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Technical Notes & Surgical Techniques

Predictors of recurrence and postoperative outcomes in patients with non-skull base meningiomas based on modern neurosurgical standards

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ABSTRACT

Background: Advances in neurosurgical techniques and neuroimaging resolution questions the modern-day reliability of the Simpson grade for predicting meningioma recurrence. Therefore, we evaluated the reliability of predictors for recurrence and outcomes in detail in patients with non-skull base meningiomas (NSBMs).
Methods: We retrospectively analyzed data from consecutive 175 NSBMs underwent surgical resection. We performed Kaplan–Meier analyses of recurrence-free survival (RFS) according to Simpson and World Health Organization (WHO) grades. Predictors of RFS and clinical deterioration were estimated by univariate and multivariate analyses. Correlation between the Simpson grade and change in Karnofsky Performance Scale scores was assessed by Fisher's exact test.
Results: Log-rank tests revealed significant correlations of both the Simpson and WHO grades with RFS for the overall cohort, convexity, and falx/tentorium meningioma. Unlike patients undergoing Simpson grade I and II resections, RFS in patients with WHO grade I and II/III tumors differed significantly from the early postoperative stage. Multivariate analysis identified tumor size, Simpson grade, and MIB-1 labeling index as significant predictors of RFS. Clinical deterioration was more frequent among patients undergoing less aggressive resection. Tumor location was the only significant predictor of clinical deterioration.
Conclusions: Our findings indicate that tumor size, Simpson and WHO grades, and MIB-1 labeling index are significant predictors of NSBM recurrence. Moreover, the risk of recurrence markedly decreases within the follow-up duration of 80 months. Aggressive resection appears to minimize the risk of recurrence without evidence of clinical deterioration. Follow-up schedules should be based on the WHO grade and extent of resection.

1. Introduction

Meningioma is the most common type of benign brain tumor, accounting for approximately one-third of all primary intracranial tumors [1,2]. Seventy to 80% of meningiomas are classified as World Health Organization (WHO) grade I and exhibit a clinically benign behavior [1]. While grade I meningiomas grow slowly and are associated with low recurrence rates following complete resection, occasional recurrence or regrowth is observed in patients with WHO grade II/III or incompletely resected tumors [3–10]. In contrast to skull base meningiomas (SBMs), such as those affecting the petroclival or cavernous sinus region, most non-skull base meningiomas (NSBMs) are completely resected and thus are associated with low postoperative recurrence rates [7,10–12]. Previous studies have reported that WHO grades and MIB-1 labeling index (MIB-1 LI) values are higher for NSBMs than for SBMs [5,7,13–16]. Thus, treatment strategies differ for NSBMs and

SBMs according to differences in the mechanisms underlying tumorigenesis, tumor progression, and effective surgical management [5,7,13,15,16].

In 1957, Simpson reported an association between recurrence rates and the extent of resection in patients with meningioma [10]. While the most aggressive form of resection (Simpson grade I resection, in which the entire tumor is resected along with the attached dura and underlying bone) minimizes the risk of meningioma recurrence, subtotal or less aggressive resection has been associated with higher recurrence rates. Because the Simpson grading system exhibits a stepwise correlation with recurrence rates, neurosurgeons are required to aim for improvements in the Simpson grade during meningioma resection [10].

Several previous studies have reported associations between meningioma recurrence and various factors, including the extent of resection, patient age and sex, tumor location and size, neuroimaging findings, WHO grade, MIB-1 LI values, and genetic and biochemical characteristics [4,6,11,15,17–29]. However, Simpson and WHO grades have been recognized as the most accurate predictors of meningioma recurrence.

After the establishment of the Simpson grading system, remarkable advances in microsurgical and intraoperative support techniques, such as neuronavigation and neuromonitoring, have maximized the extent of resection and minimized the rates of neurological complications. It is noteworthy that, in Simpson's original study, "recurrence" was defined based on clinical events, as radiographic follow-up had not yet been standardized [10]. Because modern magnetic resonance imaging (MRI) enables the detection of even small recurrences before they become symptomatic, meningioma recurrence is now detected significantly earlier than during Simpson's era. Accordingly, the significance of the Simpson grade in modern neurosurgery remains controversial. Indeed, one recent study reported that resections that left a small residual tumor attached to vital intracranial structures did not significantly increase the rate of meningioma recurrence relative to that observed for complete resection [30].

In the present study, we aimed to reevaluate the significance of the Simpson grading system in modern neurosurgery by analyzing data from a series of patients with NSBMs. Moreover, we investigated the predictors responsive to postoperative recurrence and the outcomes of NSBM.

