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Clinical Study

Treatment outcomes of 17 patients with atypical spinal meningioma, including 4 with metastases: a retrospective observational study

Sung Hyun Noh[a], Kyung Hyun Kim[a], Dong Ah Shin[b], Jeong Yoon Park[a], Seong Yi[b], Sung Uk Kuh[a], Keung Nyun Kim[b], Dong Kyu Chin[a], Keun Su Kim[a], Do Heum Yoon[b], Yong Eun Cho[a,*]

[a] *Department of Neurosurgery, Spine and Spinal Cord Institute, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea*

[b] *Department of Neurosurgery, Spine and Spinal Cord Institute, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea*

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Abstract

BACKGROUND CONTEXT: Because of the scarcity of atypical spinal meningioma, there is a lack of research on this type of tumor or its associated metastases.

PURPOSE: The aim of this study was to investigate the biological behavior of atypical spinal meningioma and identify its prognostic factors by reviewing surgical and clinical outcomes of patients with these tumors.

STUDY DESIGN: A retrospective chart review was performed.

PATIENT SAMPLE: We retrospectively reviewed the data from all patients who underwent spinal cord tumor excision between 1994 and 2017. Seventeen patients were pathologically proven to have atypical spinal meningioma.

OUTCOME MEASURES: We examined patients' neurologic status by determining their Nurick scores before and after surgery. Moreover, imaging studies, laboratory data, and the employed surgical method were analyzed retrospectively, as was the Ki-67 index and prognosis following postoperative radiation therapy.

METHODS: The ranges, locations, and pathologic diagnoses of the tumors were extracted from the radiological and pathological records of each patient. The extent of surgery and progression of disease were confirmed using postoperative enhanced magnetic resonance imaging. Patients were divided into two atypical spinal meningioma groups: primary and metastatic. The demographics, age, sex, presenting symptom duration, tumor location, Simpson resection grade, Ki-67, radiotherapy, recurrence, overall survival, and progression-free survival of patients in both groups were compared.

RESULTS: Seventeen patients were included in the analysis, of whom 12 (70%), 4 (24%), and 1 (6%) had tumors in the thoracic, cervical, and sacral regions, respectively. Complete and subtotal resections were achieved in 15 (88%) and 2 (12%) patients, respectively. Overall and progression-free survival rates in patients who underwent complete resection were longer than those in patients who underwent subtotal resection ($p<.001$). Four patients (24%) had metastatic meningiomas in the brain, among whom three were administered adjuvant radiotherapy after surgery. Two patients with intramedullary atypical spinal meningioma had metastatic tumors and experienced poorer

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* Corresponding author. Department of Neurosurgery, Spine and Spinal Cord Institute, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul 06273, Republic of Korea. Tel.: +82-02-2019-3390; fax: +82-02-3461-9229.

E-mail address: YECHO@yuhs.ac (Y.E. Cho).

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prognoses. The 5-year overall and progression-free survival rates were 84.4% and 85.2%, respectively. The Simpson resection grade, Ki-67 index, and preoperative neurologic status were found to be important prognostic factors on univariate Cox regression analysis ($p<.05$).

CONCLUSIONS: Complete resection should be considered as a primary treatment modality for individuals with atypical spinal meningioma. If subtotal resection is performed, adjuvant therapy can be administered.

Keywords: Atypical meningioma; Atypical spinal meningioma; Adjuvant therapy; Complete resection; Metastasis; Spinal cord.

Introduction

Spinal meningioma (SM) is one of the most common spinal cord tumors; an estimated 25% to 45% of all intradural spinal cord tumors are SMs [1]. These tumors account for 40% of extramedullary lesions, among which 80% are located within the thoracic spine where they usually exhibit the characteristics of benign, slow-growing tumors with no metastases [1,2]. Complete resection of the tumor is usually desirable upon diagnosis. Clinically, SMs appear between the 6th and 8th decades of life, with patients usually presenting with long-tract complaints; approximately 70% to 80% of patients are female [3]. Typical clinical symptoms include pain, gait disturbance, and paresthesia. Advances in neuroimaging techniques, as well as the use of intraoperative neuro-monitoring and the increasing reliability of contemporary surgical tools, have further improved the prognosis of SM, which was already recognized as excellent [4]. In contrast, there are only a few reported cases of atypical SM (ASM), which is a World Health Organization (WHO) grade II disease for which there is no standard therapy. Pathologically, atypical meningioma has enhanced mitotic activity (four or more mitoses per 10 high-power fields) and/or three or more of the following characteristics: increased cellularity, necrosis, small cell formation with a high nucleus-to-cytoplasm ratio, prominent nucleoli, and sheet-like growth [5]. To that end, we retrospectively reviewed 17 patients with ASM who were surgically treated at our institution, 4 of whom had metastases, to determine the associated prognostic factors and surgical outcomes.

