

Prognostic factors for patients with World Health Organization grade III meningiomas treated at a single center

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Abstract

We analyzed the characteristics of patients with World Health Organization (WHO) grade III meningioma to identify factors that may predict tumor recurrence and overall survival (OS).

We retrospectively reviewed the patients diagnosed with WHO grade III meningioma who were surgically treated at our institute between 2008 and 2016. Survival outcome was assessed by Kaplan–Meier analysis. Cox regression analyses were performed to identify the prognostic factors associated with tumor recurrence and OS.

Forty-two patients were included. The mean follow-up time was 23.2 months (range 2–75 months). At the end of analysis, 30 patients were found with tumor recurrence. The 1-year, 3-year, and 5-year recurrence-free survival (RFS) were 51.6%, 33.9%, and 12.0%, respectively. At final follow-up, 23 patients were deceased, the 1-year, 3-year, and 5-year OS were 66.2%, 39.7%, and 35.8%, respectively. Twenty-eight newly diagnosed patients were included, and the 1-year, 3-year, and 5-year RFS were 63.5%, 44.3%, and 19.4%, respectively, and the 1-year, 3-year, and 5-year OS were 74.6%, 52.5%, and 46.7%, respectively. Extent of resection was the only factor associated with tumor recurrence and OS.

WHO grade III meningioma is rare, and difficult to manage with a high rate of recurrence and poor OS. Extent of resection is an independent prognostic factor related to tumor recurrence and OS. We could not confirm the usefulness of Ki-67. We suggest that more aggressive treatment, such as safety maximizing cytoreduction by surgery, would improve treatment outcomes.

Abbreviations: HR = hazard ratio, IQR = interquartile range, MRI = magnetic resonance image, OS = overall survival, RFS = recurrence-free survival, WHO = World Health Organization.

Keywords: OS, prognostic factor, RFS, WHO grade III meningioma

1. Introduction

Meningioma arises from meninges of the brain and the spinal cord. It is the most common primary tumor and represents approximately one-third of central nervous system tumor in adult.^[1] According to World Health Organization (WHO) classification, meningiomas are divided into 3 subtypes on the basis of histologic grading.^[2] WHO grade III meningiomas account for 1% to 3% of intracranial meningiomas.^[3] Compared with other subtypes, WHO grade III meningiomas show a great propensity for tumor recurrence and aggressive illness progression.^[2]

The outcome of WHO grade III meningiomas is poor with a 5-year survival rate of 19.9% to 61% despite advances in treatment options.^[4–9] The management for these patients is challenging. Recent studies demonstrate that patients would benefit from surgical resection.^[4,6,7,10] Radiotherapy is also employed, but the efficiency is controversial.^[11–16] A handful of studies report the use of chemotherapy for WHO grade III meningiomas, whereas the efficiency is limited.^[17,18] Owing to the rarity of WHO grade III meningiomas, treatment strategies for these lesions have not reached an agreement. Further optimal management in the case of malignant meningioma is difficult to establish.

In our study, we analyze 42 patients diagnosed with WHO grade III meningioma, and try to elucidate the outcome and prognostic factors associated tumor recurrence and overall survival (OS) of patients with WHO grade III meningiomas.

2. Patients and methods

2.1. Patient selection

We retrospectively reviewed patients diagnosed with meningioma who were operated at the Department of Neurosurgery, West China Hospital of Sichuan University between 2008 and 2016. During the review period, a total of 3056 patients with meningioma were surgically treated. Of these patients, 2548 patients were identified as benign meningiomas, 463 patients were diagnosed with WHO grade II meningiomas and WHO grade III meningiomas were found in 45 patients. Pathologic reports and specimen of tumors were reviewed to confirm the diagnosis according 2007 WHO classification scheme. Three

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patients died of postoperation complications were excluded. Finally, 42 patients were included in this study. Our study was approved by our institute ethics board.

