Skull Base Meningiomas: Is Surgical Resection Enough? Outcome Evaluation and Prognostic Factors Analysis in a Single-Center Cohort

Federico Pessina[1,2] Pierina Navarria[3] Zefferino Rossini[2] Elena Clerici[3] Maurizio Fornari[2] Letterio S. Politi[1,4] Marta Scorsetti[1,3] Franco Servadei[1,2]

[1] Department of Biomedical Sciences, Humanitas University, Milan, Italy
[2] Department of Neurosurgery, IRCCS Humanitas Research Hospital, Lombardia, Italy
[3] Department of Radiotherapy and Radiosurgery, IRCCS Humanitas Research Hospital, Lombardia, Italy
[4] Department of Neuroradiology, IRCCS Humanitas Research Hospital, Lombardia, Italy

Address for correspondence Federico Pessina, Department of Neurosurgery, Humanitas University, Via Manzoni 113, 20089 Rozzano, Milan, Italy (e-mail: federico.pessina@hunimed.eu).

J Neurol Surg A Cent Eur Neurosurg 2022;83:516–522.

Abstract

Background Surgical resection represents the mainstay of treatment in skull base meningiomas (SBMs). Considering the high recurrence rate reported, an adjuvant radiation therapy (RT) treatment should be considered. The aim of this study was to evaluate the progression-free survival (PFS), overall survival (OS), and prognostic factors conditioning outcome.

Methods Patients receiving surgical resection for grade I SBMs were included. The extent of resection (EOR) was dichotomized as gross total resection (GTR) and subtotal resection (STR). RT was administered only in patients receiving STR. Clinical outcome was evaluated by brain magnetic resonance imaging (MRI) performed every 6 months for the first year and yearly thereafter.

Results From January 2000 to December 2015, 123 patients were treated. The majority were females (70.7%), with a Karnofsky Performance Score (KPS) $\geq$80 (95%), and symptoms at diagnosis (91%). GTR was performed in 30% of cases and STR in 70%. RT was performed in 18 (20.9%) patients at diagnosis and in 29 (33.7%) patients at progression. Improvement or stability of neurologic status was obtained in 78.9% of patients. The median follow-up time was 91 months (range: 40–230 months). Local recurrence occurred in 34 (27.6%) patients at a median time of 45 months (range: 6–214 months). The median, 2-, 5-, and 10-year PFS were 193 months, 89.3, 81.8, and 72.5%, respectively. On univariate and multivariate analyses, factors impacting on PFS were EOR, tumor location, neurologic postoperative status, and adjuvant RT in STR.

Conclusions A safe surgical resection followed by RT adjuvant treatment could represent the better choice to obtain local control maintaining neurologic integrity. Our data underlined the value of adjuvant RT in incompletely resected meningiomas.

Keywords
- skull base meningiomas
- surgery
- prognostic factors

received
July 1, 2020
accepted after revision
April 23, 2021
published online
December 12, 2021

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0041-1739204.
ISSN 2193-6315.

Introduction

Skull base meningiomas (SBMs) account for around 20 to 30% of all primary meningeal tumors, and among these the greater proportion are benign grade 1 lesions.[1,2]. As recently highlighted by the European Association of Neuro-Oncology (EANO) guidelines for the diagnosis and treatment of meningiomas, surgery represents the first choice of treatment, and it should aim for Simpson grade I resection.[3] The entity of surgical removal, together with histopathologic grade, is recognized as the most crucial factor affecting outcome. Indeed, the 5-year local control rate accounts for 88 to 95% in cases of Simpson grade I and II resection, shrinking to 50% in patients who received Simpson grade III and IV resection.[4–7] The anatomical location of SBMs, and their close relationship with vessels and cranial nerves, often makes it difficult to obtain a satisfactory surgical resection.[8,9] Besides, recent literature data showed how regardless of the Simpson grade reached, the "en plaque" nature of most SBMs and their bony invasiveness lead to a higher recurrence rate compared with non–skull base meningiomas (NSBMs).[10,11] In a large series by Savardekar et al that evaluated the outcome of World Health Organization (WHO) grade I meningioma patients receiving Simpson grade II and III resection, a statistically significant difference in progression-free survival (PFS) in favor of NSBMs compared with SBMs has been reported. These data further point out that the skull base location could influence the recurrence rate. However, any attempts to achieve gross total resection (GTR) should be tempered by the potential neurologic and functional consequences of reaching this goal.[8,9] . When a safe complete tumor resection is not achievable, adjuvant radiation therapy (RT) should be considered. Although its benefit following partial surgical resection has been clearly shown, questions remain concerning the optimal timing of administration, at diagnosis or at disease progression. Unfortunately, the results of retrospective series are mixed, and to date prospective data are lacking.[12–16] Several reports suggest that for patients with SBM**s** located in the cavernous sinus or close to the brain stem, a conservative surgical approach followed by radiosurgery may be a good treatment option, without impairment of a patient's quality of life.[15,17,18] Although, RT is not always a completely safe procedure, and may not be necessary for all patients with residual tumors, Ohba et al showed a significantly worse PFS for patients who underwent subtotal resection (STR) without RT compared with those receiving either GTR alone or STR followed by adjuvant RT. No statistically significant differences in PFS have been observed between groups undergoing GTR alone or STR plus RT, confirming that wherever possible an adjuvant RT treatment has to be considered.[5] Based on this background, we retrospectively reviewed the records of patients with newly diagnosed SBMs treated in our institution with surgery alone or surgery followed by adjuvant RT. The aim of this study was to evaluate the impact of different entities of surgical resection on local control, to analyze the prognostic factors eventually affecting PFS and OS, and to assess the effect of the combined treatments on local recurrence.

