

Intramedullary Medullocervical Ependymoma—Surgical Treatment, Functional Recovery, and Long-Term Outcome

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Abstract

To evaluate the long-term outcome and functional recovery of intramedullary medullocervical ependymoma (IME), the clinical charts of 38 surgically treated consecutive cases of IME were reviewed. Follow-up was obtained prospectively. The mean age of the patients (19 male and 19 female) was 35.3 years (range: 11–60 years). Complete resection was achieved in 33 (86.8%) patients. Fourteen patients worsened postoperatively; five and seven of these improved to their baseline levels within 1 and 3 months, respectively. By 1 year postoperatively, 17 patients returned to work. After a mean follow-up duration of 81.5 months, 31 patients improved or stabilized, and 3 had recurrence. The means of the modified McCormick grade (mMG) scores before the operation, at discharge, 1 year after the operation, and at the most recent evaluation were 1.76, 2.13, 1.82, and 1.84, respectively. A favorable long-term outcome of the mMG was associated with a good preoperative status (mMG I) (odds ratio [OR] = 9.956, $p = 0.008$) and well-defined tumor boundary (OR = 7.829, $p = 0.035$). Improvements in the postoperative walking dysfunction and paresthesia over time were associated with the absence of preoperative walking dysfunction ($p = 0.047$) and paresthesia ($p = 0.028$), respectively. The 12-year progression/recurrence-free survival and overall survival rates were 92.0% and 93.7%, respectively. The study suggests that the goal of surgery is to stabilize the preoperative neurological function and that a favorable outcome may be achieved in patients with good preoperative statuses and well-defined tumor boundaries. Surgery should be performed as soon as possible after the diagnoses and before the neurological functions deteriorate.

Key words: cervical cord, ependymoma, intramedullary, medulla oblongata, outcome

Introduction

Ependymomas are an uncommon group of central nervous system (CNS) neuroectodermal neoplasms constituting 2–8% of all primary CNS tumors, 30–60% of spinal cord gliomas, and up to 12% of pediatric brain tumors.^{13,15,29,30,33} A considerable number of retrospective studies on intramedullary spinal ependymomas have been reported in the last decade,^{1,5,8,12–14,16,20,22,23,26} confirming the existence of various predictors of the disease, including histology,²² preoperative neurological function,⁴ and surgical resection.⁵ Nevertheless, few of these were performed on patients harboring an intramedullary medullocervical ependymoma (IME). Additionally, many series had a long recruitment period with limited follow-up. Due to the location of the

tumor, IME results in neurological dysfunction (e.g., quadriplegia, respiration disorders, and dysphagia) that impairs the patient's quality of life.³⁶ Additionally, the high potential risk of operation and lack of accepted and recognized prognostic factors for IME have led to the absence of a standardized therapeutic strategy.^{12,19,35} Therefore, the following are of significant value to elucidate: the pertinent prognostic factors, neurological function recovery, and long-term outcome. Here, we review our 2000–2010 institutional experience with 38 cases of IME.

Materials and Methods

Patient population

A retrospective medical record review of 38 patients (19 male and 19 female; mean and median ages, 35.3 ± 11.5 and 35.5 years, respectively; range, 11–60

years) with IME who underwent surgery between January 2000 and January 2010 at the Beijing Tiantan Hospital, Capital Medical University, was conducted.

The clinical data included the patient gender,

age at surgery, symptoms, duration of symptoms, modified McCormick grade (mMG) (measured at the initial diagnosis, in the preoperative time period, at discharge after the operation, 1 year after the operation,

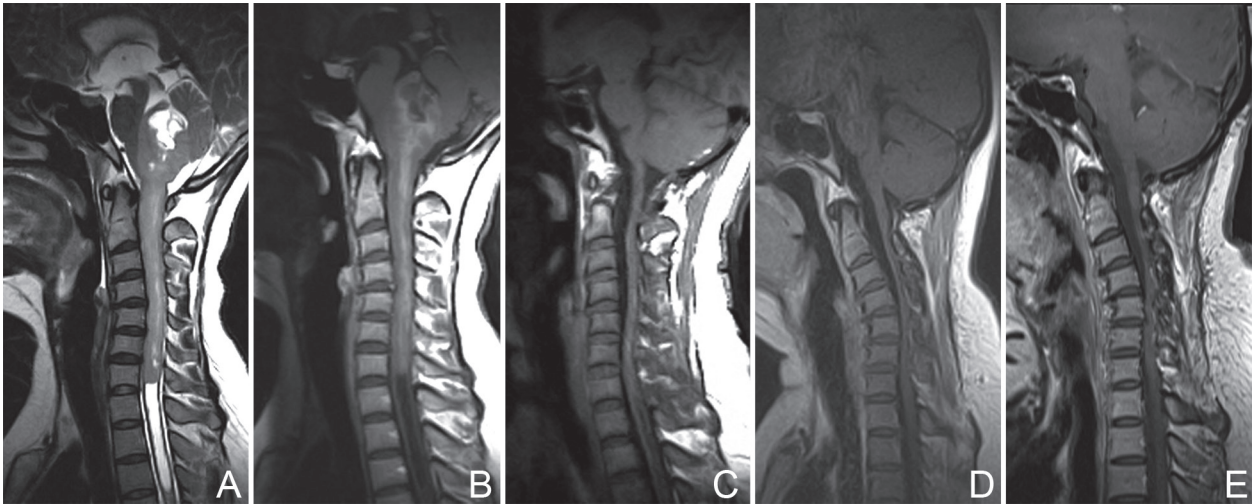


Fig. 1 Patient No. 18. Preoperative T₂-weighted MRI (A) and T₁-weighted imaging with contrast enhancement (B) showing regions with tumor involvement (from medulla oblongata rostrally to seventh cervical vertebra caudally) and a well-defined tumor boundary. Postoperative MRI scans with contrast enhancement at 1 week (C), 3 years (D), and 5 years (E), illustrating total removal of the lesion (C) and no recurrence (D, E). After a period of 80 months of follow-up, the patient improved from a preoperative mMG III to mMG II. mMG: modified McCormick grade, MRI: magnetic resonance imaging.