2.2. Parameters assessed

Data regarding patient age at surgery, sex, presenting symptom, history of previous surgery or previous radiotherapy, adjuvant radiotherapy, and salvage treatment after tumor recurrence were collected from inpatient and outpatient record. Previous surgery was defined as resection for meningiomas. Bone involvement was defined as hyperostosis, bone destruction, or bone infiltration on imaging, pathology reports, and surgery record. Tumor size was measured by maximum diameter of tumor on the basis of magnetic resonance imagings (MRI)s or surgery record. Ki-67 was extracted from pathologic reports. Tumor location was subdivided into 4 groups: convexity, skull-base, para-sagittal/para-sinus, and interventricular. The extent of resection was evaluated according to the Simpson grading scale by the use of the operative records. We defined Simpson grade I as complete resection, and Simpson grade II, III, and IV were classified as incomplete resection, no patient fell to Simpson grade V. Adjuvant radiotherapy (gamma knife or conventional radiotherapy) was given following surgical resection during study time without evidence of tumor recurrence. A redo surgery would be the first choice for patients who were found with tumor recurrence, and adjuvant radiotherapy was employed after redo surgery, but this is just an ideal strategy. If patients cannot tolerate or refuse a redo surgery, radiotherapy was suggested.

2.3. Patient follow-up

Patients were followed by neurosurgeons clinically, and MRIs and clinical evaluations were routinely obtained at 3, 6, and 12 months, and then once a year. We defined tumor recurrence as radiological evidence of tumor regrowth in cases of complete resection, or residual tumor progression in cases of incomplete resection. Recurrence-free survival (RFS) was calculated from the date of surgery to first radiological evidence of disease recurrence, or censored at the date of last follow-up in the absence of disease recurrence. OS was determined from the date of first surgery to the date of death (all causes), or last follow-up if the patient was still alive. If patients died, the cause was searched and quoted differently if related to the surgery or the progressing meningioma disease or not. A patient with no record for 1 year was considered lost to follow-up. Survival statistics were based on 2 different events: tumor recurrence and death. RFS and OS were calculated from the date of first surgery during the study time.

2.4. Statistics analysis

Quantitative variables were described using mean and range. Categorical variables were described using frequency and percentage. Survival outcome was assessed by the Kaplan-Meier method, and comparisons between groups were performed using log-rank tests. A P value <0.05 was regarded as statistically significant. Factors with a $P < .05$ on univariate analysis were incorporated into multivariate Cox proportional regression model. For the analysis, we considered both gamma knife and conventional radiotherapy equally. Statistical analysis was performed using IBM SPSS STATISTICS 22.0 (New York).

Table 1

Patients characteristics.

Characteristic	Value	Percentage (%)
Sex (female)	22	52.4
Age, y		
Mean age	50.2, Range (20–80)	
Age <50	19	45.2
Presenting symptom		
Headache	19	45.2
Visual disorders	6	14.3
Motor impairment	6	14.3
Epilepsy	8	19
others	3	7.1
History of prior surgery	13	30.9
History of previous radiotherapy	8	19
Extent of resection		
Simpson grade I	12	28.6
Tumor size, cm		
Mean tumor size	5.8, Range (3–11)	
Tumor size <6 cm	22	52.4
Tumor location		
Convexity	15	35.7
Parasagittal/parasinus	13	30.9
Skull-base	12	28.6
Interventricular	2	4.8
Bone involvement	16	38.1
Adjuvant radiotherapy	21	50
Mean Ki-67 (%)	19.9, Range (5–85)	
Ki-67 <20	21	50
Patients newly diagnosed	28	66.7

3. Results

3.1. Patients and tumor characteristics

A total of 42 patients diagnosed with WHO grade III meningioma were included (Table 1). The mean age was 50.2 years, (range 20–80 years). Fifty-two percent of the patients were female. The most common presenting symptom was headache, which occurred in 19 patients (45.2%), followed by epilepsy. Thirteen patients had a history of previous surgery, and 2 of them diagnosed as atypical meningioma progressed in WHO grade III meningioma during tumor recurrence. Previous radiotherapy (gamma knife and conventional radiotherapy) was employed in 8 patients, radiotherapy was performed in 7 patients as adjuvant treatment after resection for meningiomas, and only 1 patient selected radiotherapy as the primary treatment for meningioma. The most common location was convexity. Twelve patients (28.6%) achieved Simpson grade I resection (complete resection). Twenty-one patients received adjuvant radiotherapy after surgical resection. The mean Ki-67 index was 19.9% (range 5%–85%).

