RT. The risks of recurrence or meningioma-related death at 5 years were 16.2%, $_{95\%}$CI[12.5, 20], whereas 5-year overall survival was 86.1%, $_{95\%}$CI[82.8, 89.6]. In the multivariable Fine-Gray regression for a competing risk model, venous sinus invasion (SHR = 1.8, $_{95\%}$CI[1.1, 2.9], p0.028), extent of resection (SHR = 0.2, $_{95\%}$CI[0.1, 0.3], $p < 0.001$), and progressing meningioma (SHR = 7, $_{95\%}$CI[3.3, 14.8], $p < 0.001$) were established as independent prognostic factors of cause-specific death or meningioma progression. In contrast, age at diagnosis < 65 years (HR = 1.1, $_{95\%}$CI[1, 1.1], $p < 0.001$) and redo surgery for meningioma recurrence (HR = 2.6, $_{95\%}$CI[1.4, 5], $p = 0.00252$) were predictors of the overall survival.

Conclusions In this large series, WHO grade I meningioma treatment failure correlated with venous sinus invasion, incomplete resection, and progressing tumour; shorter survival correlated with increased age and redo surgery for recurrence. We recommend the cumulative incidence competing risk approach in WHO grade I meningioma studies where unrelated mortality may be substantial, as this approach results in more accurate estimates of disease risk and associated predictors.

Keywords WHO grade I meningioma · Recurrence · Prognostic factors · Outcome · Competing risks

Introduction

Thought to arise from arachnoidal cap cells, meningiomas are the most common intracranial extracerebral tumours. The 2016 World Health Organization (WHO) classification recognises three grades of meningioma [19]. Benign meningiomas—WHO grade I—occur more commonly in women and usually have a good outcome [7]. Malignant or grade III meningiomas are rare and aggressive with a poor prognosis [6, 8]. The biological behaviour and outcome of atypical—WHO grade II—meningiomas are intermediate [5, 9]. Despite being one of the most frequently removed intracranial tumour, there are few studies solely dedicated to benign meningiomas and their outcome; most researches are nowadays focused on grades II and III. As grade I meningiomas are slow growing tumours with a generally indolent course, long follow-up and large case numbers are needed to delineate factors influencing their outcome.

Clinical research in oncology often considers the period of time until an event of interest occurs, commonly recurrence or death. Analyses are frequently performed using the Kaplan–

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Meier (KM) method to estimate the probability of survival, the log-rank test to compare groups, and the Cox model to estimate the effect of covariates. In standard survival analyses, subjects are supposed to experience only one type of event such as death. In reality, several types of event may occur. In these cases, other events—so-called competing risks (CR)—may preclude the occurrence of the event of interest or modify the risk that the primary endpoint occurs. Thus, traditional methods of survival analysis are not designed to accommodate the competing nature of multiple events [28]. As a workaround, the cumulative incidence function (CIF) was proposed to handle this particular issue by estimating the marginal probability over time of a certain event in the presence of competing risks (CR) [4, 29]. Currently, there is no published CR survival analysis that attempts to estimate marginal probability of WHO grade I meningioma progression or cause-specific mortality.

Objective

The aim of this study was to investigate clinical and pathological factors associated with cumulative incidence of WHO grade I meningioma disease progression or related mortality using CR analysis in the presence of unrelated causes of death.