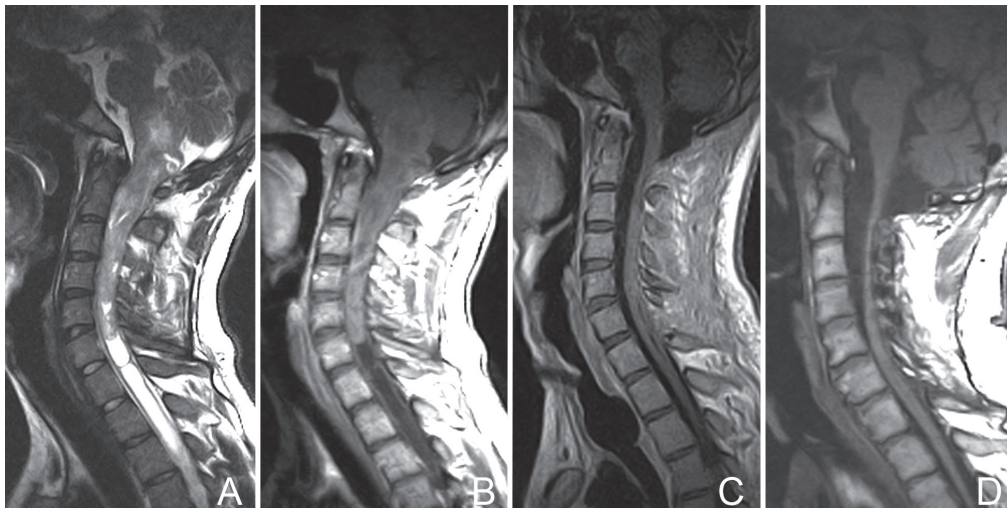


Fig. 2 Patient No. 35. Preoperative T₂-weighted MRI (A) and T₁-weighted imaging with contrast enhancement (B), showing significant deformation of the medulla oblongata and fourth ventricle, and an ill-defined tumor boundary. Postoperative MRI scans with contrast enhancement at 1 week (C) and 2 years (D), demonstrating complete resection of the lesion (C) and mild myelatrophy without recurrence (D). At 46 months postoperatively, the patient improved in neurological function with an mMG of II. mMG: modified McCormick grade, MRI: magnetic resonance imaging.

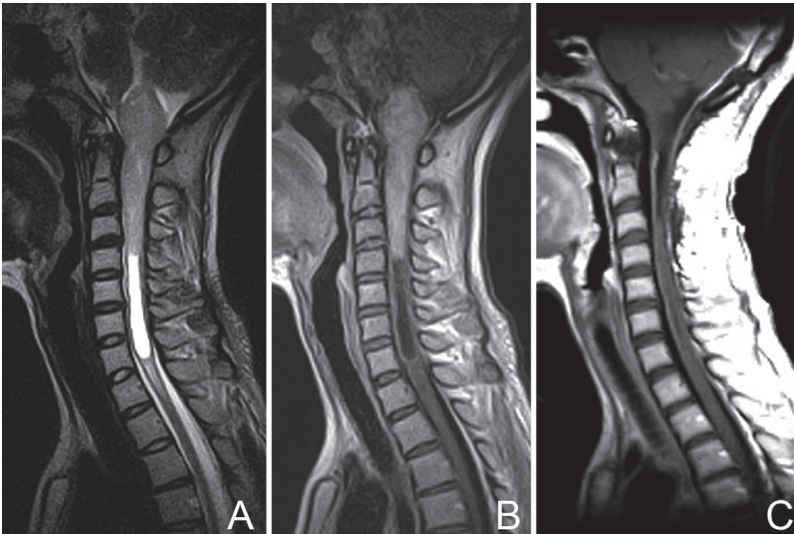


Fig. 3 Patient No. 9. Preoperative T₂-weighted MRI (A) with a well-defined tumor boundary and T₁-weighted imaging with contrast enhancement (B). Postoperative MRI scans with contrast enhancement at 1 week (C) showing total removal of the tumor. MRI: magnetic resonance imaging.