Materials and methods

Patients

We retrospectively reviewed the data from all patients who underwent spinal cord tumor excision at our institution between 1994 and 2017. Seventeen patients were pathologically confirmed to have ASM. The patients' ages ranged from 40 to 80 years old (average age, 63.1±12.55 years old). The patients were followed for an average of 68.94±72.14 months (range, 11−276 months).

Medical records investigated in this study included age, sex, presenting symptom duration, and preoperative and postoperative neurologic statuses. We examined neurologic status by using the Nurick scores before and after surgery. Moreover, imaging studies, laboratory data, and the employed surgical method were analyzed retrospectively, as was the Ki-67 index and prognosis following postoperative radiation therapy. This study was approved by the Institutional Review Board of our hospital.

The ranges, locations, and pathologic diagnoses of the tumors were evaluated from the radiological and pathological records of each patient. The extent of surgery and progression of disease were confirmed using postoperative enhanced magnetic resonance imaging (MRI). Patients were divided into two groups: the primary ASM and metastatic ASM groups. The patient demographics, age, sex, presenting symptom duration, tumor location, Simpson resection grade, Ki-67 index, radiotherapy, recurrence, overall survival (OS), and progression-free survival (PFS) in both groups were compared. OS was defined as the period between the date of diagnosis and that of final follow-up or death, whereas PFS was defined as the period between the date of diagnosis and that of the detection of tumor progression. A single skilled neuropathologist confirmed the diagnosis of ASM for all patients in the study and classified the tumors according to the WHO criteria.

Surgical procedures

All operations were conducted with patients in the prone position. For surgeries performed in 2010 onward, somatosensory-evoked and motor-evoked potentials were monitored for neurologic changes. The location of the tumor, which was determined using MRI, was confirmed with portable radiography. An incision is made at the appropriate region, the muscle was dissected from the lamina, and a laminectomy was conducted. A dural incision was performed using an intraoperative microscope. If the ASM exhibited an infiltrative pattern or was surrounded by spinal cord vasculature or nerve roots, the tumor was removed using the Cavitron Ultrasonic Surgical AspiratorCUSA. To prevent traction of the spinal cord in case of anterior and/or anterolateral region-ASM, the dentate ligament proximal to the region is separated before using the Cavitron Ultrasonic Surgical Aspirator, and complete removal or subtotal removal of the tumor was then performed. For posteriorly located lesions, the infiltrated dura was completely removed and duraplasty was performed. For anterior and/or anterolateral lesions, the infiltrated dura was coagulated, dural suturing was performed precisely, and bleeding was controlled; afterward, laminoplasty was performed. A Hemovac drain was placed at the surgical site, and the wound was closed along the margin. All surgeries were completed uneventfully.

Adjuvant therapy

In the primary ASM group, total resection of the tumor was conducted in all patients and radiotherapy was not performed. In the metastatic ASM group, total resection was achieved in two patients; one patient was treated with radiotherapy whereas the other was not. Two patients who underwent subtotal resection received radiotherapy. The extent of tumor removal was determined using postoperative enhanced MRI by a neuroradiologist.

Statistical analysis

The findings are presented as the mean values ± standard deviation or counts (percentage), as indicated. All data were analyzed using an independent two-sample *t* test. The OS and PFS were calculated using the Kaplan-Meier method, whereas the log-rank test was performed to compare the survival distributions. A Cox proportional hazards model was performed to identify significant risk factors for progression. Using these models, we used univariate analyses on all independent variables. A p value <.05 was considered indicative of statistical significance. All statistical analyses were performed using SAS (version 9.2, SAS, Cary, NC, USA).

Results

Patient demographics

Seventeen patients underwent ASM excision at our institution; their demographic data are shown in Table 1. The study included 14 women (82%) and 3 men (18%). The patients' ages ranged from 40 to 80 years old (mean age, 63.1±12.55 years old). The patients were followed for an average of 68.94±72.14 months (range, 11−276 months).