Methods

Clinical material

We performed a single-centre analytical retrospective cohort study. A neuropathology database search was carried out at the Queen Elizabeth University Hospital, Glasgow, Scotland. Inclusion criteria were meningioma diagnosed between January 2003 and December 2017, pathology diagnosis of grade I meningioma according to WHO classification of tumour of the central nervous system (CNS) 2000, 2007, or 2016 according to the date of surgery in individual cases. Spinal meningiomas were excluded from the study. All patients with a diagnosis of WHO grade I/benign meningioma were included in this study, including patients with a recurrent meningioma whose grade had progressed. All pathology reports were carefully examined. Meningioma subtype, mitosis count per 10 high power fields (HPF) (mitotic index), Ki-67 index (MIB-1), presence of necrosis, and brain invasion were separately extracted. If a meningioma previously diagnosed as grade I according to a former version of the WHO classification was found to display a brain invasion described in the histopathological report, it was then reclassified as grade II in keeping with the most recent version of the WHO classification and excluded from the study analysis. Histology slides were reviewed in cases of recurrence and compared with those from previous resections. After redo surgery, a tumour may have been reclassified as grade II or III following identification of histopathological features included in the most recent WHO CNS tumour classification. Frequently, this was an increase in mitotic index above 4 per 10 HPFs. Patient demographic and medical data were collected retrospectively. We used radiographic and surgical reports, and all available in- and out-patient records. CT and/or MRI images were studied to determine the tumour location and volume. Surgical resection was evaluated according to the Simpson grading system using the operative records [31]. We defined gross total resection (GTR) as Simpson grades 1 to 3 and incomplete resection or subtotal resection (STR) as Simpson grades IV and V. The surgical impression was compared with the early postoperative contrast-enhanced images. If radiotherapy (RT) was given, data on the technique, overall dose and time of completion were collected. Radiological relapse was defined as evidence of tumour regrowth in cases of GTR, or progression of residuum in cases of incomplete resection, on the last available contrast-enhanced scan. Patient outcome and clinical status were assessed through medical records, the patient database, and information obtained from primary care physicians.

Statistical methods

Continuous variables are reported as means and standard deviations or as medians and interquartile ranges (IQR), categorical variables as frequencies and proportions. Survival was measured from the date at meningioma surgery to the date of death or censored at last follow-up [14]. Death was defined as related to meningioma surgery or meningioma progression or to another cause. All deaths within the first postoperative month were classified as related to the meningioma surgery regardless of cause. For example, death following hip fractures due to neurologic deficits or seizures was classified as related to the meningioma disease. Failure in the CR regression (CRR) was defined as redo surgery or RT for recurrence, radiological progression or death related to the meningioma disease. In CRR, individuals who died from other causes unrelated to the meningioma disease were treated as competing events. Analyses were implemented using the proportional subdistribution hazards regression model described by Fine and Gray [11, 30]. Analyses of mortality from meningioma and from other causes accounting for CR were performed using CIF. We used the Kaplan–Meier method to estimate the overall survival (OS). Cox proportional hazard regressions were implemented to identify predictors of overall death and to estimate hazard ratios (HR) with 95% confidence intervals (95% CI) [33]. Missing data were not imputed. Primary analyses were conducted using available cases. All tests were 2-sided and statistical significance was defined with an alpha level of 0.05 ($p < 0.05$). Analysis was performed using the R programming language and software environment (R version 3.6.1 (2019-07-05)) [24]. The statistical programme and

workflow were written in R Markdown v2 with RStudio® for dynamic and reproducible research [26].

Compliance with ethical standards

This study was conducted in line with the ethical standards of the Helsinki Declaration (2008), to French data protection authority (CNIL—an independent national ethical committee) standards authorisation number 2008538 and in accordance with the STROBE statement for observational studies in epidemiology and SAMPL Guidelines [10, 17]. Informed consent was not required due to the retrospective nature of the study.

Results

Population description

Of the 505 cases collected, 146 patients were male (28.9%) (Table 1). A total of 530 surgical resections were performed. Median age at diagnosis was 56.4 years, IQR[46.2–66.5]. Twenty-five patients (5%) had been re-operated on for recurrence. Median time until redo surgery was 1.3 years, IQR[0.2, 2.6]. Eleven patients were diagnosed with a progression to grade II or III tumours. Median follow-up was 6.2 years, IQR[2.8–9.5]. Forty-seven patients (9.5%) were lost to follow-up, of which 34 had a follow-up over 5 years.

Radiotherapy

Thirty-nine patients (8.1%) received conventional external beam RT (median dose = 50.4 Gy), with most (63.9%) receiving less than 51 Gy. Three patients (0.6%) received Gamma knife® stereotactic radiosurgery, of which one had already had conventional RT. For the analysis, we considered equally any form of RT ($n = 41$). Among the 11 patients who demonstrated a tumour grade progression after redo surgery, 6 had had RT.

