Rapid Worsening of Symptoms and High Cell Proliferative Activity in Intra- and Extramedullary Spinal Hemangioblastoma: A Need for Earlier Surgery

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Abstract

Study Design   A retrospective analysis of a prospective database.

Objective   To compare preoperative symptoms, ambulatory ability, intraoperative spinal cord monitoring, and pathologic cell proliferation activity between intramedullary only and intramedullary plus extramedullary hemangioblastomas, with the goal of determining the optimal timing for surgery.

Methods   The subjects were 28 patients (intramedullary only in 23 cases [group I] and intramedullary plus extramedullary in 5 cases [group IE]) who underwent surgery for spinal hemangioblastoma. Preoperative symptoms, ambulatory ability on the McCormick scale, intraoperative spinal cord monitoring, and pathologic findings using Ki67 were compared between the groups.

Results   In group IE, preoperative motor paralysis was significantly higher (100 versus 26%, $p < 0.005$), the mean period from initial symptoms to motor paralysis was significantly shorter (3.5 versus 11.9 months, $p < 0.05$), and intraoperative spinal cord monitoring aggravation was higher (65 versus 6%, $p < 0.05$). All 5 patients without total resection in group I underwent reoperation. Ki67 activity was higher in group IE (15% versus 1%, $p < 0.05$). Preoperative ambulatory ability was significantly poorer in group IE ($p < 0.05$), but all cases in this group improved after surgery, and postoperative ambulatory ability did not differ significantly between the two groups.

Conclusions   Intramedullary plus extramedullary spinal hemangioblastoma is characterized by rapid preoperative progression of symptoms over a short period, severe spinal cord damage including preoperative motor paralysis, and poor gait ability compared with an intramedullary tumor only. Earlier surgery with intraoperative spinal cord

Keywords
► spinal hemangioblastoma in intramedullary and extramedullary location
► preoperative motor paralysis
► progress of preoperative symptom
► ambulatory ability
► early surgery

monitoring is recommended for total resection and good surgical outcome especially for an IE tumor compared with an intramedullary tumor.

Introduction

Spinal hemangioblastoma is a relatively rare tumor that accounts for up to 10% of intramedullary spinal cord tumors.[1,2] An intramedullary location is most common, but hemangioblastomas with exophytic intramedullary, intradural-extramedullary, and extradural locations have been described in a few case reports.[1,3–5] We found key differences in preoperative magnetic resonance imaging (MRI) for hemangioblastomas in different locations that permit accurate diagnosis.[6] Our previous study revealed that preoperative diagnostic MRI is particularly important in cases of intramedullary plus extramedullary (IE) hemangioblastoma for preparing a surgical plan for total resection, and a change in intramedullary high-intensity areas on the craniocaudal side of the tumor on sagittal T2-weighted imaging and a snowman sign on contrast axial T1-weighted imaging must not be missed for this type of tumor. However, the preoperative symptoms, intraoperative spinal cord monitoring, and surgical outcomes for different tumor locations have not been examined.

Several recent publications have recommended surgery before symptoms become severe.[7–10] However, preoperative motor paralysis and postoperative outcome in IE hemangioblastomas have not been clearly described because of the rarity at this location, which makes it difficult to determine the appropriate surgical timing. In 2009, we reported the surgical results for 106 intramedullary spinal cord tumors, including 16 hemangioblastoma cases with intramedullary locations only, but we only described pre- and postoperative ambulatory status and extent of tumor resection because the focus of the article was on all intramedullary spinal cord tumors.[7] Thus, the progression of symptoms, surgical outcome, intraoperative spinal cord monitoring, pathologic findings for cell proliferative activity, and optimal surgical timing have not been examined for spinal hemangioblastomas with different locations. This study is the first to determine whether the tumor location affects preoperative progression of symptoms and motor paralysis; to examine the relationship between preoperative status and surgical results; to evaluate intraoperative spinal cord monitoring and pathologic findings with Ki67; and to evaluate the optimal surgical timing for obtaining a better outcome for intramedullary and IE hemangioblastomas.