2. Methods

2.1. Patient population

We retrospectively reviewed case data from consecutive patients with meningioma whose initial treatment involved surgical resection at Kyushu University Hospital (Fukuoka, Japan) between January 2004 and December 2016, or at the National Hospital Organization Kyushu Medical Center (Fukuoka, Japan) between April 2008 and December 2016. Clinical data, including age, sex, tumor size and location, pathological characteristics, MIB-1 LI value, time to recurrence following surgery, preoperative and postoperative Karnofsky Performance Status (KPS) scores, and neuroimaging findings at the final follow-up were collected from the medical records, operative records, pathological reports, and neuroimaging records for each patient. When patients had undergone multiple surgeries, only data from the first surgery were selected. Patients without follow-up data, those with neurofibromatosis type 2, and those who had undergone preoperative radiation therapy were excluded. Due to the small number of patients (n = 13) with meningioma arising from the ventricles, these individuals were also excluded from analysis. All 13 patients had undergone Simpson grade I resection and had been pathologically diagnosed with WHO grade I meningioma. NSBMs were classified into 3 groups based on tumor location: convexity, parasagittal, and falx/tentorium.

2.2. Extent of resection

For each surgery, the extent of resection was scored according to the modified Simpson grading system, which was established by Alvernia et al. for evaluating surgical aggressiveness in modern microscopic neurosurgery [3]. In accordance with this system, we defined modified Simpson grade IIIa as near complete resection leaving a very small layer of tumor tissue at the cortex due to invasion of the pia mater, and grade IIIb as near complete resection leaving a small piece of tumor beneath the cortical vessels around the eloquent area. In the present study, modified Simpson grade IIIa and IIIb were grouped into a single Simpson grade III category. Briefly, Simpson grades were defined as follows: grade I, complete resection of the meningioma with excision of its dural attachment and abnormal bone; grade II, complete resection of the meningioma with coagulation of its dural attachment; grade III, complete resection of the meningioma alone, leaving a very small residual tumor attached to the cerebral cortex or blood vessels, or complete resection of the parasagittal meningioma with the exception of tumor components extending to the superior sagittal sinus. Partial meningioma resection was defined as Simpson grade IV. We cross-checked the Simpson grade of resections using operative records and postoperative contrast-enhanced MRI for all patients.

2.3. Pathological diagnosis

Pathological diagnosis and MIB-1 LI values for all patients were determined by experienced neuropathologists in accordance with the WHO 2016 guidelines [1]. Based on these guidelines, those previously diagnosed as "grade I meningiomas with brain invasion" were classified as WHO grade II. The percentage of MIB-1-positive cells was determined by examining them in high-power fields. For cases in which the distribution of the labeled cells was heterogeneous, the area with the highest density of MIB-1-stained nuclei was selected for examination.

2.4. Recurrence and regrowth

We defined "recurrence" as the development of a novel enhanced mass following complete resection of the meningioma, or as regrowth of the residual tumor on follow-up MRI, regardless of clinical symptoms.

2.5. Perioperative management

All patients underwent preoperative evaluation of their meningiomas via computed tomography (CT) and contrast-enhanced MRI. Tumor size was evaluated based on the maximum tumor diameter measured on enhanced T1-weighted images. Preoperative embolization was performed to reduce intraoperative blood loss for larger tumors when intravascular occlusion of the supplying vessels was achievable. Although the intervals and duration of follow-up were selected at the discretion of each physician, follow-up MRIs were obtained for all patients no less than once per year. Considering that patients with massive residual tumors have higher risk of symptomatic tumor regrowth or that patients with WHO grade II/III tumors have higher rate of cell proliferation, these patients underwent more intensive follow-up than patients who underwent complete resection or with WHO grade I meningiomas.

2.6. Postoperative outcome

Preoperative and postoperative clinical status was evaluated based on the KPS score. Postoperative KPS was defined as the score at discharge from the hospital. To evaluate the effect of surgical intervention on the KPS score, we calculated the change in KPS score (ΔKPS) by subtracting the preoperative KPS score from the postoperative KPS

score. Hence, positive and negative ΔKPS values indicated the extent of clinical improvement or deterioration following surgery, respectively.

2.7. Statistical analysis

Kaplan–Meier analysis was used to evaluate recurrence-free survival (RFS), and a log-rank test was used to compare the survival distributions. Univariate and multivariate Cox proportional hazards regression models were used to evaluate putative prognostic factors. Chi-squared tests were used to compare data among the groups. Fisher's exact tests were used to investigate the relationship between ΔKPS and the Simpson grade, while Wilcoxon 2-sample tests were used to examine differences in median MIB-1 LI values based on the WHO grade. The level of statistical significance was set at $p < 0.05$. JMP Pro version 12 (SAS Institute Inc., NC, USA) was used for all statistical analyses. These analyses were performed under the supervision of a statistical specialist.

2.8. Ethics

The Institutional Review Boards of the participating institutions (29-321, 17C292) approved this study and waived the requirement for informed consent due to its retrospective nature.