Overall survival

At data collection, 102 patients (20.5%) were dead of which 27 (5.5%) died due to their meningioma disease. The median age at death was 71.7 years, IQR [59.8, 78.6]. Eight patients died within a month of surgery and 29 within a year. OS rates at 5 and 10 years respectively were 86.1%, $_{95\%}$CI[82.8, 89.6] and 71.3%, $_{95\%}$CI[66.1, 76.9] (Fig. 2c).

Significant prognostic variables in univariate Cox regression were age at diagnosis, tumour volume, and redo surgery for meningioma recurrence (Table 2).

In adjusted Cox regression, age at diagnosis < 65 years (HR = 1.1, $_{95\%}$CI[1, 1.1], $p < 0.001$) and redo surgery for meningioma recurrence (HR = 2.6, $_{95\%}$CI[1.4, 5], $p = 0.00252$) were predictors of the overall survival (OS) (Table 3).

Table 1 Characteristics of the 505 patients

Characteristics	*n*, % or median and IQR′
Gender female	359 (71.1%)
Median age at surgery	56.4 years, IQR[46.2–66.5]
Age at diagnosis < 65 years	356 (47.9%)
Main symptom at presentation	
Motor and walking impairment	45 (12.1%)
Seizure	103 (27.8%)
Others	211 (41.8%)
Location	
Convexity	140 (29.4%)
Para sagittal/falx	117 (24.6%)
Skull base	175 (34.7%)
Others	57 (11.3%)
Side of the meningioma implantation (right vs. left)	219 (45.6%)
Tumour volume	24.9 cm^3, IQR [11.7–45.1]
Preoperative embolisation	35 (7.1%)
Resection status after the first procedure	
Simpson 1	153 (32.5%)
Simpson 2	203 (43.1%)
Simpson 3	30 (6.4%)
Gross total resection (GTR—Simpson 1, 2, and 3)	386 (82%)
Simpson 4	70 (14.9%)
Simpson 5	15 (3.2%)
Sub total resection (STR, - Simpson 4 Si 5)	85 (16.8%)
Venous sinus invasion	179 (37.9%)
Median mitoses count per 10 HPFs	1 per 10 HPFs, IQR [1, 2]
Median Ki-67 (MIB-1)	5, IQR [4–6]
Radiotherapy	39 (7.7%)
Stereotactic radiotherapy	3 (0.6%)

Competing risks regression

At data collection, 84 patients (20.9%) were dead of their meningioma disease (Fig. 1) or demonstrated a tumoral recurrence eventually treated by redo surgery or RT (Fig. 2a).

The absolute risk of benign meningioma recurrence or related death at 5 and 10 years respectively was 16.2%, $_{95\%}$CI[12.5, 20] and 24.4%, $_{95\%}$CI[19.4, 29.3] (Fig. 2b).

Significant prognostic factors in univariate proportional subdistribution hazard regression were meningioma location, side of tumour origin, venous sinus invasion, completeness of resection, meningioma subtype, and progressing meningioma (Table 2, Fig. 3). In the multivariable Fine-Gray regression for