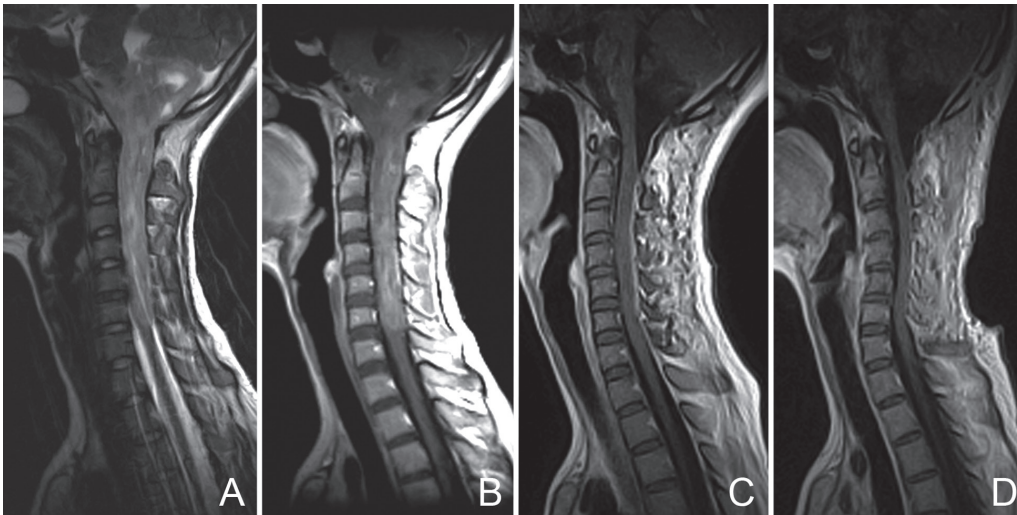


Fig. 4 Patient No. 10. Preoperative T₂-weighted MRI (A) with an ill-defined tumor boundary and T₁-weighted imaging with contrast enhancement (B) illustrating mild to moderate inhomogeneous enhancement. Postoperative MRI scans with contrast enhancement at 1 week (C) and 6 months (D) showing total resection. MRI: magnetic resonance imaging.

and most recent follow-up), tumor features (volume, length, boundary, and localization) (Figs. 1–4), radiotherapy if received, World Health Organization (WHO) classification of the ependymoma (Grade II and Grade III), postoperative complications, follow-up time, and treatment for recurrent patients. Two independent neuropathologists conducted the pathologic examinations. The follow-up was obtained prospectively in clinic or by questionnaire.

Definition of IME

Intramedullary ependymoma, involving both the medulla oblongata rostrally and cervical spinal cord caudally with a varied number of spinal levels involved, was defined as IME, while exophytic,

extramedullary, or posterior fossa/IVth ventricular ependymomas were not included. When an IME involved the medulla oblongata and only the first cervical spinal cord, the tumor location was labeled Medulla-C1.

Neurological evaluation

The patients' neurological statuses were evaluated using the mMG (Grade I, neurologically normal or with mild neurological deficits; Grade II, sensorimotor deficit affecting the function of the corresponding limb; Grade III, more severe neurological deficits, brace required; Grade IV, severe deficit, wheelchair required; Grade V, death from the disease).^{5,27)}

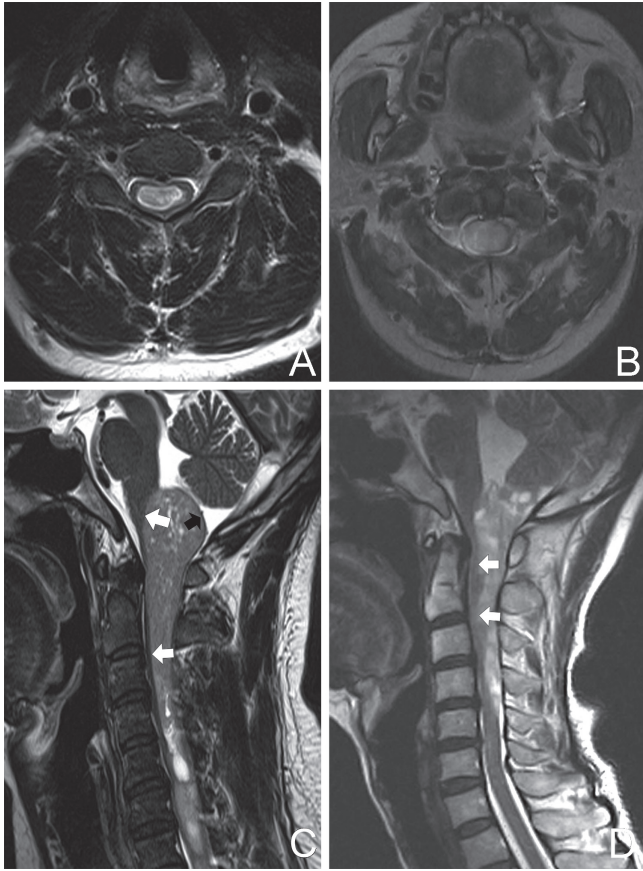


Fig. 5 Preoperative MRI scans illustrating the existence (A) or absence (B) of a subarachnoid space between the tumor and parenchyma. An isointense ring (thin-slice parenchyma) surrounding dorsal surface of the tumor (black arrow) (C) indicated an intramedullary tumor and contour line of the ventral surface of the tumor (white arrow) (C) was smooth; this tumor had a well-defined boundary even though it lacked an identifiable subarachnoid space. The contour line (white arrow) (D) was obscure and the boundary was determined to be ill defined. MRI: magnetic resonance imaging.

Radiological evaluation

In all patients, magnetic resonance imaging (MRI) scans with contrast enhancement were evaluated preoperatively, at discharge, 3 and 6 months after operation, and every 1 or 2 years thereafter. Post-operative MRI with contrast enhancement was used to evaluate the extent of surgical resection.

The definition of the tumor boundary was based only on T₂-weighted MRI scans (Fig. 5). A well-defined boundary either (A) had a clearly identifiable subarachnoid space between the tumor and healthy spinal cord or (B) lacked an identifiable subarachnoid space but the contour line between the tumor and healthy spine was smooth (Fig. 5C),

which corresponded to intraoperative findings; there was also a clearly identifiable transition between the tumor and the normal parenchyma. An ill-defined boundary was a boundary that lacked an identifiable subarachnoid space and for which the contour line was obscure. When most of the boundary was ill defined, even if some parts were well defined, the tumor boundary was determined to be ill defined.