3. Results

We evaluated data from 458 consecutive meningiomas in 447 patients treated at either of the 2 participating institutions. A total of 175 NSBMs (165 patients) were eligible for evaluation based on the criteria of the present study.

3.1. Characteristics of non-skull base meningiomas

The characteristics of the 175 NSBMs evaluated in the present study are summarized in Table 1. Forty-three (24.5%) of the tumors belonged to men, while the remaining 132 belonged to women. The median patient age at the time of surgery was 61 years (range: 20–88 years). Convexity, parasagittal, and falx/tentorium meningiomas were observed in 76 patients (78 tumors), 45 patients (45 tumors), and 49 patients (52 tumors), respectively. Simpson grades I, II, III, and IV resections were performed in 81 (46.3%), 39 (22.3%), 37 (21.1%), and 18 (10.3%) cases, respectively. While Simpson grade I resections were

performed for a large percentage of convexity meningiomas (73.0%), only 3 patients (6.7%) with parasagittal meningiomas underwent grade I resection. Histopathological diagnoses were WHO grades I, II, and III meningioma in 145 (82.8%), 29 (16.5%), and 1 (0.6%) cases, respectively. The prevalence of WHO grade II meningioma was similar for all 3 locations. The prevalence of WHO grade II/III meningioma was significantly higher among men than among women (27.9% vs. 13.6%, $p = 0.0306$). The median follow-up period or time to recurrence was 42 months (range: 1–151 months).

Preoperative embolization was performed in 10 patients, 3 of whom experienced recurrence. Only 3 patients with falx/tentorium meningioma underwent immediate adjuvant radiation therapy following resection. Although all 3 of these patients had undergone Simpson grade IV resection as well as radiation therapy targeting the residual tumor immediately following resection, 2 of them experienced recurrence.

3.2. RFS according to Simpson and WHO grades

RFS rates were analyzed according to the Simpson and WHO grades using the Kaplan–Meier method. A significant stepwise reduction in the RFS rate was observed along with an increase in the Simpson grade in tests of all patients ($p < 0.0001$, log-rank test), and in test assessing just those with convexity ($p < 0.0001$), parasagittal ($p < 0.0001$), or falx/tentorium meningiomas ($p = 0.0003$), indicating the universal usefulness of this grading system for NSBMs, regardless of their site of origin (Fig. 1). In addition, a significant stepwise reduction in the RFS rate was observed along with an increase in WHO grade in all patients ($p < 0.0001$, log-rank test), and just in those with convexity ($p = 0.0016$) or falx/tentorium meningiomas ($p < 0.0001$; Fig. 2). However, no significant differences were observed in patients with parasagittal meningiomas ($p = 0.5172$; Fig. 2).

3.3. Meningioma recurrence

Among all NSBMs, recurrence was observed in 33 (18.8%) cases (Table 2). The overall recurrence rate was significantly lower for WHO grade I meningiomas than for WHO grade II/III meningiomas (13.7% vs. 43.3%, $p = 0.0005$). A stepwise decrease in the recurrence rate and an advancement in the Simpson grade was observed for WHO grade I and II/III meningiomas. In particular, no recurrence was detected in patients undergoing Simpson grade I resection of WHO grade I NSBMs

Table 1
Characteristics of 175 primary non-skull base meningiomas in patients who underwent surgical resection.