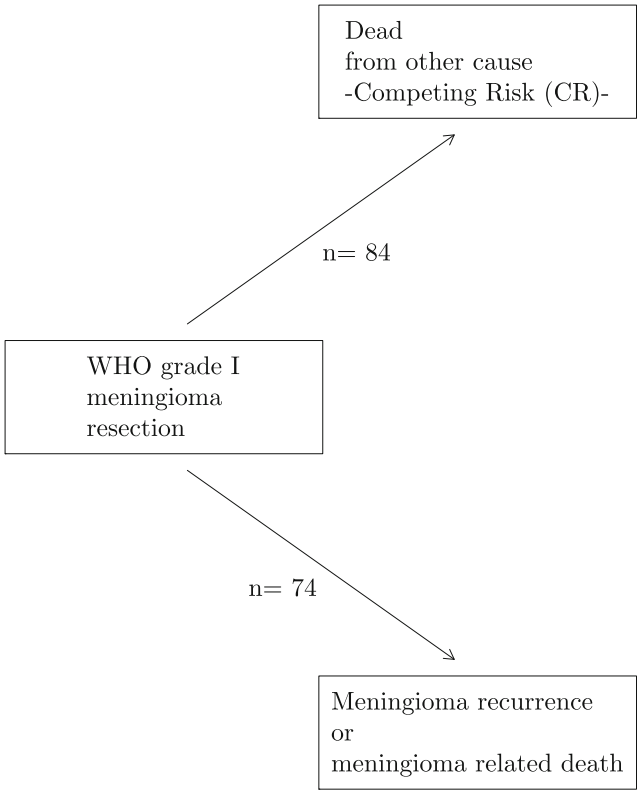

Fig. 1 Benign meningioma evolution

competing risks model, venous sinus invasion (SHR = 1.8, $_{95\%}$CI[1.1, 2.9], p 0.028), extent of resection (SHR = 0.2, $_{95\%}$CI[0.1, 0.3], $p < 0.001$), and progressing meningioma (SHR = 7, $_{95\%}$CI[3.3, 14.8], p <0.001) were established as independent prognostic factors of cause-specific death or meningioma progression (Table 4).

Discussion

In contrast to malignant neoplasms, outcome data on benign tumours are scarce as they are logically not considered as "cancer" and thus infrequently registered apart in nordic cancer registries since decades. WHO grade I meningioma has long been excluded from brain cancer registration and statistics [7]. Moreover, large institutional series often combine all 3 grades which may not be appropriate when assessing their outcome.

This study presents long-term treatment results in a series of patients with histologically confirmed benign meningioma. To date, such a survival research on WHO grade I meningiomas accounting for CR has not, to our knowledge, been published. Our population characteristics are similar to those described in dedicated studies on descriptive epidemiology with an over-representation of females and a median age at diagnosis of 56.4 years, IQR[46.2–66.5] [7, 22, 34].