Methods

Patients

The present study includes patients with newly diagnosed WHO grade I SBMs, who underwent surgical resection in our institution, from February 2000 to December 2015. Patients with a diagnosis of neurofibromatosis type 2 were excluded. All patients were treated in accordance with the principles of the Helsinki Declaration. This study was based on a retrospective analysis of treatment charts and was approved by the local ethical committee. At the time of admission, all patients gave a signed consent to the use of their data for scientific scope.

Tumor Location

Three different groups were defined in relation to tumor location: anterior cranial fossa (ACF) meningiomas including the olfactory groove and the orbital roof; middle cranial fossa (MCF) including the sphenoidal, anterior clinoid, lateral wall of the cavernous sinus, infratemporal fossa, pure cavernous sinus, and tuberculum sellae; and posterior cranial fossa (PCF) including the jugular foramen, foramen magnum, the petroclival and petrous region.

Imaging

Magnetic resonance imaging (MR) with measurement of the pre- and postoperative tumor volumes was done. The lesion volume was measured by means of volumetric MRI acquired through a 3-T MRI scanner (Siemens, Munich, Germany) before surgery through a semiautomatic region of interest (ROI) analysis with Iplan Cranial v3.0 software (Brainlab, Feldkirchen, Germany). Contrast-enhanced T1 sequences and T2 sequences were used to define the preoperative enhancing tumor volume and the interface between normal brain and enhanced areas, respectively. Extent of resection (EOR) was measured on postoperative MRI performed within 48 hours after surgery; postoperative MRI was coregistered with the preoperative dataset. Postoperative diffusion-weighted imaging (DWI) was also coregistered to rule out postoperative ischemic injury.

Treatments

The EOR was dichotomized as GTR in case of grade I and II resection according to the Simpson criteria, and STR in case of grade III and IV resection. In cases of GTR, no adjuvant RT treatment was employed. In cases of STR, an early adjuvant RT treatment has been performed in selected patients characterized by younger age ($\leq$65 years), and/or good Karnofsky Performance Score (KPS; 90–100). Different RTs were used consisting of conventional RT, stereotactic radiosurgery (SRS), or hypofractionated SRS in relation to the tumor volume and location. In cases of gross residual tumor volume or lesion located in close proximity to a critical healthy structure (optic nerves, chiasma, brainstem), conventional RT with a total dose of 50 to 54 Gy in 25 to 27 daily fractions was preferred to SRS (14 Gy in single fraction) or hypofractionated SRS (25–30 Gy in 5 fractions).

Outcome Evaluation

Clinical outcome was evaluated by neurologic examination on admission and at discharge; MRI was performed every 6 months after treatments for the first year, and annually thereafter. The 30-day postoperative morbidity and mortality were recorded. A major complication was defined as the appearance of new neurologic deficits persisting for more than 30 days after surgery and requiring a prolonged hospitalization or rehabilitation, or as a worsening of preoperative neurologic deficits. All the other complications were defined as minor. Any tumor growth resulting in symptomatic changes was considered a recurrence. In asymptomatic cases, tumor recurrence was defined as $\geq$10% of growth in diameter or volume. Time to recurrence or progression in case of residual tumor after surgery (PFS), and overall survival (OS) were reported. In addition, the characteristics of patients with recurrence were analyzed.