Comparison between primary and metastatic ASM

The Simpson resection grade is used to evaluate brain meningioma [4,6,7]. As shown in Table 2, the symptom duration, Simpson resection grade, Ki-67 index, OS, and PFS were significantly different between patients with only primary ASM versus those with metastatic disease (p<.05). The 5-year OS rate among all patients with ASM was 84.4%, whereas the 5-year PFS was 85.2% (Fig. 1).

Illustrative cases

Patient 3

This patient was a 73-year-old woman who had experienced headaches for 2 years. The MRI revealed a tumor abutting the lesser wing of the sphenoid bone on the right side of the brain (Fig. 2). Postoperative MRI confirmed the total excision of the tumor, which was pathologically diagnosed as an atypical meningioma. The patient was administered 5,040 cGy of postoperative radiotherapy to the brain. However, on a follow-up MRI 18 months later, multiple meningiomas were observed, as a result of which she underwent gamma

Table 1
Patient demographics

Case No.	Sex	Age	Symptom duration (months)	Preoperative neurologic status	Preoperative neurologic status	Tumor location	Surgical extent	Adjuvant therapy	OS (months)	PFS (months)
1	F	57	6	1	0	S1-2, IDEM	TR	X	24	24
2	F	44	1	1	0	T11, IDEM	TR	X	36	36
3	F	73	6	4	4	T3-4, IM	STR	RTx.	25	12
4	F	61	12	2	1	T10, IDEM	TR	X	96	96
5	F	59	6	1	0	C6-7, IDEM	TR	X	84	84
6	F	56	1	3	4	T9-10, IDEM	TR	RTx.	8	6
7	F	75	1	1	1	C3, IDEM	TR	X	11	11
8	F	49	2	2	1	T4-5, IDEM	TR	X	30	30
9	F	65	1	1	0	T7, IDEM	TR	X	56	56
10	F	55	24	2	1	T7, IDEM	TR	X	54	54
11	F	80	3	2	1	T8-9, IDEM	TR	X	33	33
12	M	40	1	2	4	C3-4, IM	STR	RTx.	22	11
13	F	56	4	1	0	T8-9, IDEM	TR	X	21	21
14	F	77	4	2	2	T8-9, IDEM	TR	X	95	95
15	M	71	12	3	1	C5, IDEM	TR	X	16	16
16	M	77	36	3	2	T3, IDEM	TR	X	14	14
17	F	78	12	2	1	T3-4, IDEM	TR	X	15	15

No., number; M, male; F, female; OS, overall survival; PFS, progression-free survival; C, cervical; T, thoracic; S, sacrum; IDEM, intradural extramedullary; IM, intramedullary; TR, total resection; STR, subtotal resection; RTx, radiotherapy; X, no adjuvant therapy.

Table 2
Comparison between patients with primary vs. metastatic atypical spinal meningioma

	Primary ASM (n=13)	Metastatic ASM (n=4)	p value
Sex			
Female	11	3	
Male	2	1	.957
Mean age	65.7±11.36	54.5±13.96	.119
Clinical presentation			
Pain	1	0	
Motor or gait disorders	5	1	
Paresthesia	7	3	
Symptom duration (months)	9.37±10.33	2.32±2.55	.04*
Tumor location			
C-spine	3	1	
T-spine	9	3	
L-spine	0	0	.587
Sacrum	1	0	
IDEM	13	2	
IM	0	2	
Axial topography			
Dorsal	0	0	
Dorsolateral	4	2	
Ventrolateral	7	2	
Ventral	2	0	
Lateral	0	0	
Simpson resection grade			.019*
I	4	0	
II	9	2	
III	0	0	
IV	0	2	
Ki-67 (%)	5.7±1.6	13.3±4.6	.043*
Radiotherapy			
Yes	0	3	
No	13	1	
Recurrence			
Yes	0	3	
No	13	1	
Overall survival (months)	42.7±31.43	21.3±9.43	.047*
Progression-free survival (months)	42.7±31.43	14.8±10.5	.015*

ASM, atypical spinal meningioma; C, cervical; L, lumbar; T, thoracic; IDEM, intradural extramedullary; IM, intramedullary.
* Statistically significant.

knife radiosurgery. The median marginal dose applied to an average isodose volume of 50% was 15 Gy (range, 13−18 Gy), whereas the median maximal dose applied to the same was 30 Gy. Three months later, the patient complained of paraparesis. Spinal MRI revealed spinal tumors at the T3-4 level with leptomeningeal seeding. These intramedullary spinal tumors underwent subtotal excision, and were revealed to be ASMs on pathology. The patient underwent 1,620 cGy of radiotherapy to the whole spine after her spinal surgery, but her symptoms progressively worsened and she died 3 years later.