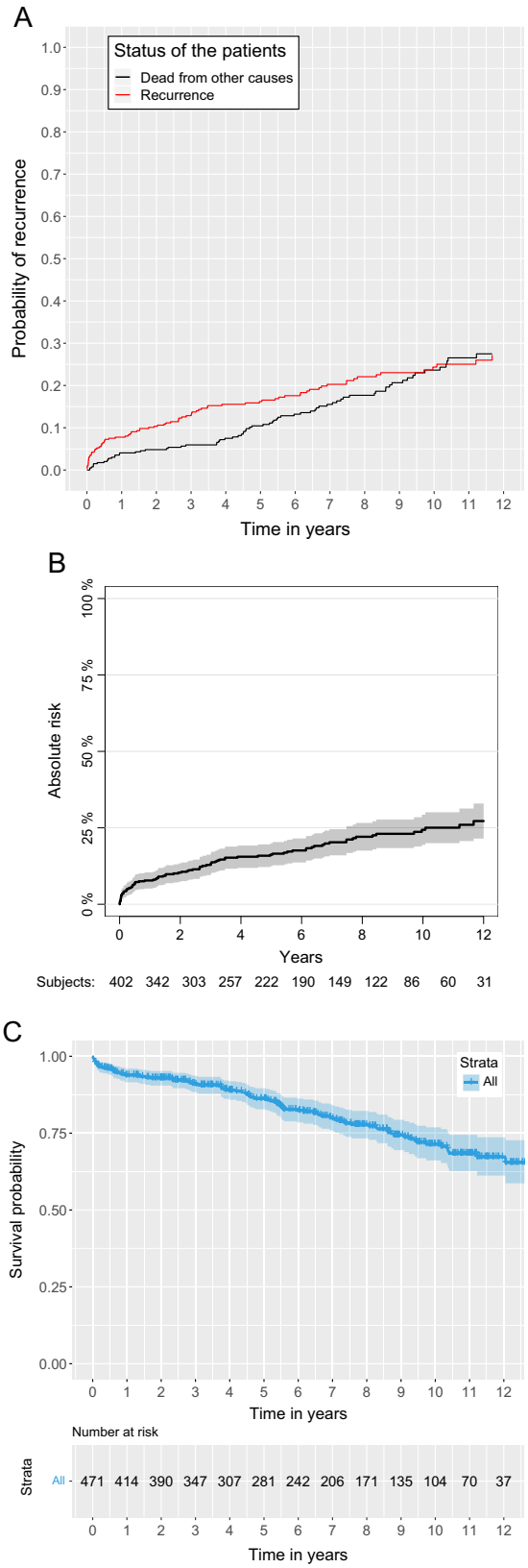

Fig. 2 Survival curves. **a** Cumulative incidences curves of unrelated death. **b** Non-parametric (Aalen-Johansen) estimation of the absolute risk of benign meningioma recurrence or related death over the time. **c** Overall survival (OS)

Table 2 Univariable cumulative incidence competing risk (CICR) of WHO grade I meningioma treatment failure and Cox regression of overall survival (OS)

Variable	Cumulative incidence competing risk			Overall survival		
	SHR[a]	[95% CI][b]	*p* value	HR[c]	[95% CI]	*p* value
Gender male	0.88	0.54, 1.43	0.6	1.38	0.91, 2.08	0.13
Age at diagnosis (continuous)	0.99	0.98, 1.01	0.5	1.06	1.04, 1.08	< 0.001
Seizure at presentation	0.65	0.37, 1.15	0.14	1.24	0.70, 2.17	0.46
Convexity vs. others locations	0.32	0.17, 0.60	< 0.001	1.38	0.88, 2.15	0.16
Parafalcine vs. others locations	0.80	0.47, 1.35	0.4	0.71	0.41, 1.22	0.21
Convexity and parafalcine vs. others locations	0.38	0.24, 0.60	< 0.001	1.05	0.68, 1.62	0.82
Side (right vs. left or middle)	0.59	0.38, 0.92	0.021	0.95	0.61, 1.47	0.81
Tumour volume (continuous)	1.00	1.00, 1.01	0.12	1.01	1.00, 1.01	0.04
Venous sinus invasion (present vs. absent)	2.70	1.73, 4.22	< 0.001	0.90	0.56, 1.43	0.65
Simpson resection grades I, II, and II (GTR) vs. IV and V	0.15	0.1, 0.24	< 0.001	0.88	0.52, 1.48	0.63
Meningothelial subtype (n = 199) vs. others	1.59	1.04, 2.43	0.034	1.08	0.71, 1.62	0.73
Mitoses count (continuous)	0.88	0.68, 1.13	0.3	1.07	0.85, 1.36	0.55
Ki-67 (continuous)	1.02	0.98, 1.06	0.26	0.84	0.52, 1.35	0.47
Progressing meningioma	7.15	3.66, 13.95	< 0.001	2.35	0.95, 5.78	0.06
Radiotherapy or Radiosurgery	NA[d]	NA	NA	1.22	0.63, 2.36	0.56
Redo surgery for recurrence	NA	NA	NA	2.35	1.25, 4.4	0.01

Overall survival

Despite a generally indolent biological behaviour, the outcome of patients treated for benign meningioma may occasionally be poor. We assessed our population OS as a means of comparison with previous studies and with our Cumulative Incidence Competing Risk (CICR) findings. However, only a few studies have reported OS of WHO grade I meningioma. Five-year OS ranges from 83 to 92% in previous studies vs. 86.1% in our cohort [3, 12, 15, 21, 22, 27, 34]. Unsurprisingly, age at diagnosis was strongly associated with the OS [3]. Among the other factors investigated, reoperation for meningioma recurrence was associated with a 2.3 times increased risk of death. Interpretation of OS of patients with WHO grade I meningioma is confounded by deaths from other causes, so-called competing risk (CR). In a study examining time to death attributable to meningioma, unrelated deaths such as those due to cancer (e.g., lung) or cardiovascular disease are competing risks (CR) that need to be addressed.