|	All non-skull base meningiomas	Convexity meningioma	Parasagittal meningioma	Falx/Tentorium meningioma
No. of meningiomas	175	78	45	52
Recurrent	33 (18.8%)	7 (8.9%)	17 (37.7%)	9 (17.3%)
Non-recurrent	142	71	28	43
Age at surgery (y)				
Median	61 [IQR: 53, 70]	61 [52, 69]	60 [53, 69.5]	62 [54, 71]
Range	20–88	20–88	30–83	37–88
Sex				
Male	43 (24.5%)	20 (25.6%)	12 (26.7%)	11 (21.1%)
Female	132	58	33	41
Tumor size (mm)				
Median	37 [IQR: 27, 50]	38.5 [26, 53.5]	41 [30.5, 54]	34 [26, 46]
Range	11–90	11–80	21–90	12–68
Simpson grade				
I	81 (46.3%)	57 (73.0%)	3 (6.7%)	21 (40.4%)
II	39 (22.3%)	12 (15.4%)	14 (31.1%)	13 (25.0%)
III	37 (21.1%)	8 (10.2%)	21 (46.7%)	8 (15.4%)
IV	18 (10.3%)	1 (1.3%)	7 (15.5%)	10 (19.2%)
WHO grade				
I	145 (82.8%)	65 (83.3%)	37 (82.2%)	43 (82.7%)
II	29 (16.5%)	13 (16.6%)	8 (17.7%)	8 (15.3%)
III	1 (0.6%)	0	0	1 (1.9%)
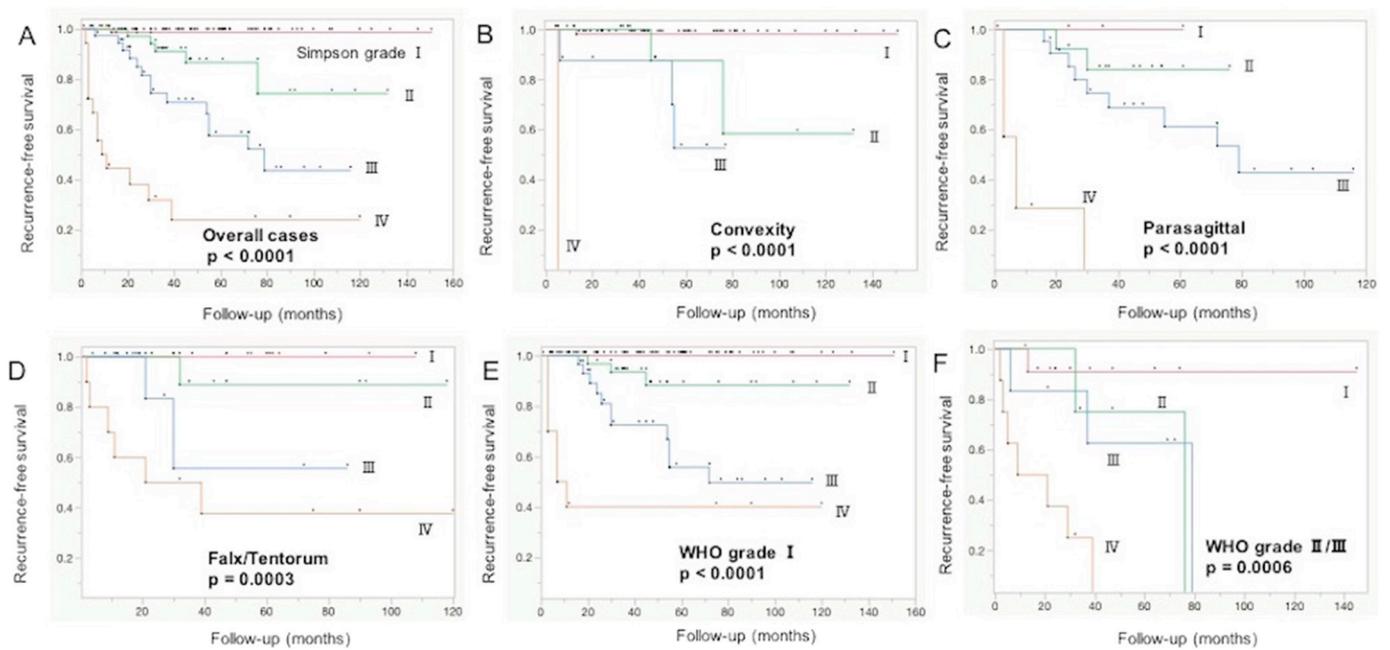
Fig. 1. Results of Kaplan–Meier analyses of recurrence-free survival according to the Simpson grade. A: Recurrence-free survival (RFS) for all patients with non-skull base meningiomas undergoing Simpson grade I-IV resection (p < 0.0001, log-rank test). B: RFS for patients with convexity meningiomas undergoing Simpson grade I-IV resection (p < 0.0001, log-rank test). C: RFS for patients with parasagittal meningiomas undergoing Simpson grade I-IV resection (p < 0.0001, log-rank test). D: RFS for patients with falx/tentorium meningiomas undergoing Simpson grade I-IV resection (p = 0.0003, log-rank test). E: RFS for patients with World Health Organization (WHO) grade I meningiomas undergoing Simpson grade I-IV resection (p < 0.0001, log-rank test). F: RFS for patients with WHO grade II/III meningiomas undergoing Simpson grade I-IV resection (p = 0.0006, log-rank test). The level of statistical significance was set at p < 0.05. The figure is only available in color online.
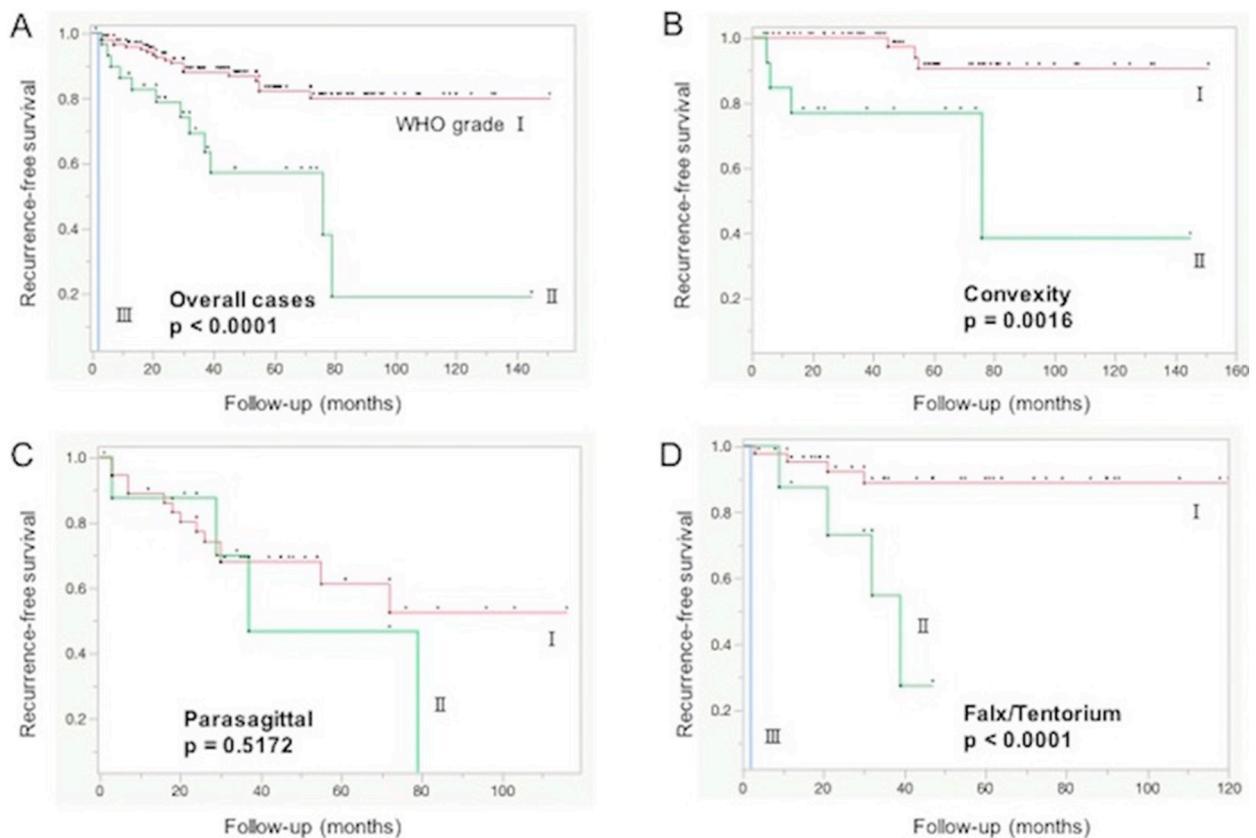