Patient 5

This patient was a 59-year-old woman. She presented with right arm pain, hypoesthesia on the left side of her body, and gait disturbance during the prior 6 months. Spinal MRI revealed a tumor at the C6-7 level (Fig. 3). The tumor was completely removed and diagnosed as an ASM on pathology. Her symptoms improved after surgery, and no recurrence was observed during 5 years of follow-up as confirmed with MRI.

Four patients with metastatic ASM

Table 3 describes the details of the four patients with metastatic ASM. Two patients had intramedullary ASMs that were metastatic; they experienced the worst prognoses. Patients 3, 6, and 12 received radiotherapy after ASM removal; none received chemotherapy. Patients 3 and 12 died of ASM recurrence, whereas Patient 6 died of primary lung cancer.

Univariate Cox regression and Kaplan-Meier analysis of survival

Factors that may potentially influence OS were analyzed using a Cox hazard model; the results are shown in Table 4. The Ki-67 index, Simpson resection grade, and preoperative neurologic status were significantly associated with OS ($p<.05$). Separate analyses revealed that the extent of surgery (complete vs. subtotal) significantly influenced survival, as complete resection produced significantly better OS and PFS rates than subtotal resection ($p<.05$) (Fig. 1).

Discussion

Based on the WHO criteria, SMs are sorted into three grades that reflect their prognoses [8]. Most SMs are benign and are categorized as WHO grade I; they comprise meningothelial, fibrous, and transitional lesions. Between 4.7% and 7.2% of SMs are atypical according to the WHO grade II criteria [8]. Although there are few published reports on ASM, research on this tumor type is scarce.

The proportion of female SM patients is higher than male patients; it was previously reported that the female and/or male ratio is 3−4:1 among patients with SM [9]. In our study, the female and/or male ratio was 4.7:1 among patients with ASM, which was similar to the ratio for SM. Furthermore, SM usually occurs between the 6th and 8th decades of life [10], and there is a significant difference between the ages of patients with low-grade meningioma and those with high-grade malignant meningioma; the latter is more frequent in younger patients [6]. In our study, the average age of patients with ASM was 63.1 years old.

The most common symptom of SM is sensory deficit, followed by gait disturbance and paraparesis [6]. In our study, the most common symptom of ASM was paresthesia, followed by motor weakness. The average duration of symptoms in patients with SM in our study was 11.8 months, which is close to the range reported in the literature (12−24 months) [11]. For ASM, however, the mean duration of symptoms was 7.7±9.52 months; moreover, there was a significant difference between the mean duration of