Table 3 Adjusted Cox regression for WHO grade I meningioma overall survival

Variable	HR[a]	[95% CI][b]	*p* value
Age at diagnosis < 65 years	1.06	1.04, 1.08	**< 0.001**
Tumour volume < 26.1 cm^3 (median)	2.64	1.41, 4.97	**0.0025**

[a] Hazard ratio

[b] 95% confidence interval

p value in boldface underlines the statistically significant outcome measure (HR)

Cumulative incidence function and competing risk

The CICR method allows an estimate of the incidence of meningioma recurrence or death while taking the CR of unrelated death into account. We decided to consider as initial treatment failure any event related to the meningioma disease. Once the tumour recurred, several options ranging from redo surgery to conservative management are possible but are unlikely to lead to long-term tumour control if that was not achieved by the first procedure. Figure 2b shows a significant risk of benign meningioma treatment failure of 16.2%, $_{95\%}$CI[12.5, 20] at 5 years. After 10 years, nearly one quarter of patients had presented with a recurrence eventually re-treated or had died of their meningioma disease.

There is no consensus on the most appropriate duration of meningioma follow-up after treatment. A totally resected benign tumour is very unlikely to recur after 5 years but, if excision is incomplete, late regrowth or slow progression of residual tumour may be missed if follow-up is not long enough. Long-term MRI follow-up of benign meningioma is costly and also unnecessary for a significant proportion of patients. Therefore, clinical, radiological, and histopathological criteria that predict recurrence or progression are useful to guide duration of follow-up surveillance. This study is the first of its kind to perform this type of statistical analysis, and hence, there are no similar results. Sicking et al. included all