Fig. 2. Result of Kaplan–Meier analyses of recurrence-free survival according to the World Health Organization grade. A: Recurrence-free survival (RFS) for all patients with non-skull base meningiomas (p < 0.0001, log-rank test). B: RFS for patients with convexity meningiomas (p = 0.0016, log-rank test). C: RFS for patients with parasagittal meningiomas (p = 0.5172, log-rank test). D: RFS for patients with falx/tentorium meningiomas (p < 0.0001, log-rank test). The level of statistical significance was set at p < 0.05. The figure is only available in color online.

Table 2

Recurrence rates according to the Simpson grade and World Health Organization grade.

	Total	Simpson I	Simpson II	Simpson III	Simpson IV
WHO I	20/145 (13.7%)	0/70 (0%)	3/34 (8.8%)	11/31 (35.4%)	6/10 (60.0%)
WHO II/III	13/30 (43.3%)	1/11 (9.0%)	2/5 (40.0%)	3/6 (50.0%)	7/8 (87.5%)
Total	33/175 (18.8%)	1/81 (1.2%)	5/39 (12.8%)	14/37 (37.8%)	13/18 (72.2%)

(0/70 cases). Kaplan–Meier analyses validated these findings, as independent analyses revealed that a significant stepwise reduction in the RFS rate and an increase in the Simpson grade occurred in WHO grade I and II/III meningiomas (Fig. 1E, F).

3.4. Timing of recurrence

We examined the RFS curves to verify the timing of recurrence detection. All recurrences of meningioma in our cohort were detected within 80 months of follow-up, regardless of the Simpson and WHO grades (Figs. 1A, 2A). Recurrence was detected within 40 months for all falx/tentorium meningiomas, and in all cases of Simpson grade IV resection (Fig. 1A, D). Notably, differences in the rate of recurrence could be detected between the Simpson grades I and II resections starting at approximately the 24-month follow-up (Fig. 1A). Such timing stands in remarkable contrast to that observed between WHO grades I and II/III meningiomas, in which differences in recurrence became apparent shortly after surgery in all NSBMs (Fig. 2A).