Statistical Analysis

Standard descriptive statistics (mean standard deviation and cross-tabulation analysis) were used to describe the general data behavior. Survival and recurrence time observations were computed according to the method of Kaplan–Meier analysis, starting from the date of surgical treatment. Median PFS and OS were reported with relative 95% confidence interval (CI). The median survival time is obtained from $\hat{S}(t)$, the Kaplan–Meier product limit estimate of the survivor function. Confidence bounds of the survivor function are calculated based on the asymptotic variance of $\ln[-\ln \hat{S}(t)]$, as described in Kalbfleisch and Prentice.[19] The upper (lower) confidence limits for the median survival times are defined as the first time at which the upper (lower) confidence limit for $\hat{S}(t)$ is $\leq$0.5. A not-reached indicator (nr) was specified if the survival estimate resulted above the 50% level in the considered observation time. Upper confidence bound of median survival time was labeled as "ne" if not evaluable with the above method for a specific group of patients in the considered time of observation. The log-rank test was used to carry out the univariate analysis, to investigate the prognostic role of individual variables. Individual variables evaluated were gender, age (median), KPS (70, 80, 90–100), anatomical location (anterior, middle, and posterior cranial fossae), extent of surgical resection (GTR or STR), tumor volume, RT performed early or at progression, and evolution of neurologic symptoms in comparison with meningioma onset. Univariate Cox model was applied for the remaining variables. Multivariate Cox regression model was used as a method to estimate the independent association of our variable set with OS and PFS. The analysis was performed using MedCalc statistical software v 17.7 (MedCalc Software, Ostend, Belgium).

Results

Patients, Treatments, and Outcome

From February 2000 to December 2015, 123 grade I SBM patients who underwent surgical resection were included in this analysis. The majority were females (70.7%), with a KPS $\geq$80 (95%), and symptomatic at diagnosis (91%). GTR was performed in 37 (30.1%) patients, and STR in 86 (69.9%) patients. Adjuvant RT was performed only in case of STR, in 18 (20.9%) patients at diagnosis and in 29 (33.7%) patients at disease progression. Improvement or stability of the neurologic status after surgery was obtained in 97 (78.9%) patients, whereas worsening and/or occurrence of new neurologic deficits was recorded in 26 (21.1%) patients. Medical complications such as pneumonia, deep vein thrombosis, and urinary tract infection occurred in 9.3% of cases. Mortality related to postoperative complications occurred in 2 (1.6%) patients. Details about patients, tumors, and treatment characteristics are given in ►**Table 1**.

Progression-Free Survival and Overall Survival Analysis

The median follow-up time was 91 months (range: 40–230 months) for the whole cohort, and 87 months (range: 40–230 months) for alive patients. Local recurrence or progression occurred in 34 (27.6%) patients at a median time of 45 months (range: 6–214 months). The median PFS time, and the 2-, 5-, and 10-year PFS rates were 193 months (95%CI: 172–199), 89.3 ($\pm$2.8), 81.8 ($\pm$3.6), and 72.5 ($\pm$5.1)%, respectively, as shown in ►**Fig. 1**. At the last follow-up, 120 patients are still alive and 3 died for causes unrelated to the tumor. The median OS time was not reached and the 2-, 5-, and 10-year OS rates were 98.4% (1.1%), 96.6% (1.7%), and 96.6% (1.7%), respectively, as shown in ►**Fig. 2**.

Prognostic Factors Analysis

Gender, age, KPS, and lesion size were not found to be prognostic factors for PFS. On univariate and multivariate analyses, tumor location (ACF/MCF/PCF), EOR (GTR vs. STR), postoperative neurologic status (no symptoms/stable compared with pre-operative status/new), and use of adjuvant RT at diagnosis versus at disease progression were identified as factors significantly impacting PFS. Details about prognostic factor analysis affecting PFS are shown in ►**Table 2**.