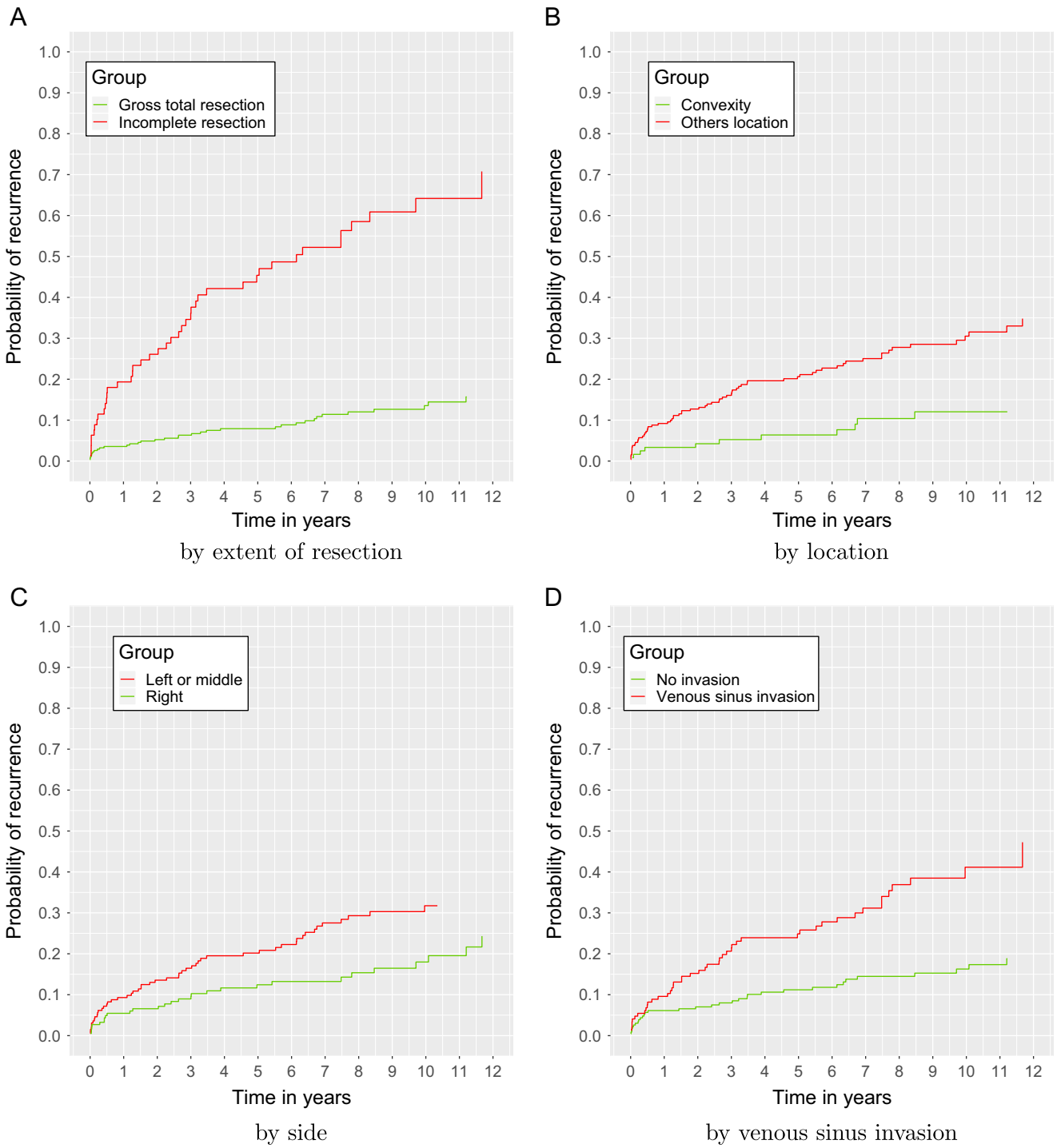

Fig. 3 Cumulative incidences curves comparisons by extent of resection (**a**), by location (**b**), by side (**c**), and by venous sinus invasion (**d**)

grades of meningioma in their study and found an average 5-year progression-free survival (PFS) of 86.4%, but OS was not investigated. Meling et al. reported a mean 5-year PFS of 80% with a mean 5-year OS of 85% [21]. Reported recurrence rates are variable ranging from 0 to 22.5% at 5 years with atypical meningioma being associated with a higher risk of relapse [3, 16]. There is a need for more accurate results stratified by WHO grade in order to address the heterogeneity of meningioma populations and to better counsel and monitor the patients.

Macroscopic characteristics and surgery

Since the seminal publication of Donald Simpson in 1957, there is general agreement about the importance of completeness of resection [31]. Simpson's original publication defined

Table 4 Adjusted cumulative incidence competing risk (CICR) of WHO grade I meningioma treatment failure

Variable	SHR[a]	[95% CI][b]	*p* value
Venous sinus invasion (present vs. absent)	1.77	1.07, 2.95	**0.028**
Simpson resection grades I, II (TR) vs. III, IV, and V	0.21	0.13, 0.35	**< 0.001**
Progressing meningioma	7.03	3.34, 14.83	**< 0.001**

[a] Subdistribution hazard ratio

[b] 95% confidence interval

p value in boldface underlines the statistically significant outcome measure (HR)

grade III resection as follows: a macroscopically complete removal of the intradural tumour, without resection or coagulation of its dural attachment, or alternatively, of its extradural extensions. Our analysis is focused on GTR which may left in place dura mater invaded by meningioma such as venous sinus wall that were not resected or coagulated. This may explain why venous sinus invasion was established as an independent prognostic factor of cause-specific death or meningioma progression. For all grades of meningioma, extent of resection has been shown to affect the risk of recurrence [20]. For grade II and III tumours, Simpson grading is the most powerful predictor of both PFS and OS [2, 5, 6, 9, 13, 32, 35]. A Simpson grade I resection is usually most easily achieved when the tumour is located on the convexity. It will likely be more difficult for tumours on the skull base that infiltrate surrounding neural and vascular structures. Thus, skull base location is a risk factor for incomplete resection, and sub-totally removed meningiomas may continue to grow [18]. On univariable CRR, we found that volume, venous sinus invasion, and side were predictors of treatment failure. These variables were not significant on adjusted regression analysis. This illustrates the likely complex interaction between these covariates and completeness of resection. A right-sided meningioma, not invading a venous sinus (therefore located on the convexity) measuring less than 26.1 cm^3, has a greater likelihood of being completely removed than a larger left-sided tumour with a broad dural base insertion possibly invading critical structures.