3.5. Predictive factors for recurrence

We further aimed to identify the independent predictors of RFS following the resection of NSBMs. Univariate analyses of data from all cases suggested that patient age, tumor size, location (convexity vs. parasagittal), Simpson grade, WHO grade (I vs. II/III), and MIB-1 LI were significantly associated with RFS (Table 3). Among these factors, tumor size and Simpson grade significantly influenced RFS, regardless of the site of origin. The WHO grade was identified as a significant predictive factor of RFS for convexity and falx/tentorium meningiomas, but not for parasagittal meningiomas. In contrast, MIB-1 LI was identified as a significant predictor of recurrence for falx/tentorium meningiomas only.

Multivariate Cox regression analysis revealed that tumor size, Simpson grade, and MIB-1 LI were significant predictors of RFS among all cases of NSBM (Table 4). Although the prevalence of WHO grade II/III meningioma was significantly higher among men than among

Table 4

Multivariate Cox regression analysis of the prognostic factors of recurrence-free survival (RFS) in the whole cohort of patients with non-skull base meningiomas.

	Non-skull base meningiomas (total)		
	HR	95% CI	p value
Age (years)	0.98	0.95–1.02	0.5541
Sex, male vs. female	0.87	0.38–1.89	0.7439
Size (mm)	1.06	1.03–1.09	**< 0.0001**
Simpson grade II vs. I	10.4	1.65–200.7	**0.0106**
Simpson grade III vs. I	29.3	5.88–531.2	**< 0.0001**
Simpson grade III vs. II	2.81	1.05–8.83	**0.0384**
MIB-1 LI (%)	1.06	1.00–1.12	**0.0464**

Boldface type indicates statistical significance.

Table 5

Association between the Simpson grade and change in Karnofsky Performance Status (ΔKPS = postoperative KPS − preoperative KPS).

	ΔKPS < 0 (deterioration)	ΔKPS = 0 (no change)	ΔKPS > 0 (improvement)
Simpson grade I	8 (9.9%)	54 (66.7%)	19 (23.4%)
Simpson grade II	4 (10.2%)	32 (82.0%)	3 (7.7%)
Simpson grade III	10 (27.0%)	21 (56.7%)	6 (16.2%)
Simpson grade IV	5 (27.8%)	9 (50.0%)	4 (22.2%)
Total	27 (15.4%)	116 (66.3%)	32 (18.3%)

The prevalence of patients who experienced clinical deterioration was greater among patients undergoing less aggressive resection than among those undergoing aggressive resection.

women, sex was not identified as an independent predictor of RFS in the multivariate analysis. Because the WHO grade and MIB-1 LI were significantly associated with one another (p < 0.0001, Wilcoxon 2-sample test), only MIB-1 LI was included in the multivariate analysis.

3.6. Postoperative outcome

To determine the association between surgical aggressiveness and postsurgical clinical improvement, we evaluated changes in patient status following meningioma resection based on ΔKPS. The association between ΔKPS and the Simpson grade is detailed in Table 5. While two-thirds of patients exhibited no change in status following resection, the prevalence of patients whose clinical status had deteriorated was higher in cases of less aggressive resection than in cases of more aggressive resection (approximately 27% vs. 10%). A Fisher's exact test revealed that the difference between ΔKPS and the Simpson grade reached statistical significance (p = 0.0289), indicating that aggressive resection contributes to improvements in clinical status in patients with NSBMs. While univariate analysis indicated that a Simpson grade of III/IV (vs.

Table 3

Univariate Cox regression analysis of prognostic factors for recurrence-free survival.

	All non-skull base meningiomas			Convexity meningioma			Parasagittal meningioma			Falx/Tentorium meningioma		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Age (y)	1.03	1.00–1.07	**0.0258**	1.07	0.99–1.16	0.0732	1.10	0.97–1.06	0.3744	1.04	0.98–1.12	0.1483
Sex, male vs. female	1.39	0.63–2.85	0.3923	2.70	0.53–12.3	0.2117	0.77	0.21–2.21	0.6469	2.06	0.43–7.85	0.3300
Size (mm)	1.06	1.03–1.08	**< 0.0001**	1.09	1.03–1.17	**0.0003**	1.05	1.02–1.08	**0.0016**	1.07	1.03–1.13	**0.0009**
Simpson grade			**< 0.0001**			**0.0004**			**0.0001**			**0.0008**
Simpson grade II vs. I	10.65	1.71–204.2	**0.0093**									
Simpson grade III vs. I	31.70	6.37–574.3	**< 0.0001**									
Simpson grade III vs. II	2.97	1.13–9.23	**0.0260**									
WHO grade II and III vs. I	3.93	1.90–7.85	**0.0004**	7.75	1.70–39.5	**0.0096**	1.44	0.40–4.08	0.5364	7.20	1.89–29.3	**0.0048**
MIB-1 LI (%)	1.09	1.04–1.12	**0.0002**	1.06	0.93–1.15	0.2689	1.08	0.96–1.19	0.1646	1.16	1.06–1.29	**0.0004**
Location, Falx/Tent. vs. Conv.	2.22	0.82–6.24	0.1109									
Location, Parasag. vs. Conv.	4.94	2.12–12.8	**0.0002**									

Boldface type indicates statistical significance.