Tumors consisted of two independent parts, the posterior fossa part and spinal parts. The tumor volume was calculated as the sum of the two parts by the Coniglobus formula, which was described by the following: $V_{\text{tumor}} = (D_1 \times D_2 \times D_3)/2$, where D_1 , D_2 , and D_3 were the maximal diameters in the axial, sagittal, and coronal T₁-weighted MRI scans, respectively, with administration of gadolinium.

Surgical technique

For all patients, a standard midline incision was made, and suboccipital midline approach and laminoplasty were performed to avoid future spinal instability. Intraoperative monitoring of evoked potentials, including spinal cord somatosensory evoked potentials (SEPs), motor-evoked potentials, and brainstem auditory evoked potential (BAEP), was adopted to prevent neurosurgical functional impairment. During the operation, needle electrodes were used to record the BAEPs. If the monitor showed intraoperative abnormalities in Waves I, III, or V, such as the prolongation of the latency by 10%, an amplitude that decreased by 50%, or significant changes in the form of the Wave, the surgeon stopped, corrected the dangerous manoeuvres, identified the tumor boundary, and reduced the brainstem retraction. The spinal midline was identified as precisely as possible before the myelotomy was performed to reduce neurological deficits; in our series, this was performed with consideration of the anatomic landmarks of the posterior spinal arteries on the normal spinal cord rostral and caudal to the lesion. Additionally, intraoperative ultrasonography and dorsal cord mapping were used in 5 (13.2%) and 4 (10.5%) patients, respectively, because anatomic landmarks had shifted due to severe deformation of the spinal cord from a significant space-occupying effect. The strip electrode for dorsal cord mapping was a multielectrode grid containing eight parallel Teflon-coated steel wires that were spaced 1 mm apart. Peripheral electrodes were placed at the bilateral tibial, ulnar, or median nerves. The grid was placed on the dorsal column surface. After stimulating one of the bilateral peripheral nerves, the multielectrode grid recorded the conducted SEPs from the dorsal surface overlying the lesion. The amplitude corresponded to the topographic

anatomy of the dorsal cord. The maximum amplitude indicated a dense aggregation of the dorsal column fibres. The midline was located between the two maximum amplitudes.

Statistical analysis

We used the “mean \pm standard deviation” to describe all measurement data. Logistic regression analysis (IBM SPSS Statistical Package v. 19.0) was performed to evaluate the effects of the age, gender, duration of the symptom, preoperative mMG (I or II–IV), tumor boundary (well or ill defined) (Fig. 5), and tumor location (number of spinal levels with tumor involvement) on the most recent mMG. The incidences of the postoperative neurological function improvement (walking function, motor weakness, and paresthesia), tumor progression/recurrence (P/R), and overall survival as a function of time postoperatively were analyzed with Kaplan–Meier method.¹⁴⁾ A *p* value < 0.05 was considered significant.

Results

Preoperative findings

The average duration of a symptom was 20.1 ± 32.3 months (range: 1–144 months). On admission, all patients presented with neurological deficits of variable severity. Pain was nonspecific in 22 (57.9%) patients and was primarily localized in the neck or head (90.9%) and shoulder (9.1%). Paresthesia, motor weakness, and walking deficits occurred in 21 (55.3%), 12 (31.6%), and 12 (31.6%) patients, respectively. Other symptoms included bladder dysfunction (*n* = 11, 28.9%), headache (*n* = 10, 26.3%), dizziness (*n* = 6, 15.8%), vomiting (*n* = 4, 10.5%), ataxia (*n* = 3, 7.9%), nausea (*n* = 3), involuntary neck movement (*n* = 2, 5.3%), and cranial nerve (CN) deficits (CN XII, *n* = 4; CNs IX–XI, *n* = 10; CN VIII, *n* = 3; CN VII, *n* = 2; and CN VI, *n* = 2). One patient (2.6%) was diagnosed as neurofibromatosis Type 2. The means of the tumor length (range: 1.5–20 cm) and tumor volume (range: 1.5–62.5 cm³) were 5.9 ± 3.6 cm and 19.4 ± 15.0 cm³, respectively. The tumor was involved in a mean of 3.5 ± 1.8 levels (range: 2–8 levels). A well-defined tumor boundary was observed in 24 (63.2%) patients and the remaining patients (14, 36.8%) had ill-defined tumor boundaries.

Four patients (10.5%) rejected operation after considering the surgical risks at the initial diagnosis when the mMG was recorded as an initial mMG (mMG I, *n* = 2; mMG II, *n* = 2). All four patients were followed up closely, and they unfortunately experienced neurological function deterioration;

as a consequence, the mMG declined from I to II in two patients and from II to III in the other two patients during a mean observation period of 25 ± 7.4 months (range: 18–34 months) preoperatively. After their neurological statuses were sufficiently aggravated, the four patients were retransferred to our hospital and decided to accept surgical treatment. The remaining 34 (89.5%) patients accepted the operations that we recommended to them at the first clinical consultation in our hospital, as their initial mMGs were similar to their preoperative mMGs (Table 1). Two patients (5.3%) had a previous operation before being admitted to our hospital. The preoperative mMGs were as follows: Grade I, *n* = 18; Grade II, *n* = 11; and Grade III, *n* = 9; the mean and median of the grade were 1.8 ± 0.8 and 2, respectively.