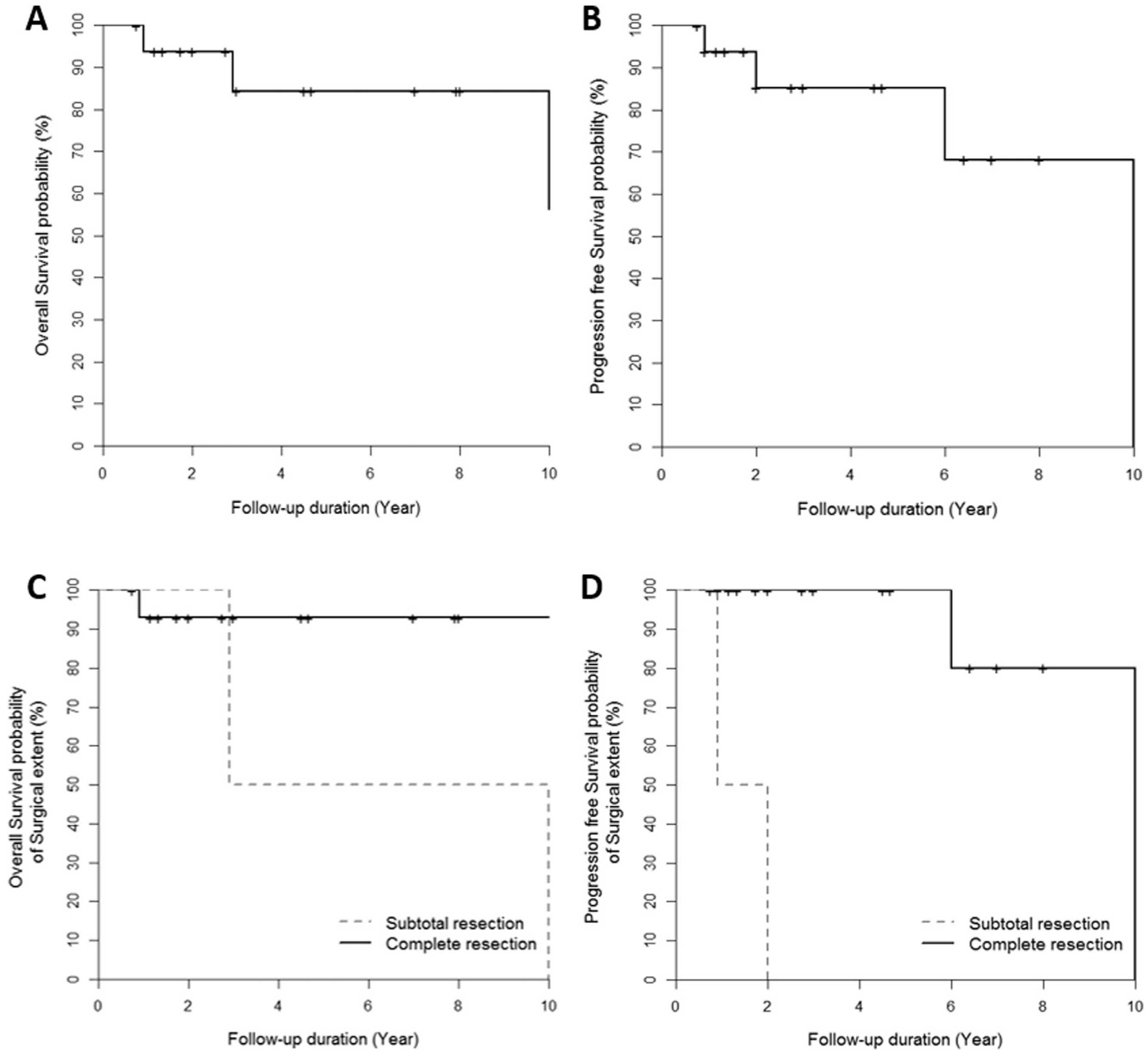

Fig. 1. (A) Overall survival of patients with atypical spinal meningioma (ASM). The 5-year overall survival rate for all patients was 84.4%. (B) Progression-free survival of patients with (ASM); the 5-year progression-free survival rate was 85.2%. (C) Overall survival of patients who underwent complete versus subtotal resection (log-rank p value <.001). (D) Progression-free survival of patients who underwent complete versus subtotal resection (log-rank p value <.001).

symptoms in patients with primary versus metastatic ASM ($p<.05$). The standard diagnostic tool of SM is MRI, where the tumor is usually observed as an isointense lesion on the spinal cord using T1- and T2-weighted imaging that is enhanced when using contrast medium (gadolinium) [6]. Similar to SM, ASM presents as an isointense signal on T1- and T2-weighted MRI and shows T1 enhancement with homogeneity.

The thoracic spine is reportedly the most common location of SMs (64%−84% of incidences), whereas 14% to 27% are cervical and 2% to 14% are lumbar [9]. In our study, ASMs most commonly occurred in the thoracic spine followed by the cervical spine. Most were intradural extramedullary lesions, although two patients had intramedullary lesions. According to Setzer et al., the most common site of SM dural attachment is the ventrolateral region (41.2%), followed by the dorsolateral (21.2%), lateral (13.8%), ventral (7.5%), and purely dorsal (3.8%) regions [6]. In our study, the most common location of ASM dural attachment was the ventrolateral region (52.9%) followed by the dorsolateral region (35.3%).

The main purpose of surgery is complete tumor excision and decompression of the spinal cord. Dorsally located tumors can be completely removed with or without resection of the adhered dura. Ventral tumors should first be debulked to exposing the area between it and the spinal