At the end of analysis, 30 patients were found with tumor recurrence with a mean follow-up time of 23.2 months (Table 2). The 1-year, 3-year, and 5-year RFS were 51.6%, 33.9%, and 12.0%, respectively (Fig. 1A). The mean time to recurrence was 13.9 months (range 1–51 months). Of these recurrent cases, 13 patients were found with a history of previous surgery, and 7 patients had a history of previous radiotherapy, adjuvant radiotherapy was performed in 15 patients. Twelve patients with tumor recurrence selected a redo surgery, and adjuvant radiotherapy was employed in 7 of them. Temozolomide was selected as a salvage treatment in 1 patient after tumor recurrence.

Characteristics	Value
No. of recurrent patients	30
Mean following-up, mo	23.2, range (2–75)
With history of previous surgery	13
With history of radiotherapy	7
Complete resection	2
Adjuvant radiotherapy	15
Mean time to recurrence, mo	13.9, range (1–51)
Salvage treatment	
Repeat resection only	5
Radiotherapy only	2
Repeat resection + adjuvant radiotherapy	7
Chemotherapy	1
Survival	5

At the last follow-up, 23 patients were deceased, and all of them died of primary disease. The 1-year, 3-year, and 5-year OS were 66.2%, 39.7%, and 35.8%, respectively (Fig. 1B).

Twenty-eight patients who were newly diagnosed with WHO grade III meningiomas were included in this study. Seventeen patients were found with tumor recurrence, and 12 patients died of tumor progression. The 1-year, 3-year, and 5-year RFS were 63.5%, 44.3%, and 19.4%, respectively (Fig. 1C). The 1-year, 3-year, and 5-year OS were 74.6%, 52.5%, and 46.7%, respectively (Fig. 1D).

3.2. Factors associated with tumor recurrence for all patients

On univariate analysis, several prognostic factors were found. RFS was significantly superior in patients without history of

previous surgery (Fig. 2A, $P = .002$). Compared with incomplete resection, patients with complete resection showed a significant better RFS (Fig. 2B, $P < .001$). A tumor size < 6 cm was also related to a low recurrence rate (Fig. 2C, $P = .015$). Patients with a tumor located in convexity region had a lower recurrence rate than those with a tumor located in other regions (Fig. 2D, $P = 0.021$). Whereas, Ki-67 did not have an impact on RFS. Other variables including sex, age, history of previous radiotherapy, adjuvant radiotherapy, and bone involvement had no impact on RFS. We hypothesized that Ki-67 index associated with recurrence, and warranted subsequent multivariate Cox regression analysis. According to further multivariate COX regression analysis, extent of resection was the only factor associated with tumor recurrence (Table 3, $P = .008$).

3.3. Factors associated with OS for all patients

On univariate analysis, several prognostic factors were also found. A history of previous surgery was associated with worse OS (Fig. 3A, $P = .003$). Patients with tumors completely resected showed a superior OS than patients with incompletely resected (Fig. 3B, $P = .005$). A higher Ki-67 index was associated with worse OS (Fig. 3C, $P = .031$). On multivariate analysis, complete resection was also the only beneficial factor for OS (Table 3, $P = .026$).