Materials and Methods

The subjects were 28 consecutive patients (17 men and 11 women) with intramedullary spinal hemangioblastoma who underwent surgery in our department between 1993 and 2013. All patients gave informed consent, and the study plan was approved by the Ethics Committee of Nagoya University. The mean age of the patients was 43 years old (range 21 to 68 years old), and the mean postoperative follow-up period was 10.0 years (2 to 19 years). The tumor locations were intramedullary only in 23 cases (82%, group I) and IE in 5 cases (18%, group IE). Six cases with intramedullary tumors were complicated with von Hippel Lindau (VHL) disease (21%). All cases of IE tumors were sporadic without multiple tumors.

The MRI findings, preoperative symptoms, preoperative motor paralysis, period from onset of initial symptoms to paralysis, period from onset of initial symptoms to surgery, pre- and postoperative ambulatory abilities based on the McCormick scale,[11,12] intraoperative spinal cord monitoring, extent of tumor resection, tumor recurrence, need for reoperation, and pathologic findings were compared between groups I and IE.

Ambulatory ability was evaluated using the modified McCormick scale (I = normal gait, II = mild gait disturbance not requiring support, III = gait with support, IV = assistance required, and V = wheelchair needed), with McCormick grades I and II defined as a good independent ambulatory status without support.

The extent of tumor resection was evaluated using four categories: total resection, subtotal resection, partial resection, and biopsy. Total resection was attempted in all cases and was defined in the standard manner as removal of 100% of the tumor based on a microscopically documented clean surgical field at the end of the procedure and a clean intraoperative surgical bed in ultrasonography. Total resection was abandoned if the amplitude of evoked potentials in monitoring disappeared without intraoperative restoration, which indicates impending neurologic paralysis. Spinal cord monitoring was performed using the somatosensory evoked potential (SSEP) up to 1999 and the compound muscle action potential (CMAP) from 2000.[13,14] A case in which a small tumor fragment was deliberately left in place was considered to have undergone subtotal resection, based on intraoperative ultrasonography indicating 80 to 99% resection. Similarly, 50 to 80% and <50% resection were defined as partial resection and biopsy, respectively. The extent of resection was confirmed using MRI at 1 month postoperatively. The tumor was pathologically diagnosed postoperatively based on the histologic type, and the Ki67 activity was determined as an index of cell proliferative activity.

This study was retrospective, but all the data was available for the factors described above in a prospective database of cases at our institute alone, in contrast to our previous multicenter study.

An unpaired t test and Fisher exact probability test in SPSS statistics 22 software (SPSS, Inc., Chicago, Illinois, United States) were used for statistical analysis, with $p < 0.05$ taken to indicate statistical significance.

Surgical Procedure

After exposure of the dura mater, ultrasound was used to confirm the tumor location. Especially, power Doppler images

clearly show feeding vessels, and the hemangioblastoma is easily identified. If a reddish orange tumor is seen through the pia mater, entry can be performed at the site, but if the tumor is not visible, the approach is from the dorsal median sulcus. The margin between the tumor and the spinal cord is relatively clear. Although the tumor is separated from the spinal cord with mucosal elevator and hook-type microdissector, inflow and outflow vessels are coagulated and resected, and then the tumor is coagulated, shrank, and solidified. It can then be removed as a single mass. Because the tumor bleeds easily and may cause heavy bleeding, incision of the tumor should be avoided. For an IE tumor, the extramedullary component is removed first, and then the intramedullary tumor is removed. The spinal cord is monitored during surgery, and if amplitude reduction to <30% is detected, the operation is interrupted and the operative field is filled with warm saline.[15] The operation can be resumed when the waveform recovers. Cysts and syrinxes associated with the tumor may remain on intraoperative ultrasound and MRI immediately after the operation, but these gradually reduce and finally disappear after total resection of the tumor, and shunting is not needed (►Fig. 1A, B).