Surgery and morbidity

Overall, gross total resection (GTR) was achieved in 33 (86.8%) patients, and there was subtotal resection (STR) in 5 (13.2%) patients without surgical mortality. The reasons for GTR failure were an ill-defined tumor boundary (*n* = 4) and the loss of SEPs in the right upper extremity (*n* = 1). Overall, histological examination revealed a benign ependymoma (WHO Grade II) in 35 (92.1%) patients and an anaplastic ependymoma (WHO Grade III) in 3 (7.9%) patients (Cases 7, 29, and 33). Surgical morbidity occurred in 16 patients (42.1%), including respiratory difficulty (*n* = 9, 23.7%), lower CN function impairment (new onset [*n* = 2, 5.3%]; worsening of preexisting impairment [*n* = 3, 7.9%]), cerebrospinal fluid leakage (*n* = 2, 5.3%), intracranial infection (*n* = 2, 5.3%), pneumonia (*n* = 1, 2.6%), development of a stress ulcer (*n* = 1, 2.6%), and hydrocephalus (*n* = 1, 2.6%). Tracheostomy was performed to prevent suffocation or respiratory failure in 11 (28.9%) patients due to respiratory difficulty (*n* = 8) and severe lower CN deficiencies (*n* = 3). Five of the eight patients required ventilator assistance for 16.4 ± 14.8 days (range: 5–41 days) due to severe respiratory dysfunction, and of all the patients improved and could breathe independently before discharge. The tracheostomies were closed at 42.4 ± 34.1 days (range: 18–138 days) after surgery. We recommended radiotherapy to patients with STR. Three of the five STR cases and one patient with anaplastic ependymoma underwent postoperative adjuvant radiotherapy (gamma knife, *n* = 1; linear accelerator, *n* = 3) immediately after discharge from the hospital.

Short-term outcomes

Compared to the preoperative mMG, the mMG at

Table 1 Clinical data of the 38 cases of intramedullary medullocervical ependymoma

No.	Age (years)	Sex	Tumor location	Chief complaints at admission	Tumor border	DS (months)	mMG			Surgical removal	Main surgical complication	FUP (months)	P/R	Recent status
							Initial	Pre-	Post-1 year					
1	24	F	Medulla-C1	Motor weakness, leg	WD	3	II	III	II	TR		141	No	AWD
2	40	F	Medulla-C1	Paraparesis	WD	6	III	III	II	TR	Dysphagia	139	No	NED
3	36	M	Medulla-C1	Pain, neck	WD	2	I	I	I	TR		138	No	AWD
4	36	M	Medulla-C4	Paresthesia, hands and legs	WD	144	II	IV	IV	TR	Respiratory deficit	133	No	AWD
5	40	M	Medulla-C2	Paresthesia, hands and legs	WD	24	I	I	I	TR		131	No	NED
6	33	F	Medulla-C4	Paresthesia, hand	WD	12	II	III	III	TR		130	No	AWD
7	32	F	Medulla-C2	Pain, neck	WD	18	I	I	I	TR		122	No	AWD
8	36	F	Medulla-C1	Pain, neck	WD	3	I	I	I	TR	Intracranial infection	116	No	NED
9	24	F	Medulla-C4	Paresthesia, hand	WD	18	I	I	I	TR		115	No	AWD
10	35	M	Medulla-C6	Paresthesia, hand and leg	ID	36	II	IV	III	TR	Respiratory deficit	114	No	AWD
11	33	M	Medulla-C3	Paraparesis	ID	1	III	IV	III	STR	Intracranial infection	114	No	AWD
12	32	M	Medulla-C3	Paresthesia, hands and legs	WD	2	I	I	I	TR		105	No	AWD
13	11	M	Medulla-C5	Motor weakness, hand and leg	WD	18	III	III	III	TR	Respiratory deficit	97	No	AWD
14	60	M	Medulla-C1	Pain, neck	ID	6	I	II	II	TR	CSF leak	95	No	AWD
15	20	M	Medulla-C1	Motor weakness, hand and leg	ID	3	II	I	I	TR		95	No	NED
16	35	F	Medulla-C2	Pain, neck	WD	1	I	I	I	TR		82	No	AWD
17	18	F	Medulla-C1	Pain, hand	WD	132	I	III	II	TR	Dysphagia	51	Yes	DOD
18	36	F	Medulla-C7	Paresthesia, hand and leg	WD	24	III	IV	III	TR	Dysphagia	80	No	AWD
19	26	M	Medulla-C1	Paraparesis	WD	12	I	III	II	TR	Respiratory deficit	45	Yes	DOD
20	42	M	Medulla-C1	Pain, neck	ID	6	II	III	III	TR	Dysphagia	78	No	AWD
21	14	M	Medulla-C1	Motor weakness, leg	ID	12	II	I	I	TR		75	No	NED
22	29	F	Medulla-C2	Paresthesia, hands	ID	48	III	III	II	STR	Respiratory deficit	75	No	AWD
23	39	F	Medulla-C2	Pain, neck	WD	12	I	I	I	TR		71	No	AWD
24	38	M	Medulla-C3	Tetraparesis	ID	7	III	IV	III	TR	CSF leak	61	No	AWD
25	25	F	Medulla-C2	Paresthesia, hand	WD	1	I	II	I	TR		60	No	AWD
26	28	F	Medulla-C4	Paresthesia, hands and legs	ID	3	II	II	II	STR		59	No	AWD
27	46	F	Medulla-C2	Tetraparesis	WD	14	I	III	I	TR		56	No	NED
28	46	M	Medulla-C4	Motor weakness, hand and leg	WD	84	I	III	II	STR		53	No	AWD
29	58	F	Medulla-C1	Paraparesis	WD	18	I	II	I	TR		53	No	NED
30	41	F	Medulla-C6	Tetraparesis	WD	12	II	III	I	TR		50	No	AWD
31	29	M	Medulla-C1	Pain, neck	WD	2	I	I	I	TR	Respiratory deficit	48	No	NED
32	57	M	Medulla-C1	Paraparesis	ID	3	I	III	II	TR	Respiratory deficit	47	No	AWD
33	30	F	Medulla-C1	Pain, neck	WD	6	I	I	I	TR		48	No	NED
34	43	M	Medulla-C3	Paresthesia, hands	ID	9	I	III	II	TR		48	Yes	AWD
35	24	M	Medulla-C6	Tetraparesis	ID	12	III	IV	II	TR	Respiratory deficit	46	No	AWD
36	45	F	Medulla-C1	Paresthesia, legs	WD	7	I	II	I	TR		45	No	AWD
37	44	F	Medulla-C3	Paresthesia, hands and legs	ID	36	II	II	II	TR		42	No	AWD
38	55	M	Medulla-C1	Paresthesia, hand and leg	ID	6	II	II	II	STR		42	No	AWD