3.4. Factors associated with tumor recurrence and OS for newly diagnosed patients

In total, 28 newly diagnosed patients were included in this study (Table 4). On univariate analysis, extent of resection (Fig. 4A, $P = .001$), tumor size (Fig. 4B, $P = .046$), and tumor location (Fig. 4C, $P = .005$) have impact on RFS, complete resection

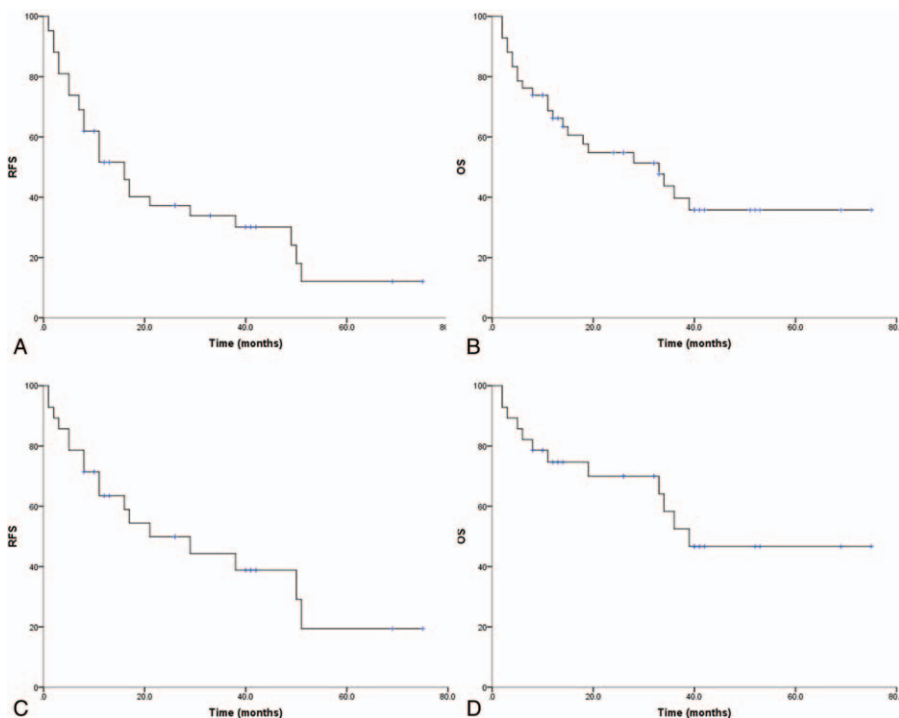


Figure 1. Survival curves. (A) Recurrence-free survival for all patients. (B) Overall survival for all patients. (C) Recurrence-free survival for newly diagnosed patients. (D) Overall survival for newly diagnosed patients.