Table 6
Univariate and multivariate Cox regression analysis of prognostic factors of the deterioration of clinical status in the whole cohort of patients with non-skull base meningiomas.

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age (years)	1.03	0.99–1.07	0.0575	1.02	0.99–1.06	0.1827
Sex, male vs. female	1.36	0.52–3.29	0.5079	1.35	0.49–3.50	0.5525
Size (mm)	1.01	0.98–1.03	0.4649	1.00	0.97–1.03	0.9340
Simpson grade, III and IV vs. I and II	3.38	1.46–7.97	**0.0045**	1.77	0.70–4.54	0.2289
WHO grade, II and III vs. I	2.41	0.90–6.06	0.0779	1.96	0.65–5.67	0.2252
Location, Others. vs. Conv.	5.75	2.09–20.33	**0.0004**	4.83	1.60–18.26	**0.0043**

Boldface type indicates statistical significance.

I/II) and a parasagittal or falx/tentorium location (vs. convexity) were significant predictors of clinical deterioration, multivariate analysis revealed that only the parasagittal or falx/tentorium location (vs. convexity) was significant (Table 6). This result suggested that aggressive resection does not result in clinical deterioration.

4. Discussion

In the present study, we aimed to evaluate the reliability of predictors for the postoperative recurrence and outcomes of NSBMs following surgical resection based on modern neurosurgical standards. Our analyses verified that tumor size, WHO grade, MIB-1 LI, and Simpson grade are significant predictors of NSBM recurrence. Furthermore, our findings suggested that the risk of recurrence following NSBM resection markedly decreases as the duration of follow-up increases, and all recurrences were observed within 80 months after surgery. This study revealed that aggressive resection minimizes the risk of recurrence and does not result in clinical deterioration in patients with NSBMs.

4.1. Significance of the Simpson Grade

The Simpson grade has been recognized as being one of the most reliable predictors of postoperative meningioma recurrence. However, since the establishment of the Simpson grading system, numerous other factors, including male sex, old age, lack of calcification, peritumoral edema, skull base location, high MIB-1 LI, loss of chromosome 1P, and expression of vascular endothelial growth factor have been identified as putative predictors of meningioma recurrence [4,6,11,15,17–29]. Furthermore, in the 60 years since the publication of Simpson's original paper, microscopic neurosurgical techniques and neuroimaging resolution have progressed tremendously, calling into question the reliability of the Simpson grade for the prediction of recurrence [9,30,31]. Sughrue et al. evaluated the significance of the Simpson grading system in modern neurosurgery, and observed only a negligible benefit of aggressive meningioma resection involving removal of the attached dura and underlying bone relative to removal of the tumor alone or resection that left a small portion of the tumor attached to vital structures [31]. As the authors observed very low recurrence rates for patients undergoing Simpson grade III and IV resection, they concluded that the extent of resection does not affect RFS rates significantly for meningioma. However, they argued that the long-term effects of preoperative embolization (e.g., necrotization of tumor tissue) may help prevent recurrence even after Simpson grade IV resection. In contrast, other recent studies involving larger numbers of patients have identified the Simpson grade to be a significant predictor of meningioma recurrence [4,8,32–34]. Nanda et al. evaluated the relevance of the

Simpson grading system and RFS for 458 patients with WHO grade I meningioma [8]. The authors reported a significant correlation between the Simpson grade and RFS when all cases were included, as well as when only patients with convexity meningiomas and SBMs were included. However, the authors were unable to determine the respective significance of the Simpson grade in patients with falx, tentorium, or parasagittal meningiomas due to the low number of patients. In the present study, we observed significant correlations between the Simpson grade and RFS for all patients with NSBMs regardless of the WHO grade. Furthermore, similar significant correlations were observed for each group when the tumors were divided based on location (convexity, parasagittal, and falx/tentorium), demonstrating the reliability of the Simpson grade for NSBMs regardless of the site of origin. In addition, we observed that modified Simpson grade III resection was associated with significantly higher rates of recurrence than Simpson grade I or II resection. These findings indicate that leaving a very small residual tumor attached to the cerebral cortex, blood vessels, or dural tissue may lead to an increase in recurrence rate, supporting the significance of aggressive microsurgical resection in the treatment of NSBMs.