Results

Preoperative characteristics in groups I and IE are shown in ►Table 1. Age in group IE tended to be higher than that in group I, but with no significant difference. Four of the five IE tumors were located in the conus region (80%). On the preoperative MRI, intramedullary syrinxes or edema on T2-weighted imaging did not differ significantly between the groups. Strong contrast enhancement of the tumor was present on T1-weighted imaging in all 28 cases, and the axial images were particularly useful for differentiation between tumors in groups I and IE (►Fig. 1C, D).[6] In group IE, the extramedullary components fully occupied the spinal canal and compressed the spinal cord from the outside.

The initial symptom was numbness or pain in 25 cases (89%). Preoperative pain tended to be more common in group IE (80%), with a similar tendency for preoperative bladder and bowel disturbance (►Table 1). There was a significantly higher rate of preoperative motor paralysis in group IE (5/5 [100%] versus 6/23 [26%], $p < 0.005$), with a preoperative manual muscle test score of about 1 point lower in group IE. The mean periods from onset of the initial symptom to motor paralysis and to surgery were significantly shorter in group IE, indicating aggravation of symptoms in a significantly shorter period in group IE ($p < 0.05$). Significantly fewer patients were in preoperative McCormick classes I and II in group IE (20% versus 78%, $p < 0.05$; ►Fig. 2).

The extent of tumor resection, postoperative course, perioperative systemic complications, intraoperative spinal cord monitoring findings, and pathologic findings in the two groups are shown in ►Table 2. Total resection was achieved in 24 cases (86%), and there were 2 cases with subtotal resection and 2 with partial resection. The rates of total resection did not differ significantly between the groups. All 4 patients in whom total resection was not achieved
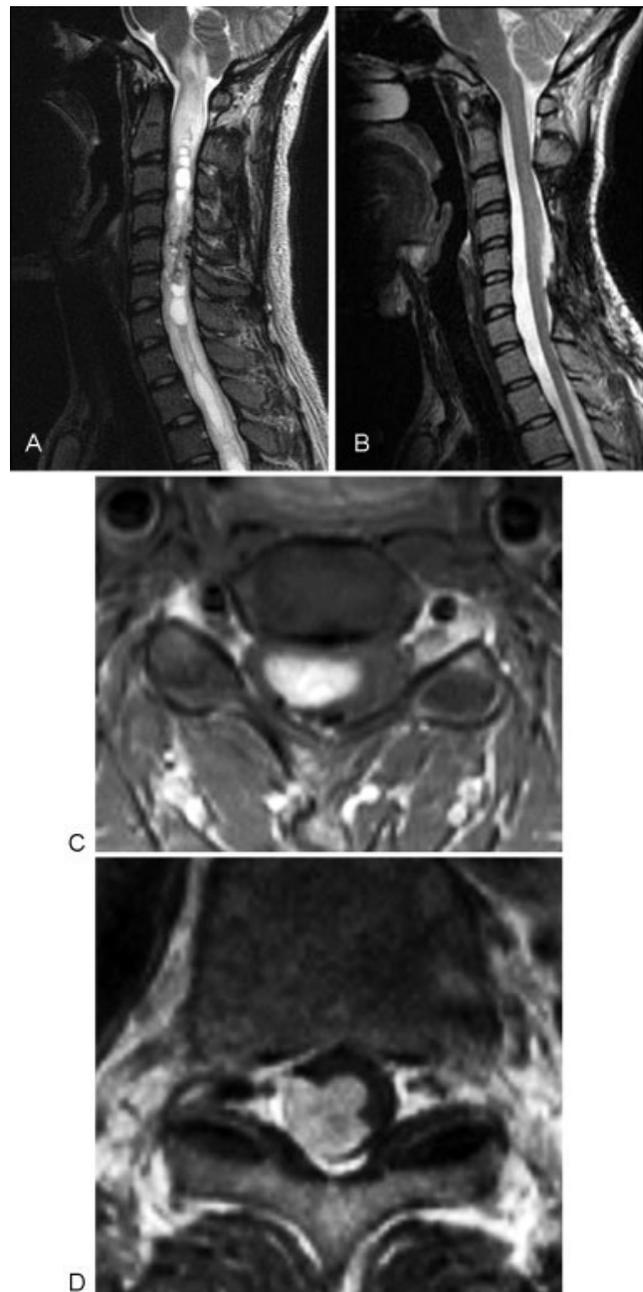