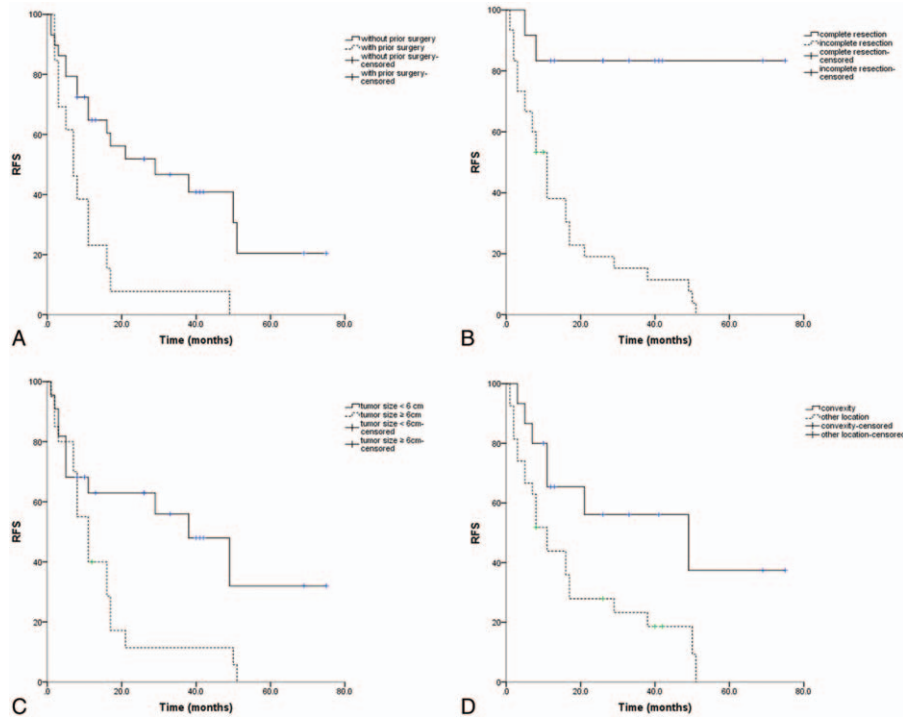


Figure 2. Recurrence-free survival curves for all patients. (A) Recurrence-free survival by history of prior surgery. (B) Recurrence-free survival by extent of resection. (C) Recurrence-free survival by tumor size. (D) Recurrence-free survival by tumor location.

predicted superior rate of OS in univariate analysis (Fig. 4D, $P = 0.044$), and patients with higher Ki-67 index did not demonstrate a worse RFS or OS. It suggested an association between Ki-67 index and RFS, OS that did not reach significance but did warrant subsequent multivariate Cox regression analysis. Further multivariate analysis revealed that extent of resection was associated with longer RFS (Table 4, $P = .048$) and better OS (Table 4, $P = .031$).

4. Discussion

WHO grade III meningioma is a rare subtype of meningiomas with poor prognosis. Management of WHO grade III meningiomas is challenging for clinicians because of high recurrence rate and low survival rate. Owing to the rarity of WHO grade III meningiomas, only sparse studies regarding on WHO grade III

meningiomas were carried out, and risk factors related to tumor recurrence and OS were poorly understood. In our study, we analyzed 42 patients diagnosed with WHO grade III meningiomas, elucidated the outcome and prognostic factors for tumor recurrence and OS of these patients. In our series, 22 patients were female; small size of this series may result in female preponderance. The mean age of the 42 patients was close to the mean age of patients with WHO grade I and II meningioma (50.2 vs. 52.2 years). Headache was the most common presenting symptom. Thirteen patients had a history of surgery, and 2 of them had a history of surgery for WHO grade II meningioma. Complete resection was achieved in 12 patients (28.6%). Twenty-one patients received adjuvant radiotherapy. At last following-up, 30 patients were found with tumor recurrence, and 23 patients died. The 1-year, 3-year, and 5-year RFS were 51.6%, 33.9%, and 12.0%, respectively. The 1-year, 3-year, and 5-year

Table 3
Prognostic factors of RFS and OS for all patients.

Variable	RFS		OS	
	Univariate	Multivariate	Univariate	Multivariate
Sex	0.251		0.120	
Age (<50 vs. ≥50), y	0.819		0.847	
History of previous surgery	0.002	0.484	0.003	0.542
History of previous radiotherapy	0.511		0.456	
Extent of resection	<0.001	0.008	0.005	0.026
Tumor size (<6 vs. ≥6)	0.015	0.272	0.102	
Tumor location (convexity vs. other location)	0.021	0.212	0.181	
Bone involvement	0.405		0.593	
Adjuvant radiotherapy	0.342		0.592	
Ki-67 (<20 vs. ≥20)	0.225	0.080	0.031	0.072

OS=overall survival, RFS=recurrence-free survival.