4.2. Suggestion for follow-up schedules

Regardless of the Simpson or WHO grade, all recurrences were detected within 80 months following resection, suggesting that patients who do not develop recurrence within approximately 7–8 years following surgery may be considered "recurrence free." Similarly, Sughrue et al. observed no recurrence after the 8-year follow-up [31]. However, several conflicting reports have been published. Mansouri et al. demonstrated that NSBM recurrence persisted even after 100 months, while the recurrence of SBMs had reached a plateau by this stage [6]. As the appropriate limit of the follow-up period after meningioma surgery remains to be determined, unlimited/indefinite follow-up is perhaps the most acceptable choice for the modern neurosurgeon. Nevertheless, our findings suggest that the risk of recurrence following Simpson grade I resection of WHO grade I NSBMs is very low, indicating that long-term follow-up may not be necessary in such cases.

We observed that the recurrence of NSBMs following Simpson grade II resection could be detected beginning at the 24-month follow-up, and postoperative recurrence was observed earlier for WHO grade II/III tumors than for WHO grade I tumors. A previous retrospective study reported similar results, demonstrating that RFS did not differ between patients who had undergone Simpson grade I and II resection within the first 24 months after surgery [4]. Hence, the impact of a Simpson grade I resection can only be identified at the midterm follow-up and beyond, perhaps because several years are required for remnant meningioma cells in the coagulated dura to grow into a mass that can be detected via MRI following Simpson grade II resection. In contrast, a higher rate of cell proliferation is observed for WHO grade II/III meningiomas, which may explain the discrepancy in the recurrence rates between WHO grades in the early postoperative period. These findings suggest that the requirements for postoperative follow-up schedules should be based on the type of tumor and extent of resection.

4.3. Aggressive resection does not result in deterioration of clinical status

Previous researchers have recommended less aggressive surgery or radiosurgery for the treatment of SBMs, as aggressive resections of such tumors have been associated with postoperative complications such as cranial nerve disturbance and cerebrospinal fluid leakage [31,35,36]. However, such complications are unlikely to occur following NSBM resection. Indeed, our results indicated that clinical deterioration was observed more often in patients who had undergone less aggressive resection than aggressive resection, and aggressive resection was not significantly associated with the deterioration of clinical status in the multivariate analysis in patients with NSBM. Altogether, these findings

suggest that NSBMs should be treated via aggressive resection when recurrence risk and postoperative clinical status are taken into consideration.

4.4. Study strengths and limitations

In the present study, we identified significant predictive factors for recurrence and postoperative outcomes for NSBMs in modern neurosurgery through a detailed evaluation based on the Simpson grade, WHO grade (WHO 2016 classification), MIB-1 LI, and KPS score for all patients with NSBM. Moreover, our investigation is advantageous in that we utilized a consistent definition for recurrence based on MRI findings, rather than CT images or symptom presentation, and complied with modern neurosurgical standards. While previous studies that involved detailed evaluations such as ours are rare, our study possessed some limitations of note.

First, we included only a small number of patients who had undergone adjuvant radiation therapy. McGovern et al. reported that patients with meningioma treated via subtotal resection plus adjuvant radiation therapy exhibited 5-year RFS rates comparable with those observed in patients who had undergone gross-total resection alone [7]. Furthermore, Rogers and Mehta suggested that adjuvant radiation therapy following subtotal resection can improve the local control of meningiomas [37]. In the present study, we could not evaluate the benefit of adjuvant radiation therapy due to the small number of patients (n = 3, 2 of whom developed recurrences) who had undergone such treatment. While postoperative radiation therapy for residual meningioma tissue may decrease the risk of recurrence, complete resection is recommended for patients with NSBMs based on the accumulated evidence regarding the risk of recurrence, postoperative outcomes, radiological complications, and economic costs.

Additional limitations include the sample size differences among the tumor locations, insufficient clinical data related to baseline characteristics, incomplete exclusion of potential selection biases due to the non-randomized study design, and the selection of a limited number of patients treated at only 2 institutions. In addition, we were unable to perform multivariate analyses of RFS based on tumor location due to the small sample size or to evaluate the benefit of preoperative embolization due to the small number of patients who had undergone these treatment. Thus, further studies are required to clarify these issues.

An important limitation of this study is the length of the follow-up periods. The follow-up periods were relatively short mainly because we included patients who dropped out of follow-up. Indeed, some previous studies have followed-up patients for a median of over 5–7 years [3,4,7,9]. Due to the slow-growing nature of meningiomas, much longer follow-up periods may be required to observe recurrences.

5. Conclusions

Our findings indicate that, even based on modern neurosurgical standards, the Simpson grade is significantly associated with RFS following the resection of NSBMs, and aggressive resection for NSBMs minimizes the risk of recurrence and does not result in the deterioration of clinical status. Our results further indicate that postoperative NSBM recurrence primarily occurs within the first 80 months, and the timing of recurrence was different among Simpson and WHO grades, suggesting that the requirements for postoperative follow-up schedules should be based on the type of tumor and extent of resection. Multiple factors, such as the extent of resection, histopathological characteristics, MIB-1 LI value, tumor size, and location, should be considered when evaluating recurrence and outcomes following meningioma surgery.

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