Fig. 1 (A) Characteristic magnetic resonance imaging findings for intramedullary hemangioblastoma at C5 include a wide high-intensity area on the craniocaudal sides of the tumor on T2-weighted imaging. (B) Syrinxes naturally disappear postoperatively after total tumor resection, and shunting is not needed. (C) A clearly and densely contrasted tumor on contrast T1-weighted imagining (T1WI) as a "focal sign" is seen in intramedullary location only. (D) An intramedullary plus extramedullary hemangioblastoma showing a characteristic "snowman sign" on contrast T1WI. An extramedullary tumor occupied all the spinal canal in all cases in the intramedullary plus extramedullary hemangioblastoma group, and the spinal cord was severely compressed from the intramedullary and extramedullary sides.

had worsening of symptoms postoperatively and underwent reoperation.

For intraoperative spinal cord monitoring, SSEP was used in 7 cases and CMAP in 21. In monitoring using CMAP, the amplitude was stable in 17 of the 21 cases (81%) and paralysis did not occur postoperatively. The amplitude increased in

Table 1 Preoperative differences in MRI and symptom course based on the tumor location

Items	Group I (n = 23)	Group IE (n = 5)	p Value[a]
Age (y)	41.2 (± 14.6)	50.8 (± 19.3)	0.22
Gender (male/female)	13/10	4/1	–
Level of tumor			
Cervical spine	10	0	–
Thoracic spine	9	1	
Cervicothoracic spine	2	0	
Conus region	2	4 (80%)	
Length of intramedullary HIA on sagittal T2WI (vertebrae)	13.1 (± 3.1)	10.2 (± 2.6)	0.81
Findings on contrast axial T1WI	Focal	Snowman sign	–
Preoperative symptoms			
Pain	43% (9 cases)	80% (4 cases)	0.16
BBD	26% (6 cases)	60% (3 cases)	0.19
Patients with preoperative paralysis	26% (6 cases)	100% (5 cases)	<0.005
Details of preoperative paralysis			
Preoperative MMT	4.5 (± 0.99)	3.2 (± 1.3)	0.47
Period from onset of initial symptoms to motor paralysis (mo)	11.9 (± 9.5)	3.5 (± 3.7)	<0.05
Period from onset of initial symptoms to surgery (mo)	19.9 (± 19.3)	4.5 (± 3.6)	<0.05