Discussion

SBMs account for 20 to 30% of all primary meningeal tumors, and the greater proportion of them are benign grade I lesions.[1,2] With the advances in surgical techniques over the past 30 years, meningiomas have been considered a chronic disease. In this context, it is crucial to consider the risk of recurrence and symptomatic progression when deciding on treatment, especially for SBMs.[10,11,19] To come up with a fair therapeutic strategy, different factors have to be considered. Several retrospective studies highlighted a higher recurrence pattern for SBMs compared with NSBMs, ascribing this to the inability to achieve a Simpson grade I resection. Notwithstanding, this theory has to be reconsidered when we analyze separately SBMs and NSBMs undergoing Simpson grade I or II resection. Indeed, no significant differences in PFS between the two groups have been observed when Simpson grade II resection is achieved, whereas a worse PFS has been recorded in case of Simpson grade I resection for SBMs, suggesting that skull base location could

Table 1 Patients, tumor, and treatment characteristics

Variables	Total no. of patients: 123	%
Gender		
Male	36	29.3
Female	87	70.7
Median age, y (range)	59 (15–89)	
KPS		
60–70	6	4.9
80–90	61	49.6
100	56	45.5
Tumor location		
Anterior cranial fossa (ACF)	26	21.1
Olfactory groove	20	57.8
Orbital roof	6	21.1
Middle cranial fossa (MCF)	71	
Sphenoidal	35	
Anterior clinoidal	15	
Infratemporal fossa	2	
Cavernous sinus	2	
Tuberculum sellae	17	
Posterior cranial fossa (PCF)	26	
Jugular foramen	3	
Foramen magnum	1	
Petroclival	14	
Petrous	8	
Median tumor diameter, mm (range)	39 (12–66	
Symptoms at diagnosis		
Yes	112	91.0
No	11	9.0
Surgery: EOR		
GTR (Simpson I–II)	37	30.1
STR (Simpson III–IV)	86	69.9
Treatments		
Surgery alone	105	85.4
Surgery + adjuvant RT at diagnosis	18	14.6
RT at disease progression	29	23.6
Treatments according with EOR		
Surgery alone GTR	37	30.1
Surgery alone STR	39	31.7
STR + RT at diagnosis	18	14.6
STR + RT at progression	29	23.6

Abbreviations: EOR, extent of resection; GTR, gross total resection; RT, radiation therapy; STR, subtotal resection.

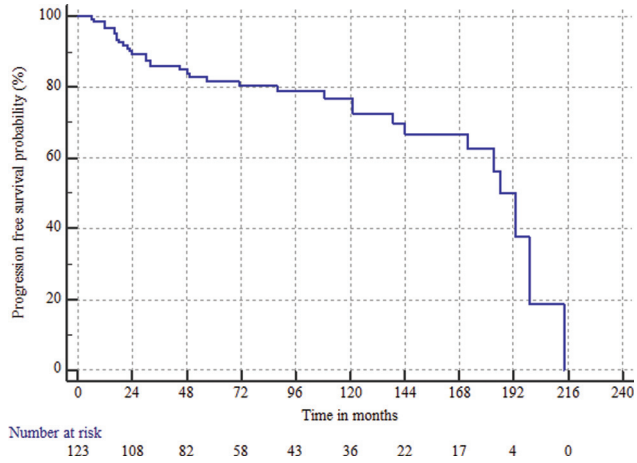

Fig. 1 Progression-free survival (PFS) time.

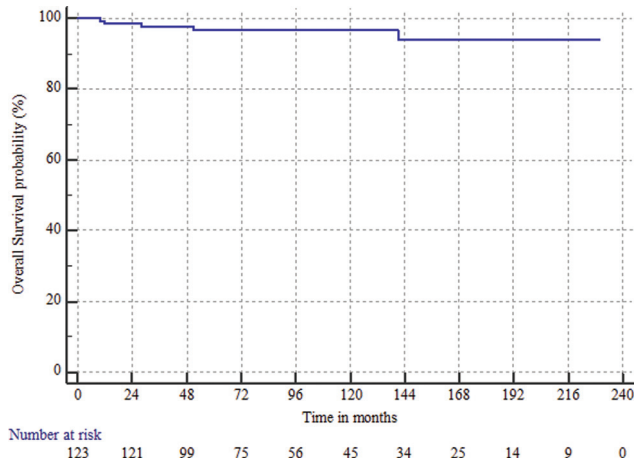

Fig. 2 Overall survival (OS) time.