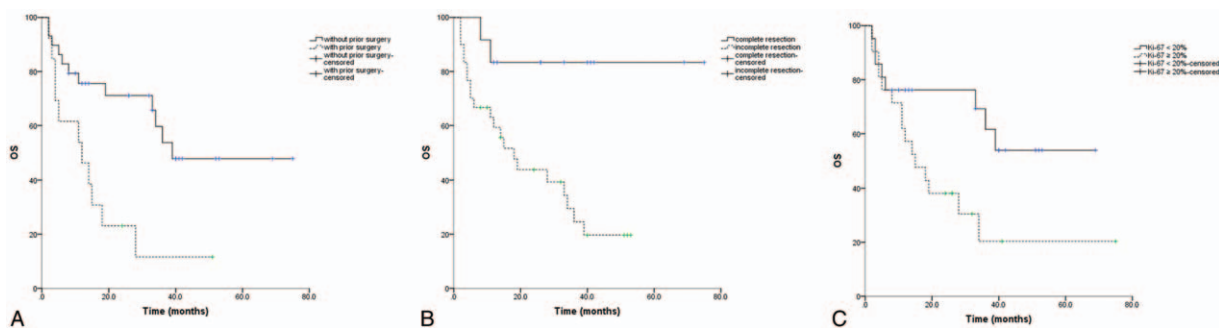


Figure 3. Overall survival curves for all patients. (A) Overall survival by history of prior history. (B) Overall survival by extent of resection. (C) Overall survival by Ki-67 index.

OS were 66.2%, 39.7%, 35.8%, respectively. Extent of resection was identified as independent prognostic factor associated with tumor recurrence and OS; Ki-67 index failed to predict tumor recurrence and OS. In total, 28 newly diagnosed patients were included, the 1-year, 3-year, and 5-year RFS were 63.5%, 44.3%, and 19.4%, respectively, and the 1-year, 3-year, and 5-year OS were 74.6%, 52.5%, and 46.7%, respectively. We analyzed the newly diagnosed patients separately, and extent of resection was the only prognostic factor related to RFS and OS.

4.1. Surgery

Since the seminal publication of Simpson in 1957, there is a general agreement about the importance of resection completeness for meningiomas, since the residual meningiomas may continue to grow.^[19] Complete resection surgery was an ideal choice for patients with WHO grade III meningiomas. Compared with benign cases, a Simpson grade I resection was much more difficult to achieve, especially venous sinus wall or skull-base was involved. In our study, only 9 patients (26.5%) achieved a Simpson grade I resection. The extent of resection is the most powerful prognostic factor for recurrence for all grades of meningiomas. Our study showed patients with tumor resected completely had a superior outcome than those with incomplete resection, which was in accordance with some studies.^[4,6,7,20] Choi et al^[20] reported a cohort with 37 patients diagnosed with WHO grade III meningiomas, and extent of surgical resection was identified as prognostic for local control and OS, but the patients were analyzed together with WHO grade II patients. Sughrue et al found that, compared with patients received gross-total resection, patients treated with near-total resection at initial or repeat surgery had extended OS.

Meanwhile, the author also noticed the risks of aggressive gross-total resection.^[7] Champeaux et al^[4] presented a series of 62 patients, and highlighted that complete or subtotal resection improved OS.

4.2. Radiotherapy

Radiotherapy was a choice for management of patients with WHO grade III meningioma. Owing to the high recurrence rate and poor outcome of WHO grade III meningiomas, it appears that the majority of neurosurgeons would refer patients with partially resected WHO grade III meningiomas to radiotherapy.^[10,21] In our study, 21 patients received adjuvant radiotherapy after surgical resection, but we could not confirm the efficiency of radiotherapy, which was consistent with Champeaux et al.^[4] On the contrary, several studies addressed the usefulness of radiotherapy in the management of WHO grade III meningiomas. Balasubramanian et al reported that radiotherapy was associated with increased OS, and Zhao et al reported that radiotherapy was associated with increased PFS and OS in WHO grade III meningiomas.^[5,6]

4.3. Ki-67

The Ki-67 index is a useful predictor of risk of tumor recurrence.^[22] Perry et al summarized different studies of mean Ki-67 and reported a range of 11% to 16.3% in WHO grade III meningiomas, and Ki-67 beyond 4% indicated an increased recurrence rate.^[23] In our study, the mean Ki-67 index was 19.9% (range 5%–85%). Bruna et al identified Ki-67 as the prognostic factor related to tumor recurrence and OS.^[24] In our series, we failed to identify Ki-67 as the independent factor

Table 4
Prognostic factors of RFS and OS for newly diagnosed patients.