AWD: alive with deficit; DOD: die of disease; DS: duration of symptoms; FUP: follow-up period; ID: ill defined; mMG: modified McCormick grade; NED: no evidence of deficit; P/R: progression/recurrence; Pre-: preoperative; Post-: postoperative at discharge; STR: subtotal resection; TR: total resection; WD: well defined.

Table 2 Transition of the postoperative mMG categorized based on the preoperative mMG

Preoperative mMG	At discharge				1 year				Recent					Total	
	I	II	III	IV	I	II	III	IV	I	II	III	IV	V		
I	13	3	2		14	3	1		14	3				1	18
II	2	6	3		3	7	1		3	6	1			1	11
III			3	6		2	5	2	1	4	3	1			9
Total	15	9	8	6	17	12	7	2	18	13	4	1	2	38	

mMG: modified McCormick grade.

Table 3 Transition of the postoperative neurological symptoms categorized using the preoperative neurological symptoms

Preoperative	At discharge			1 year			Recent			Total
	Wor	Un	Im	Wor	Un	Im	Wor	Un	Im	
Paresthesia	11	8	2	5	4	12	2	5	14	21
No paresthesia	11	6		4	13		3	14		17
Motor weakness	2	7	3	2	2	8		2	10	12
Full strength	13	13		8	18		6	20		26
Walking deficit	4	5	3	2	4	6	2	2	8	12
Normal gait	5	21		3	23		1	25		26

Im: improve, Un: unchange, Wor: worsen.

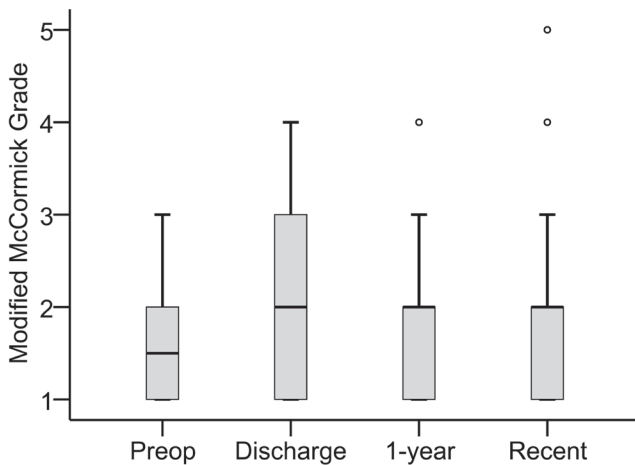


Fig. 6 Average preoperative, postoperative, and follow-up mMGs showing an increase in the score immediately after surgery, a return to the preoperative levels by 1 year after surgery, and a stabilized score at the most recent follow-up evaluation compared to that of 1 year after surgery. Circles indicate outliers. mMG: modified McCormick grade.

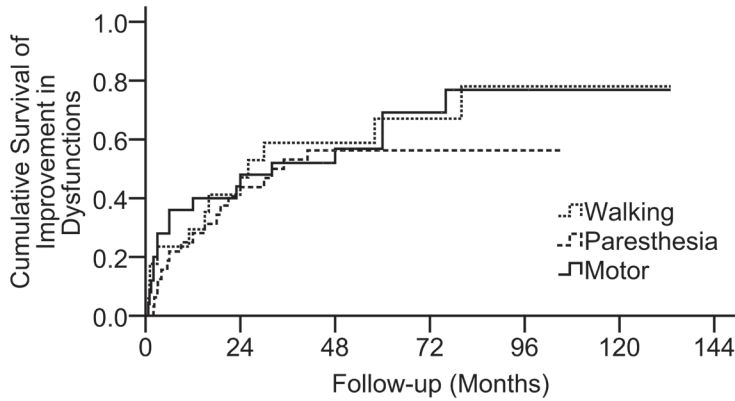
discharge improved in t patients (5.3%), stabilized in 22 (57.9%), and worsened in 14 (36.8%), including 6 of the 9 patients for whom the preoperative mMG

was III and 8 of the 29 preoperative mMG I and II cases (Table 2). The worsening of the mMG at discharge was related to a poor preoperative mMG (odds ratio [OR], 5.250; 95% confidence interval [CI], 1.052–26.197; p = 0.044). The mean of the mMG was 2.1 ± 1.1, which was significantly worse than the preoperative mMG (t = -3.366, p = 0.002) (Fig. 6). Changes in paresthesia, motor weakness, and walking deficits are described in Table 3. New onset of paresthesia, motor weakness, and walking deficits occurred in 11 (28.9%), 13 (34.2%), and 5 (13.2%) patients, respectively. In 14 patients with perioperative neurological decline, 5 (35.7%) and 7 (50%) patients improved to their baseline within 1 and 3 months, respectively.