Abbreviations: BBD, bladder bowel disturbance; group I, intramedullary tumor group; group IE, intramedullary plus extramedullary tumor group; HIA, high-intensity area; MMT, manual muscle test; MRI, magnetic resonance imaging; T1WI, T1-weighted image; T2WI, T2-weighted image.
Note: Parentheses indicate standard deviation or number of cases.
[a]Fisher exact probability test or unpaired t test.
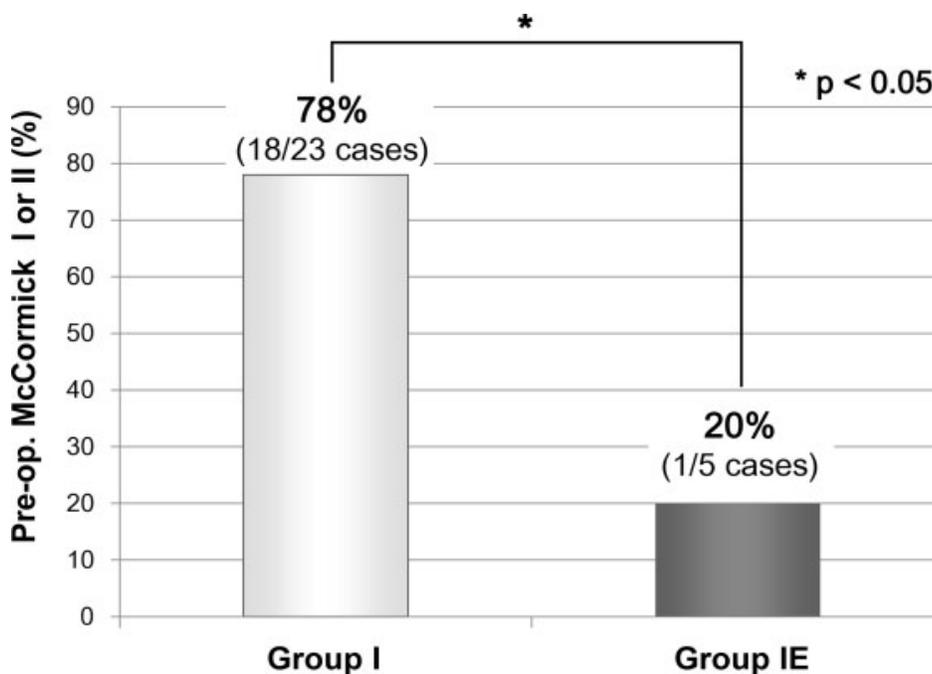
Fig. 2 The percentage of cases with stable independent ambulation (McCormick classes I and II) preoperatively was significantly lower in the intramedullary plus extramedullary hemangioblastoma group (group IE) than in the intramedullary group (group I).

1 case and decreased to <30% in 4 (to a mean of 19% in all 21 cases), with recovery of the amplitude in 2 of these cases during the operation. In the other 2 cases (both in group IE), the amplitude at the end of the operation was smaller than that before resection of the tumor. Both of these patients had temporary lower extremity muscle weakness postoperatively but had recovered from motor paralysis at 3 and 8 days after surgery, respectively. As shown in ►**Table 2**, significantly more cases in group IE had an intraoperative decrease of amplitude in CMAP monitoring (p < 0.05).

Table 2 Tumor resection, reoperation, perioperative systemic complications, intraoperative spinal cord monitoring, and pathologic findings based on the tumor location

Item	Group I ($n = 23$)	Group IE ($n = 5$)	p Value[a]
Total resection (%)	83% (19/23)	100% (5/5)	0.34
Reoperation (%)[b]	100% (4/4)	0%	–
Perioperative systemic complications (%)	17% (4/23)	20% (1/5)	0.66
Headache	3	0	
Superficial infection	1	0	
Delayed wound healing	0	1	
Intraoperative spinal cord monitoring (% deterioration in amplitude of CMAP)[c]	6.2% (1/16)	60% (3/5)	<0.05
Ki67 (%)	1.0% ($\pm$ 0.21)	15% ($\pm$ 9.1)	<0.05

Abbreviations: CMAP, compound muscle action potential; group I, intramedullary tumor group; group IE, intramedullary plus extramedullary tumor group.
[a]Fisher exact probability test or unpaired t test.
[b]All cases requiring reoperation were those in which total resection was not achieved.
[c]Twenty-one cases underwent CMAP.

The postoperative pathologic diagnosis was confirmed as hemangioblastoma in all patients. The mean Ki67 activity was significantly higher in group IE compared with that in group I (15 versus 1%, $p < 0.05$).

Ambulatory status based on McCormick class in all cases is shown in ►**Table 3**. Five cases in group I had worsening of the McCormick class postoperatively. Three of these cases were monitored using SSEP, and the SSEP findings did not change in these cases. Only 2 of the 21 cases (9.5%) that underwent surgery with CMAP monitoring had a worsened McCormick class at final follow-up: a patient with a history of several operations for VHL disease who worsened from class I to III and a patient with deterioration of symptoms after partial tumor resection who worsened from class II to III. Both of these patients underwent reoperation.