lead to a higher recurrence rate.[10,20,21] As suggested by a recent study, probably the use of the Simpson method, for defining the extent of surgical resection in SBMs, could be questionable.[8] The en plaque nature and the bony invasiveness of the SBMs in contrast to NSBMs might explain this increased risk of relapse over the first 10 years of follow-up, neutralizing critical variables such as the EOR or the tumor grade.[7,8,10,21] All these factors make it difficult to achieve a complete tumor resection in SBMs, indicating that an adjuvant RT treatment should be considered. In this context, we decided to conduct a systematic evaluation of newly diagnosed WHO grade 1 SBMs treated in our institution, with the aim to assess the impact of different entities of surgical resection on local control rate, and to analyze the prognostic factors eventually affecting PFS. Surgical resection has been performed in all patients in the first instance, followed by adjuvant RT in selected cases receiving subtotal surgical resection (STR). Particularly, early adjuvant RT has been administered in younger patients (≤65 years) with good KPS (90–100) considering their potentially longer life expectancy. The other subtotally resected SBM patients were observed with clinical and radiologic follow-up. The results obtained were comparable with previous published studies,

Table 2 Prognostic factors identified as conditioning progression free survival (PFS)

Variables	No. of patients	Median PFS (mo)	2-y PFS (%)	5-y PFS (%)	10-y PFS (%)	*p*-value, univariate	*p*-value, multivariate	HR
Location								
ACF	26	172	84.6 (±7.0)	72.6 (±8.8)	51.9 (±13.9)	0.05	0.004	0.43 (0.24–0.77)
MCF	71	186	89.7 (±3.6)	86.8 (±4.1)	81 (±5.1)			
PCF	26	193	92.6 (±5.0)	87.7 (±6.7)	87.7 (±6.7)			
EOR								
GTR	37	nr	97.1 (±2.8)	97.1 (±2.8)	97.1 (±2.8)	0.0004	0.002	21.83 (2.96–160.65)
STR	86	172	86.0 (±3.7)	75.5 (±4.8)	68.0 (±6.0)			
Post-operative symptoms								
No symptoms	65	199	89.4 (±3.7)	85.9 (±4.3)	85.9 (±4.3)	0.018	0.19	1.34 (0.85–2.09)
Same as pre-operatively	31	121	90.3 (±5.3)	69.0 (±8.7)	55.2 (±11.7)			
New	26	193	87.8 (±6.6)	87.8 (±6.6)	79.0 (±10.2)			
Treatments								
Surgery alone	105	186	87.4 ± 3.2	78.6 ± 4.1	73.1 ± 5.0	0.0468	0.0292	0.10 (0.01–1.79)
Surgery + adjuvant RT at diagnosis	18	nr	100	100	100			
Treatments according to EOR								
Surgery alone GTR	37	nr	97.1 ± 2.8	97.1 ± 2.8	97.1 ± 2.8	< 0.0001	0.0009	10.34 (2.61–40.87)
Surgery alone STR	39	nr	95.1 ± 3.3	89.3 ± 5.1	89.3 ± 5.1			
STR + RT at diagnosis	18	nr	100	100	100			
STR + RT at progression	29	45	64.3 ± 9.0	42.9 ± 9.3	25 ± 8.1			

Abbreviations: ACF, anterior cranial fossa; EOR, extent of resection; GTR (Simpson grade I–II), gross total resection; HR, hazard ratio; MCF, middle cranial fossa; nr, not reached; PCF, posterior cranial fossa; PFS, progression-free survival; RT, radiation therapy; STR (Simpson grade III–IV), subtotal resection.

with a 5-year PFS rate of 81.8%, and a recovery of the neurologic functions in the vast majority of patients (88%).[14,15,17–20] The prognostic factors for PFS are the amount of surgical resection, tumor location, and administration of adjuvant RT at diagnosis or at disease progression. Particularly, almost all patients with PCF meningioma receiving GTR had a controlled meningioma at 5 and 10 years. In our series, the large part of relapse occurred in STR meningiomas, requiring a rescue treatment at a relatively short time from diagnosis. We have chosen not to proceed to repeated surgery because of the high risk neurologic deficits. In a nonfatal disease, such as meningiomas, keeping a functional integrity is pivotal.[22] All patients with recurrence received RT at disease progression. To date, there is no consensus regarding the indications for RT, RT schedule, and the optimal timing of employing RT, whether at diagnosis or at progression. Adjuvant RT at diagnosis has been performed only in case of STR, in selected patients characterized by a younger age (≤65 years) and a good KPS (90–100), taking into account the longer life expectancy, and the patient's wish. The 5-year PFS rate was comparable in case of GTR or STR plus adjuvant RT at diagnosis (97 and 100%, respectively), dropping to 89 and 42%, in patients who received STR alone or STR plus RT at disease progression (p-value < 0.0001). In a recent retrospective study, Lee et al confirmed these data, showing a significant improvement of recurrence-free survival (RFS) in patients who underwent STR followed by adjuvant radiotherapy ($p = 0.0016$).[23] However, most of the published papers focused on grade II NSB atypical meningiomas, whereas the role of RT in grade I SBMs is still under investigation. It would seem that similarly to NSBMs, adjuvant RT could be suggested in cases of subtotally resected SBMs, considering their high risk of recurrence. Although RT is not without toxicity, the availability in our institution of a modern RT technique, such as the intensity-modulated radiation therapy (IMRT), able to deliver a high dose to the tumor with maximum sparing of organs at risk (OARs), allowed us to perform a safe RT treatment. Using this approach, no severe side effects were recorded, and the neurologic status remained stable or improved in almost