At 1 year postoperatively, the mMG scores (mean, 1.8 ± 0.9), which improved in 5 (13.2%) patients, stabilized in 26 (68.4%), and worsened in 7 (18.4%), were similar to the preoperative mMGs (t = -0.572, p = 0.571). Seven (53.1%) of the 32 patients with postoperative paresthesia, 10 (40%) of 25 with postoperative motor weakness, and 5 (35.7%) of 14 with postoperative walking deficits improved by various degrees (Table 3). By 1 year postoperatively, 17 (44.7%) patients had a full- or part-time job.

Long-term outcomes

At the final assessment, 3 (7.9%) patients relapsed



Percent Improved (%)

Walking	47.1	58.8	67.1	78.0	78.0
Paresthesia	43.7	56.2	56.2	56.2	NA
Motor	48.0	56.8	69.1	76.9	76.9

Fig. 7 Kaplan–Meier plots illustrating the incidence of the postoperative walking, sensory, and motor function improvement as a function of time. By 96 months postoperatively, 78.0% of patients with postoperative walking deficit symptoms had improvement in these symptoms (to normal gait), 56.2% with postoperative paresthesia had improved (to minimal or none), and 76.9% with postoperative motor weakness had improved to full or near-full strength. These dysfunctions improved at similar rates. The vertical axis is indicated as percentage.

according to MRI scans after a mean recurrence-free period of 32.7 months, among whom 2 (5.3%) died of recurrence without treatment and 1 patient underwent total resection and obtained a good outcome. Thirty-six patients were still alive after a mean follow-up duration of 81.5 ± 33.7 months (range: 41.6–140.8 months). Compression of the spinal cord by misplaced or mobile lamina of the vertebral arch did not occur after laminoplasty in any of the patients. The improvements in the symptoms observed at the end of the follow-up are detailed in Table 3. By 96 months postoperatively, in patients with postoperative paresthesia, motor, or walking dysfunction, paresthesia symptoms improved to minimal or none in 56.2%, motor weakness improved to full or near-full strength in 76.9%, and walking deficits improved to normal gait in 78.0% (Fig. 7). Improvement in postoperative paresthesia (Fig. 8A) and walking dysfunction (Fig. 8B) over time were associated with the absence of preoperative paresthesia (log rank = 4.826, $p = 0.028$) and walking deficits (log rank = 3.961, $p = 0.047$), respectively.

The most recent mMG scores (mean, 1.8 ± 1.1) were as follows: Grade I, $n = 18$; Grade II, $n = 13$; Grade III, $n = 4$; Grade IV, $n = 1$; and Grade V, $n = 2$, which were similar to the preoperative mMGs ($t = -0.464$, $p = 0.646$), indicating that the main effect of operation was to stabilize the preoperative neurological function. In a comparison between the preoperative and most recent mMGs, 8 (21.1%) patients improved, 23 (60.5%) were stable, and 7 (18.4%) worsened, including 2 (5.3%) deaths. On the whole, 32 (84.2%) patients lived independently, and among them, 14 (36.8%) patients were able to

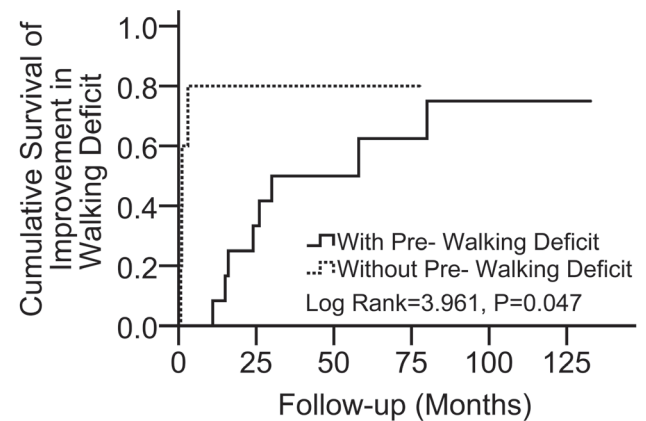
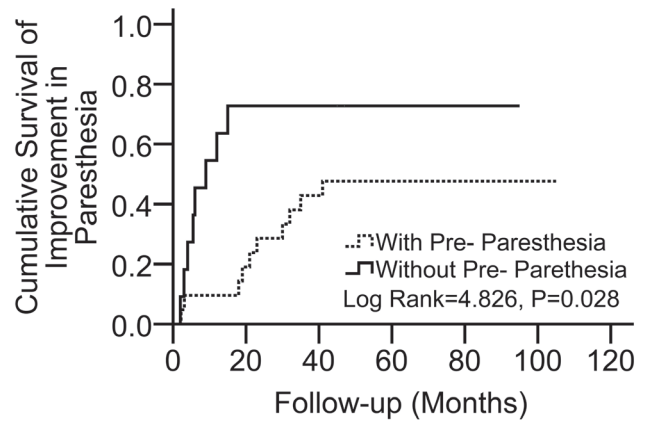


Fig. 8 Kaplan–Meier plots demonstrating the incidence of postoperative paresthesia (A) and walking deficit (B) improvement over time, based on the presence or absence of preoperative paresthesia and walking dysfunction, respectively. The absence of preoperative paresthesia and walking dysfunction was associated with favorable long-term improvement in paresthesia (to minimal or none) and walking dysfunction (to normal gait), respectively. The vertical axis is indicated as percentage.