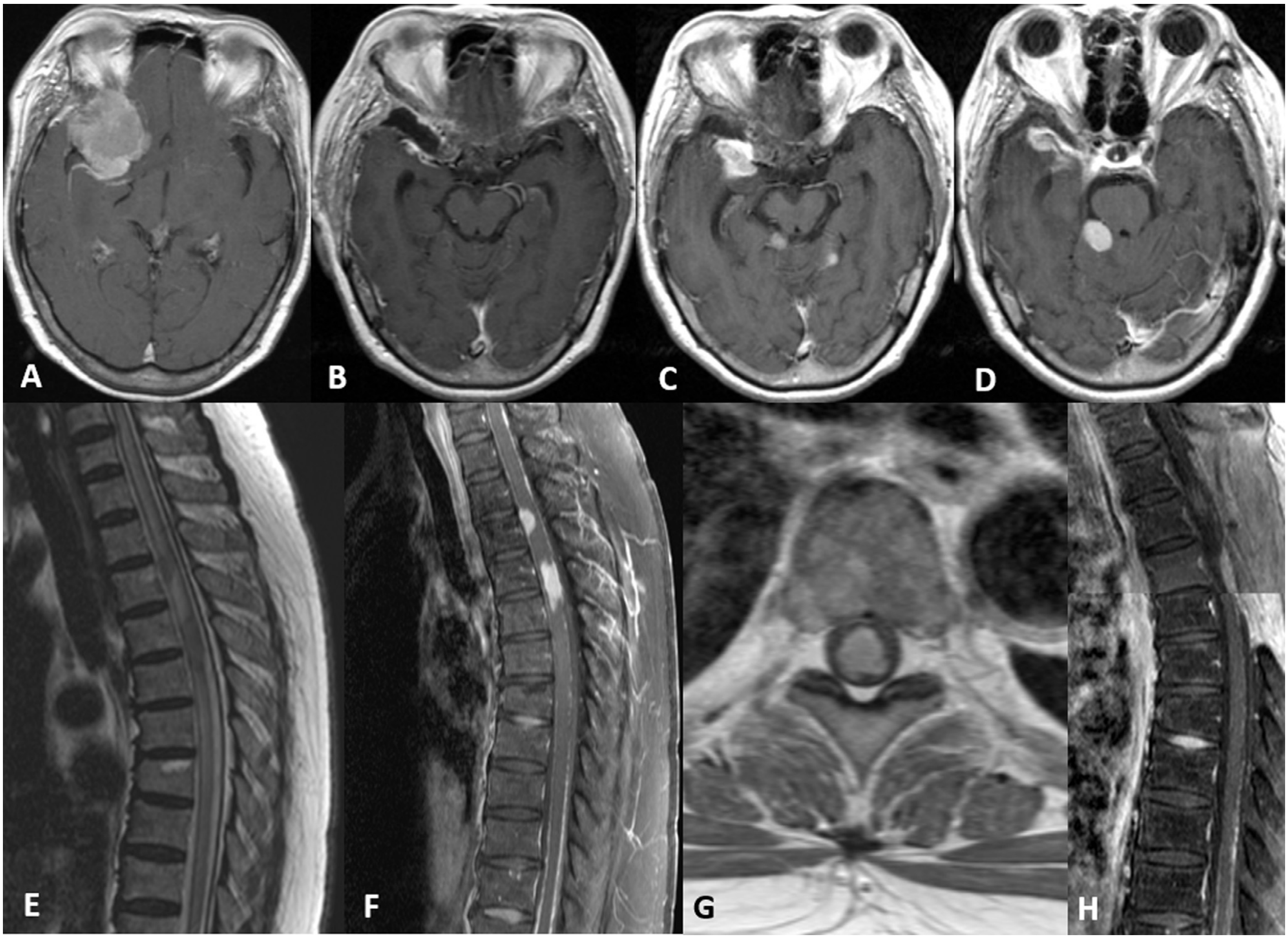

Fig. 2. A patient with metastatic atypical spinal meningioma who underwent subtotal tumor removal. Brain MRI showed a tumor abutting the lesser wing of the sphenoid bone on the right side (A). The tumor was completely excised, as shown on postoperative MRI (B). Multiple meningiomas were found on MRI 18 months later (C and D). Spinal MRI revealed tumors at the T3-4 level with leptomeningeal seeding 2 years after the original surgery (E−G). The intramedullary spinal tumors at T3-4 underwent subtotal resection (H). MRI, magnetic resonance imaging.

cord before it can be completely removed [11]. The SM recurrence rate following subtotal resection (Simpson grades III and IV) is much higher than that following total resection (Simpson grades I and II) [11]. In a study by Nakamura et al., six patients who underwent incomplete tumor resection required repeat surgery in a relatively short time [7]. A previously reported series had a complete resection rate of 82% to 99% [6]; however, their proportion of highly malignant tumors was lower than in our series. The dural adherence was coagulated in most cases (15%−89%), and only in 14% to 57% of the cases were dural adherence resections performed with duraplasty using a patch graft [1]. Given that the recurrence rate is very low, there is no need to achieve Simpson grade I in all grade I meningiomas. However, in patients with grades II and III meningioma, a Simpson grade I resection is crucial to lower recurrence rates and improve survival [6]. In our study, Simpson grades I (23.5%), II (64.7%), and IV (11.8%) resections were performed. There were no recurrences in patients who underwent Simpson grades I and II complete resections. In those with metastatic ASM, Simpson grade IV resection was performed in the intramedullary regions of two patients who later experienced recurrence and died within 1 year. The remaining two patients with metastases underwent Simpson grade I resection and experienced no recurrence. Thus, even in ASMs, complete tumor excision appears to prevent recurrence. Dziuk et al. also reported that complete resection is important for long-term control of nonbenign meningiomas [12], as was also observed in our study.