all patients treated. In the last 10 years, aiming to identify worst prognosis meningioma patients, histopathologic diagnosis and immunochemical and molecular profile assessments were introduced and strongly improved.[24] DNA methylation is one of the best studied epigenetic regulators of gene transcription and plays a significant role in cancer biology. Two recent studies provide evidence of the importance of global methylation profiles in molecular subclassification of meningiomas.[25,26] Olar et al first demonstrated that unsupervised clustering of deoxyribonucleic acid (DNA) methylation data classified meningiomas into two distinct subgroups: a clinically favorable prognostic subgroup and a clinically unfavorable meningioma methylation subgroup with a median RFS of 16.35 and 8.27 years, respectively.[25] Sahm et al focused their analyses on the prediction power of methylation classes within WHO grades in 52 patients in the discovery cohort divergently (i.e., a benign methylation class but a higher WHO grade and intermediate methylation class but WHO grade I histology). Patients molecularly assigned to an intermediate methylation class with WHO grade I meningiomas showed an outcome similar to patients with more aggressive WHO grade II meningiomas.[26] In this context, methylation class analysis can represent a strong factor for PFS prediction, addressing the eventual use of adjuvant treatment in selected cases.

We are aware that the present study has several limitations, especially the retrospective nature, the heterogeneity of the cohort in relation to treatment received, and the absence of molecular assessment. However, the results recorded allowed us to better understand the clinical outcome of SBM patients and to underline prognostic factors to be considered in a therapeutic approach. As suggested by a recent review, the risk of symptomatic recurrence of meningiomas following surgical resection greatly varies, depending on the type of population, and there is a need for deeper analysis on the relationship between recurrence and tumor location and the complete molecular profile.[19] Overall, SBMs represent a population with a higher recurrence rate, due to the difficulty in achieving complete surgical resection and intrinsic microscopic local invasiveness. Our findings suggest that in complex cases, a safe surgical resection followed by adjuvant RT could be a better option to obtain adequate local control while maintaining neurologic integrity. Our findings underline the value of adjuvant RT in incompletely resected SBMs.

Author Contribution

FP and PN performed most of the study and drafted the manuscript. FS and MS contributed to the conception of this study. ZF, EC, and MS participated in the acquisition of the data, and LP and MF assisted in the interpretation of the results.

Funding

None.

Conflict of Interest

None declared.