Variable	RFS		OS	
	Univariate	Multivariate	Univariate	Multivariate
Sex	0.453		0.257	
Age (<50 vs. ≥50)	0.953		0.590	
Extent of resection	0.001	0.048	0.044	0.031
Tumor size (<6 vs. ≥6)	0.046	0.638	0.327	
Tumor location (convexity vs. other location)	0.005	0.187	0.067	
Bone involvement	0.838		0.499	
Adjuvant radiotherapy	0.472		0.650	
Ki-67 (<20 vs. ≥20)	0.949	0.177	0.521	0.149

OS=overall survival, RFS=recurrence-free survival.

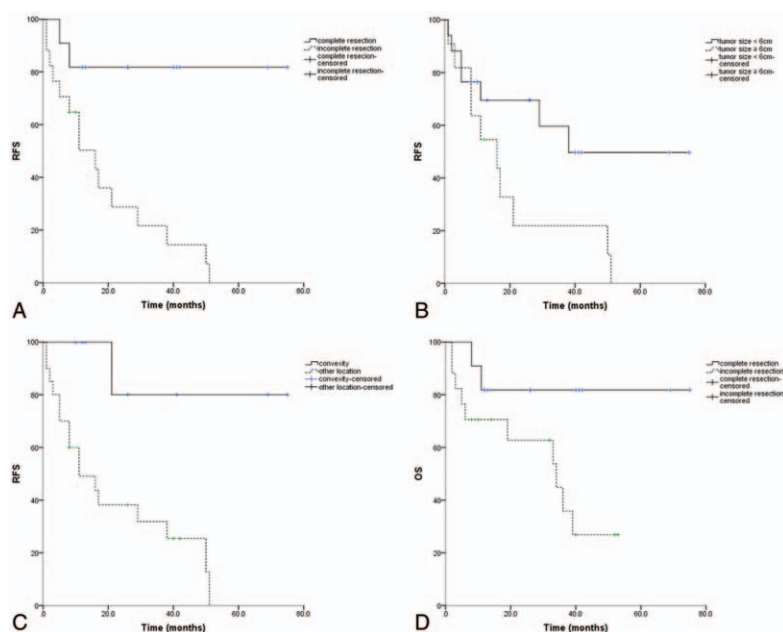


Figure 4. Survival curves for newly diagnosed patients. (A) Recurrence-free survival by extent of resection. (B) Recurrence-free survival by tumor size. (C) Recurrence-free survival by tumor location. (D) Overall survival by extent of resection.

associated with tumor recurrence and OS either for all patients or newly diagnosed patients.

4.4. Limitations

This is one of the largest retrospective study to evaluate the outcome and prognostic factors associated with tumor recurrence and OS of patients with WHO grade III meningiomas to the best of our knowledge. However, this study had several limitations. One weakness is this study's retrospective nature. Moreover, the decision to employ radiotherapy for patients was not randomized, and for the analysis, we considered both gamma knife and conventional radiotherapy equally, thus biases were introduced, objectively. As the rarity of WHO grade III meningiomas, small size of the sample was also a weakness of this study. Larger retrospective, prospective, randomized, or multicenter clinical trials are needed to evaluate the prognostic factors in the patients with WHO grade III meningiomas.

5. Conclusions

In conclusion, WHO grade III meningioma is rare, and difficult to manage with a high rate of recurrence and poor overall survival. Extent of resection is an independent prognostic factor related to tumor recurrence and OS. We could not confirm the usefulness of Ki-67. We suggest that more aggressive treatment, such as safety maximizing cytoreduction by surgery, would improve treatment outcomes.

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