Meningioma metastases most commonly occur in the lung, liver, lymph nodes, and bone [13]; spinal metastases are extremely unusual [14]. In an analysis of 396 meningiomas, Enam et al. found that 92.4%, 5.8%, and 1.8% are grades I, II, and III tumors, respectively [15]. The metastasis rate for all meningiomas was 0.76%, although the proportion of grade III metastasis was 42.8%. Mahmood et al. reported 319 patients with meningioma among whom only 2 (0.6%) had spinal metastases (to the lumbar vertebral body and spinal subarachnoid space, respectively) [14]. All our patients with metastatic ASM had lesions that arose from grades II and III intracranial meningiomas.

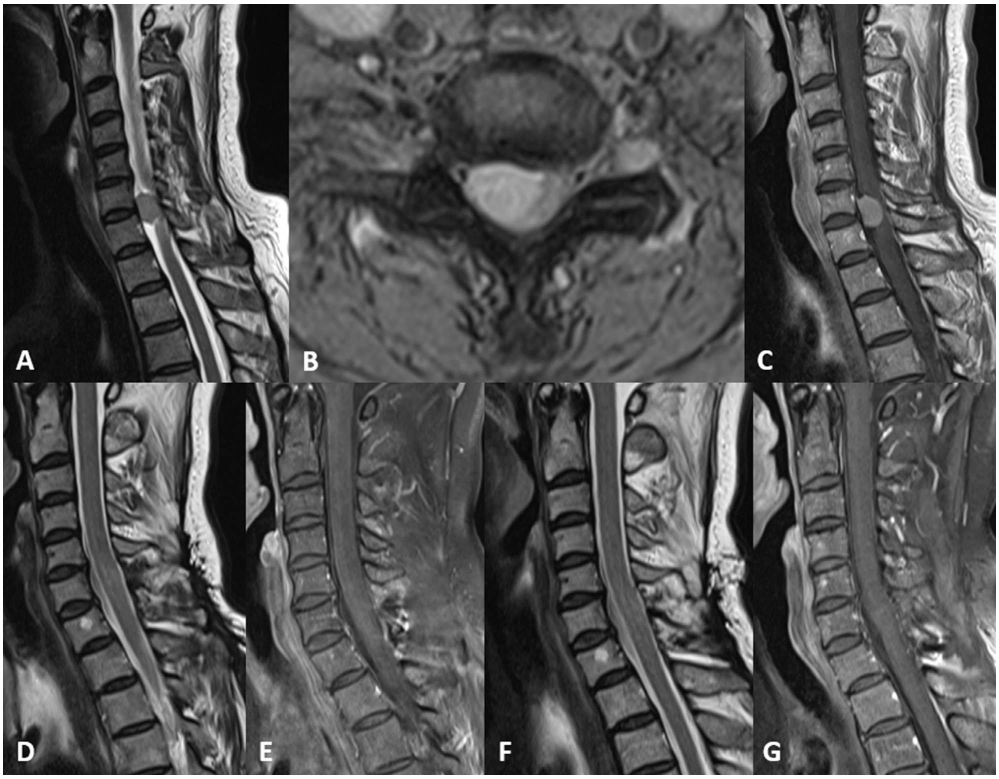

Fig. 3. A patient with primary atypical spinal meningioma who underwent complete tumor resection. A spinal tumor at C6-7 was found using MRI (A−C). The tumor was located in the ventrolateral region and was excised completely (D and E). Follow-up MRI 5 years later showed no recurrence (F and G). MRI, magnetic resonance imaging.