The cases in McCormick classes I and II at final follow-up had better preoperative McCormick grades (►**Fig. 3**). In contrast, only 22% of patients in preoperative McCormick classes III, IV, and V achieved independent ambulation postoperatively ($p < 0.05$). In groups I and IE, the percentage of cases in McCormick classes I and II at final follow-up was also

Table 3 Pre- and postoperative ambulatory ability based on the McCormick scale in all cases

Preoperative McCormick class	Postoperative McCormick class at final follow-up				
	I	II	III	IV	V
I	9	0	2[b]	0	0
II	4 (3 + 1[a])	2	1[b]	1[b]	0
III	1[a]	0	3	0	1[b]
IV	1	0	2[a]	0	0
V	0	0	1[a]	0	0

[a]Cases in the intramedullary plus extramedullary group.
[b]Cases with postoperative aggravation of gait ability (all in the intramedullary group).

related to the preoperative independent ambulation status (►**Fig. 3**). However, there was no significant difference in the rate of postoperative independent ambulation (65% in group I and 40% in group IE, ►**Fig. 4**), despite the significant difference preoperatively. All IE cases had improved ambulatory status after surgery (►**Table 3**).

Discussion

We previously reported 16 cases of intramedullary spinal hemangioblastoma, with the conclusion that good preoperative ambulatory ability was associated with postoperative independent ambulatory ability and that total excision of tumors was required.[7] However, we did not evaluate the preoperative symptoms, duration from initial symptoms to motor paralysis, intraoperative spinal cord monitoring, surgical outcome, and pathologic findings for cell proliferative activity, and IE spinal hemangioblastomas were not examined in our previous study. This information is also lacking in other studies because the IE location has only been described in a few cases. Thus, this work is the first comparative study of these factors in intramedullary and IE spinal hemangioblastomas.

Cases with IE tumors had obviously severe spinal cord damage preoperatively based on the higher rates of bladder and bowel disturbance and motor paralysis, shorter duration from initial symptoms to motor paralysis, and lower rate of independent gait, compared with cases with an intramedullary tumor location alone. In all IE cases, the intramedullary tumor had ruptured the pia mater of the spinal cord, progressed into the extramedullary area, occupied the whole of the spinal canal, and caused severe spinal canal stenosis. Thus, for IE tumors, the severity of damage to the spinal cord may be related to the size of the extramedullary tumor component. Mechanical compression of the spinal cord from the IE sides after onset of initial symptoms may increase damage to the spinal cord in a short time. Ozawa et al also suggested that the pia mater maintains the elastic force of the spinal cord.[16] Therefore, once the pia mater is ruptured and the elastic force is reduced, the spinal cord may
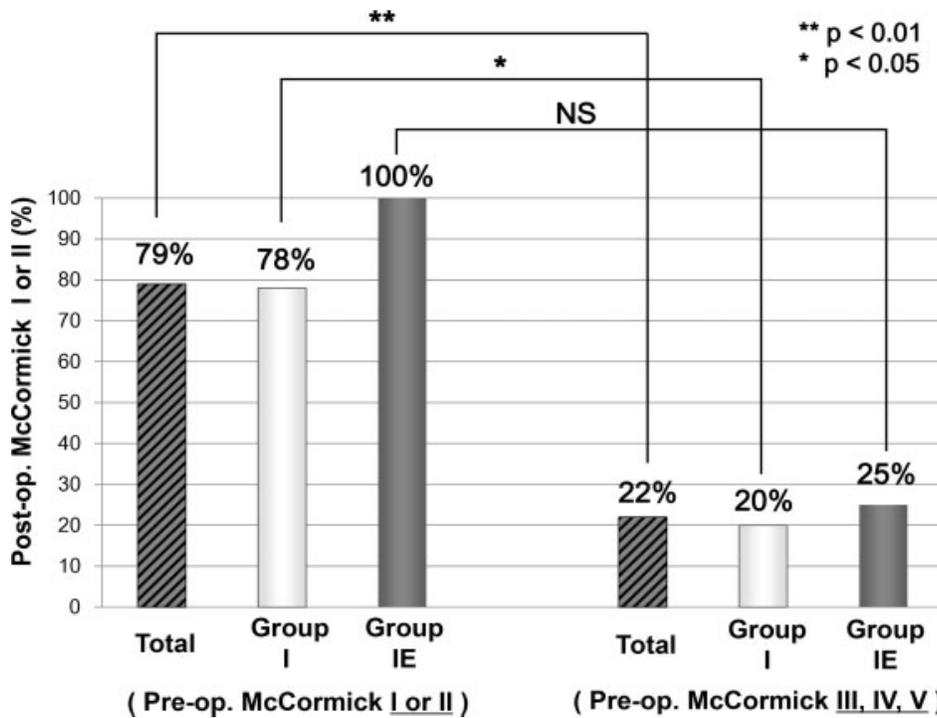
Fig. 3 Better preoperative ambulatory ability was significantly associated with good postoperative ambulation, with probabilities of achieving good postoperative results for patients in preoperative classes I and II of 79% in all patients, 78% in the intramedullary only group (group I), and 100% in the intramedullary plus extramedullary group (group IE). In contrast, improvement of postoperative independent ambulatory ability was difficult for cases with severe preoperative symptoms, with probabilities for patients in preoperative classes III, IV, and V of 22% in all patients, 20% in group I, and 25% in group IE.