Symptomatic presentation was found to be a predictor of the extent of resection, possibly because larger tumours are more likely to be symptomatic [18]. The bigger the tumours, the more likely they are to be symptomatic.

As the accuracy of radiation delivery has improved following imaging and targeting developments, RT has played an increasing role in the management of WHO grade I meningiomas. This higher precision has allowed an increase in the delivered dose, currently usually 54 Gy in three-dimensional conformal radiotherapy.

Following GTR, we recommend imaging surveillance for 3 years in cases of convexity meningioma, up to 6 years for other locations, and up to 8 years for incomplete resection with no evidence of residual tumour progression. Nonetheless, in a few studies, long-term follow-up which showed an unexpected excess mortality and disease-specific mortality supports for prolonged radiologic surveillance, especially in the case of non-radical treatment [15, 23].

Microscopic characteristics

WHO grade I meningiomas have typically a mitosis count of less than 4 per 10 HPFs. The use of the Ki-67/MIB-1 labelling for cellular markers of proliferation provides a potential means to circumvent the problems related to the mitotic index. Despite being frequently assessed, Ki-67 labelling is not a characteristic of the WHO classification. It is not uncommon to encounter meningiomas that display no formal aggressive features, including inconspicuous mitoses but with raised Ki-67 labelling of up to 20 or 30% as was the case for several of the patients in our series [1].

A small group of aggressive meningioma emerged despite an initial WHO grade I grading. No particular clinical or histopathological characteristics were identified in these patients apart from the extent of resection. Of the patients who had an incomplete resection (STR) at first, 22.4% were re-operated on vs. 1.6% in the case of GTR, and this difference is highly significant ($p < 0.001$). Moreover, the times between successive operations were shorter in cases of STR (median = 0.5 year) vs. GTR (median = 2.7 years) ($p = 0.0591$), just failing to reach statistical significance.

Of those patients who were re-operated, 46% displayed microscopic features requiring a WHO CNS tumour classification upgrade. However, no histopathological data were available for the meningiomas which relapsed and were treated by RT or simply observed.

In common with other intracranial neoplasms such as gliomas, the microscopic characteristics of meningiomas are not fixed and may evolve. As only certain meningiomas undergo transformation, there might be a combination of genetic predispositions and external factors influencing this transformation, which is strongly associated with a worse outcome (SHR = 7, $_{95\%}$CI[3.3, 14.8], $p < 0.001$).

Limitations

The retrospective nature of the study, together with the lack of clarity regarding treatment rationales and non-homogenous

management strategies without random assignment, needs to be considered when evaluating the results. A central neuropathology review was not possible due to limited resources. However, a study of histopathologic assessment between "parent institutions" and central review found a high concordance of 93.0% for WHO grade I meningioma for grading [25]. Nonetheless, the inclusion of further patients and extended follow-up would be helpful in validating our findings.

Conclusion

In this large series, WHO grade I meningioma treatment failure correlated with venous sinus invasion, incomplete resection, and progressing tumour; shorter survival correlated with increased age and redo surgery for recurrence. We recommend the cumulative incidence competing risk approach in WHO grade I meningioma studies where unrelated mortality may be substantial, as this approach results in more accurate estimates of disease risk and associated predictors.

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Author contribution CC: conceived and designed the analysis/collected the data/performed the analysis/wrote the paper. DH: collected the data/revision of the work. LD: collected the data/revision of the work/final approval. MRR: conceived and designed the analysis/revision of the work/final approval.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this retrospective study, formal consent was not required.

Abbreviations *CI,* confidence interval; *CICR,* cumulative incidence competing risk; *CIF,* cumulative incidence function; *CR,* competing risk; *CRR,* competing risk regression; *GTR,* gross total resection; *HPF,* high power field; *HR,* hazard ratio; *IQR,* inter quartile range; *KM,* Kaplan–Meier; *OS,* overall survival; *PFS,* progression-free survival; *RT,* radiotherapy; *SHR,* subdistribution hazard ratio; *STR,* sub total resection; *TR,* total resection; *WHO,* World Health Organization

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