Although complete resection prevents recurrence of metastatic ASM, subtotal resection requires additional treatment; radiotherapy and chemotherapy are recommended as adjuvant therapies in such cases. Generally, radiotherapy is performed in patients with high grade and recurrent SMs, and is generally administered to patients with remnant meningiomas after surgical resection of high-grade lesions, those with recurrent meningiomas after subtotal resection, or those in whom surgery is unsafe for clinical or anatomical reasons [1]. Data from preliminary studies indicate that CyberKnife frameless stereotactic radiosurgery is safe and effective with single fraction therapy for benign spinal lesions, including meningioma [16]. Kawaguchi et al. reported that adjuvant radiation was administered to patients with ASM, although it was not effective [17]. In our study, three patients with ASM received radiotherapy, two of whom died following recurrence. Regarding chemotherapy, hydroxyurea is reportedly an effective treatment, although this agent may only delay the progression of disease in benign meningioma [18]. Kawaguchi et al. found that their administered dose of 1,000 mg/day (20 mg/kg/day) of hydroxyurea was not effective [17], whereas Cramer et al. administered 20 mg/kg/day to a patient in whom the outcome was uncertain [19].

Setzer et al. found that invasion of the arachnoid and/or pia mater and a poor preoperative McCormick grade were significantly associated with poor long-term results on multivariate analysis [6]. In our univariate model, the Ki-67 index, Simpson resection grade, and preoperative neurologic status were significantly associated with survival. The Ki-67 index has long been considered a powerful morphological predictor of a tumor's biological behavior [20]. Upon investigating preoperative neurologic statuses using the Frankel and McCormick scales, Raco et al. reported that long-term preoperative symptoms and severe preoperative damage are associated with worse outcomes [4]; this was also the case in another study [21]. We found that the Ki-67 index, Simpson resection grade, and preoperative neurologic status are significant prognostic factors for patients with ASM.

Limitations of this study

This study had several limitations. It comprised a small number of patients with ASM because of the disease's rarity. Ours was not a randomized control study but a retrospective observational case series performed at a single institution. Additionally, there was heterogeneity in the treatment method of patients with metastatic ASM; as no standard treatment guidelines for ASM currently exist, such heterogeneity was unavoidable. Prospective studies will be conducted using well-guided evidence-based protocols with adequate controls.

Table 3
Details of the four patients with metastatic atypical spinal meningioma

	Case 3	Case 6	Case 8	Case 12
Sex	Female	Female	Female	Male
Age	73	56	49	40
Tumor location	T3-4 IM	T9-10 IDEM	T4-5 IDEM	C3-4 IM
Previous surgical extent	1st OP CR (Rt. frontal)	1st OP CR (Lt. temporal) 2nd OP CR (Lt. temporal)	1st OP CR (Lt. temporal)	1st OP CR (Petroclival lesion) 2nd OP STR (C3-4, IM)
Pathology	1st OP (Atypical meningioma)	1st OP (Meningothelial meningioma) 2nd OP (Clear cell meningioma)	1st OP (Atypical meningioma)	1st OP (Anaplastic Meningioma) 2nd OP (Atypical meningioma)
Adjuvant therapy	RTx. 5,040 cGy (Brain) After 1st OP GKR 30 Gy (Brain) 1,620 cGy (Spine) After 2nd OP	RTx. 5,040 cGy (Brain) After 2nd OP 1,620 cGy (Spine) After 3rd OP	RTx. 2,800 cGy (Brian) After 1st OP	RTx. 5,400 cGy (Brain) After 1st OP 5,040 cGy (Spine) After 2nd OP
Ki-67 (%)	12	11	10	20
Overall survival (months)	25	8	30	22
Progression free survival (months)	12	6	30	11

C, cervical; T, thoracic; IDEM, intradural extramedullary; IM, intramedullary; OP, operation; CR, complete resection; STR, subtotal resection; RTx, radiotherapy; GKR, gamma knife radiosurgery.
Patients 3, 6, and 12 died.

Table 4
Univariate Cox regression analysis of overall survival

Factor	HR	95% CI	p value
Age	0.962	0.872−1.061	.435
Symptom duration	0.810	0.507−1.294	.378
Ki-67	1.335	1.034−1.725	.027*
Simpson resection grade	3.299	1.068−10.194	.038*
Preoperative neurologic status	2.929	1.003−8.550	.049*
Postoperative neurologic status	10.444	0.068−1612.159	.362

HR, hazard ratio; CI, confidence interval.
* Statistically significant.

Conclusion

Our data indicate that complete resection should be considered as a primary treatment modality for individuals with ASM: if subtotal resection is performed, adjuvant therapy can then be administered. The Simpson resection grade, Ki-67 index, and preoperative neurologic status are important prognostic factors for patients with ASM.

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