References

1 Claus EB, Bondy ML, Schildkraut JM, Wiemels JL, Wrensch M, Black PM. Epidemiology of intracranial meningioma. Neurosurgery 2005;57(06):1088–1095, discussion 1088–1095
2 Rohringer M, Sutherland GR, Louw DF, Sima AA. Incidence and clinicopathological features of meningioma. J Neurosurg 1989;71 (5, Pt 1):665–672
3 Goldbrunner R, Minniti G, Preusser M, et al. EANO guidelines for the diagnosis and treatment of meningiomas. Lancet Oncol 2016; 17(09):e383–e391
4 Alvernia JE, Dang ND, Sindou MP. Convexity meningiomas: study of recurrence factors with special emphasis on the cleavage plane in a series of 100 consecutive patients. J Neurosurg 2011;115(03): 491–498
5 Ohba S, Kobayashi M, Horiguchi T, et al. Long-term surgical outcome and biological prognostic factors in patients with skull base meningiomas. J Neurosurg 2011;114(05):1278–1287
6 Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 1957;20(01): 22–39
7 Pessina F, Navarria P, Clerici E, et al. Intracranial meningiomas: a systematic analysis of prognostic factors for recurrence in a large single institution surgical series. World Neurosurg 2019;123: e273–e279
8 Mansouri A, Klironomos G, Taslimi S, et al. Surgically resected skull base meningiomas demonstrate a divergent postoperative recurrence pattern compared with non-skull base meningiomas. J Neurosurg 2016;125(02):431–440
9 Savardekar AR, Patra DP, Bir S, et al. Differential tumor progression patterns in skull base versus non-skull base meningiomas: a critical analysis from a long-term follow-up study and review of literature. World Neurosurg 2018;112:e74–e83
10 Nanda A, Bir SC, Maiti TK, Konar SK, Missios S, Guthikonda B. Relevance of Simpson grading system and recurrence-free survival after surgery for World Health Organization Grade I meningioma. J Neurosurg 2017;126(01):201–211
11 Cornelius JF, Slotty PJ, Steiger HJ, Hänggi D, Polivka M, George B. Malignant potential of skull base versus non-skull base meningiomas: clinical series of 1,663 cases. Acta Neurochir (Wien) 2013; 155(03):407–413
12 Komotar RJ, Iorgulescu JB, Raper DM, et al. The role of radiotherapy following gross-total resection of atypical meningiomas. J Neurosurg 2012;117(04):679–686
13 Mair R, Morris K, Scott I, Carroll TA. Radiotherapy for atypical meningiomas. J Neurosurg 2011;115(04):811–819
14 Rogers L, Zhang P, Vogelbaum MA, et al. Intermediate-risk meningioma: initial outcomes from NRG oncology RTOG 0539. J Neurosurg 2018;129(01):35–47
15 Tanzler E, Morris CG, Kirwan JM, Amdur RJ, Mendenhall WM. Outcomes of WHO Grade I meningiomas receiving definitive or postoperative radiotherapy. Int J Radiat Oncol Biol Phys 2011;79 (02):508–513
16 Goldsmith BM, Campos JM. Comparison of urine dipstick, microscopy, and culture for the detection of bacteriuria in children. Clin Pediatr (Phila) 1990;29(04):214–218
17 Miao Y, Lu X, Qiu Y, Jiang J, Lin Y. A multivariate analysis of prognostic factors for health-related quality of life in patients with surgically managed meningioma. J Clin Neurosci 2010;17 (04):446–449
18 Saraf S, McCarthy BJ, Villano JL. Update on meningiomas. Oncologist 2011;16(11):1604–1613
19 Kalbfleisch JD, Prentice RL. Marginal likelihoods based on Cox's regression and life model. Biometrika 1973;60(02):267–278
20 McGovern SL, Aldape KD, Munsell MF, Mahajan A, DeMonte F, Woo SY. A comparison of World Health Organization tumor grades at recurrence in patients with non-skull base and skull base meningiomas. J Neurosurg 2010;112(05):925–933

21 Ayerbe J, Lobato RD, de la Cruz J, et al. Risk factors predicting recurrence in patients operated on for intracranial meningioma. A multivariate analysis. Acta Neurochir (Wien) 1999;141(09): 921–932
22 Pieper DR, Al-Mefty O. Management of intracranial meningiomas secondarily involving the infratemporal fossa: radiographic characteristics, pattern of tumor invasion, and surgical implications. Neurosurgery 1999;45(02):231–237, discussion 237–238
23 van der Vossen S, Schepers VP, Berkelbach van der Sprenkel JW, Visser-Meily JM, Post MW. Cognitive and emotional problems in patients after cerebral meningioma surgery. J Rehabil Med 2014; 46(05):430–437
24 Lee KD, DePowell JJ, Air EL, Dwivedi AK, Kendler A, McPherson CM. Atypical meningiomas: is postoperative radiotherapy indicated? Neurosurg Focus 2013;35(06):E15
25 Sughrue ME, Kane AJ, Shangari G, et al. The relevance of Simpson Grade I and II resection in modern neurosurgical treatment of World Health Organization Grade I meningiomas. J Neurosurg 2010;113(05):1029–1035
26 Olar A, Wani KM, Wilson CD, et al. Global epigenetic profiling identifies methylation subgroups associated with recurrence-free survival in meningioma. Acta Neuropathol 2017;133(03):431–444
27 Sahm F, Schrimpf D, Stichel D, et al. DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. Lancet Oncol 2017;18(05):682–694