weaken and become less able to resist mechanical compression by the tumor, with subsequent worsening of symptoms.

Interestingly, in pathologic findings, the Ki67 activity was less than 1% in all cases with an intramedullary tumor, but averaged 15% in IE cases in which the tumor progressed from the intramedullary to the extramedullary region. This result suggests that IE tumors have high cell proliferative activity and grow faster than an intramedullary tumor. Therefore, an IE tumor can be diagnosed using characteristic contrast MRI

Fig. 4 The percentage of cases with stable independent ambulation (McCormick classes I and II) postoperatively did not differ significantly between groups I and IE, although there was a significant difference preoperatively. Abbreviation: group I, intramedullary only; group IE, intramedullary plus extramedullary; NS, not significant.

findings,[6] and rapid aggravation of spinal cord impairment is possible, even if compression of the spinal cord and spinal cord–related symptoms are mild. It is unclear why IE cases have a more aggressive pathology. High Ki67 activity has only been reported in two previous reports, including one case of intradural-extramedullary hemangioblastoma, in which the reason for high proliferation was not described.[17] In an investigation of 25 cases of hemangioblastoma with VHL disease, Shively et al found Ki67 activities of <2% in the mesenchymal structure, 3 to 30% in the epithelioid structure, and 100% in red blood cell precursors of extramedullary hematopoiesis foci.[18] Thus, proliferative activity differed in the different stages of progression, and it was concluded that downstream hemangioblastoma differentiation is associated with increasing proliferative activity. All our IE cases were sporadic without VHL disease, but the same idea of increased proliferative activity with tumor progression may apply in sporadic IE tumors that have differentiated over a long time course and have a tendency to be found in older patients. Alternatively, intramedullary and IE hemangioblastomas may differ in proliferation activity because they are different original phenotypes of hemangioblastoma.

In this study, IE hemangioblastoma was mostly located at the conus (80%), which may account for the high rate of preoperative pain in IE tumors. Stromal cells in hemangioblastoma are derived from the vascular stroma of the pia-arachnoid region, and exophytic growth may occur at any level of the spinal cord. Previous reviews have described hemangioblastoma in the thoracic spinal cord, but the detailed level of the tumor location has been unclear.[1]
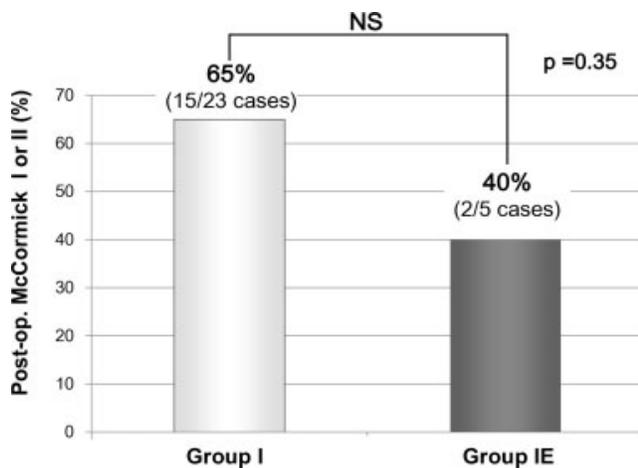
Corr et al reported an IE hemangioblastoma at T7.[19] In a study of intramedullary spinal cord tumors, Ishikawa et al described 22 spinal intramedullary tumors, and exophytic growth was seen in only 5 cases, including 2 astrocytomas and 1 case each of mixed glioma, ependymoma, and hemangioblastoma.[20] The most common site was the conus (3 of the 5 cases). Collection of more cases is clearly required to define the common location of IE hemangioblastoma. However, we speculate that frequent exophytic growth may be anatomically related to thin white matter at the conus and associated with gradient spinal cerebrospinal fluid velocity or pressure impact in this region.[21] The current study also suggests that the wide subarachnoid space at the conus may allow massive exophytic growth with severe spinal cord symptoms at the first hospital visit.

Early surgery is recommended for intramedullary spinal hemangioblastoma based on the finding of an association of better preoperative ambulatory ability with better postoperative ambulatory ability, which is consistent with results from our previous study. Additionally, the current study indicated that this strategy should be applied to both I and IE tumors. Earlier surgical intervention in IE tumors resulted in all cases having improved postoperative ambulatory ability; however, the rate of postoperative independent gait ability was only 60% because of preoperative severe spinal cord damage. Thus, further improvement of surgical results for IE tumors requires tumor resection as soon as possible after diagnosis.

Total surgical resection of spinal hemangioblastoma is required because all cases in which total resection was not achieved showed postoperative tumor enlargement and intramedullary syrinxes or edema, with worsening of symptoms, and all required reoperation for total tumor resection. Worsening of symptoms caused by a residual tumor is probably inevitable in this tumor, and total tumor resection is especially essential for IE tumors with the high cell proliferative activity.

Intraoperative spinal cord monitoring caused significant aggravation in IE cases, which may be because of the more severe preoperative spinal cord damage from the intra- and extramedullary directions in IE tumors. However, although IE cases had significantly more severe motor paralysis and poor ambulatory ability, all these cases had improved ambulatory status after total tumor resection and without reoperation. Surgery was suspended based on spinal cord monitoring aggravation. Thus, these findings suggest the need for prudent surgical procedures and suspension based on intraoperative spinal cord monitoring (CMAP) for IE hemangioblastoma. Because total tumor resection is required for hemangioblastoma, the cases with severe preoperative symptoms, including paralysis, should be especially carefully monitored during surgery. The recent use of multimodal monitoring combining SSEP, CMAP, and D-wave may avoid missing subtle spinal disorders during surgery.[14,22,23] We also recommend the use of multimodal monitoring in surgery for intramedullary tumors.

The small number of cases is a limitation of this study, which is unavoidable given the rarity of intramedullary spinal cord hemangioblastoma and the even more uncommon IE location. Accumulation of more cases is needed, including comparative data with cases with nonsurgical treatment. However, this study provides useful data on symptom aggravation, surgical outcome, and pathologic cell proliferative activity for spinal hemangioblastomas in different locations.

Conclusion

Patients with IE spinal hemangioblastoma have rapid preoperative progression of symptoms over a short period, severe spinal cord damage including preoperative motor paralysis, and poor gait ability compared with those with an intramedullary tumor only. IE tumors tended to occur in the conus region and caused preoperative pain. Total resection of the tumor is required in surgery for spinal hemangioblastoma to avoid the need for reoperation. Intraoperative spinal cord monitoring is required for total resection and a good surgical outcome, particularly for an IE tumor. These results and the high cell proliferative activity in IE tumors found in this study suggest that earlier surgery is particularly important for these tumors.

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