Table 4 Favorable prognostic factors for intramedullary medullocervical ependymoma

Variables		Recent mMG		Multivariate logistic regression		
		I	II–V	OR	95% CI	p
Gender	Male	6	13			0.269
	Female	12	7			
Age, years	≥ 35	10	11			0.858
	< 35	8	9			
Duration of symptoms, months	≥ 18	4	8			0.164
	< 18	14	12			
Preop mMG	II–IV	4	16	Ref		0.008
	I	14	4	9.956	1.846–53.690	
Tumor boundary	Ill defined	2	12	Ref		0.035
	Well defined	16	8	7.829	1.155–53.088	
Tumour localization, levels	4–8	3	12			0.097
	2–3	15	8			

CI: confidence interval, mMG: modified McCormick grade, OR: odds ratio, Ref: reference.

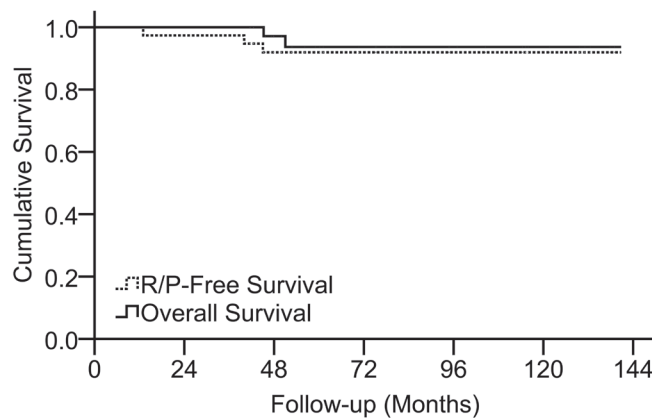


Fig. 9 Kaplan–Meier survival analysis illustrating the long-term recurrence-free survival rate and overall survival rate in the series. The vertical axis units are indicated as percentages.

Cumulative Survival (%)	0	24	48	72	96	120	144
R/P-Free Survival	100	97.4	92.0	92.0	92.0	92.0	92.0
Overall Survival	100	100	97.1	93.7	93.7	93.7	93.7

carry out normal activity with or without minor signs of disease, 12 (31.6%) patients could carry out normal activity with effort and some signs or symptoms of disease, and 6 (15.8%) patients could care for themselves without assistance (Table 2). A favorable long-term neurological function outcome was associated with the preoperative status (mMG I) (OR, 9.956; 95% CI, 1.846–53.690; p = 0.008) and a well-defined tumor boundary (OR, 7.829; 95% CI, 1.155–53.088; p = 0.035) (Table 4). The P/R-free survival rate was 97.4% at 3 years and 92.0% at 5, 10, and 12 years. The overall survival rate was 100% at 3 years and 93.7% at 5, 10, and 12 years

(Fig. 9).

Additional statistical analysis

Due to the small number of patients with STR, lesions of WHO grade III, and postoperative radiotherapy, analyses of the effect of histopathology, surgical resection, or radiotherapy on the long-term outcome were not performed. The association between the long-term neurological outcomes and improvement of the postoperative symptoms (paresthesia, motor weakness, and walking deficits) with the following variables was not independently significant (p > 0.05): age, gender, duration of symptoms, and

tumor location (number of involved spinal levels).

Discussion

The main focus of the present study was the neurological status outcome and incidence of functional improvement over time in 38 consecutive cases of IME resection performed over a 10-year period. The mMG²⁷⁾ includes four different levels to describe a patient's independence status. Although detailed neurological evaluation shows a slight improvement or deterioration in status during follow-up, the mMG on postoperative examination does not change accordingly,¹²⁾ especially in distinguishing "slight deficit" from "no evidence of disease." Thus, it is evident that the mMG does not sufficiently characterize the patient status. Therefore, in many studies, the mMG was modified according to the research design, and the grades were redefined^{12,23,26)} or a new grade was added to the evaluation system (e.g., mMG I was redefined as "no deficit"¹²⁾ or "neurologically normal"¹⁾). In our series, the final status was additionally evaluated as "alive with deficit" or "no evidence of deficit" to identify the status of patients with or without deficit who had a recent follow-up status of mMG I; the status of patients who died from the disease was defined as "Grade V, die from the disease" (Table 1).

Surgery

Most reports acknowledge that the extent of tumor removal was the most significant prognostic factor influencing the postoperative outcome, with minimal postoperative neurological deficits.^{2,5,8,13,14,18,22–27,29,30,33,35,37)} GTR was found to be superior to partial resection with radiation.^{14,30)} GTR at the time of initial surgery should be the primary goal in the removal of these lesions.²³⁾

One study found that the primary goal of the operation was to stabilize the state of illness,¹⁾ as reported by previous authors,^{12,14,26,32)} which did not significantly differ from our goal. Many surgeons suggest that surgery must be performed as soon as possible in patients with evolving neurological deficits or before the onset of deterioration.^{1,4,9–12,26,29,31)} The indications for surgery should be carefully discussed with patients who did not have any preoperative neurological deficits but who instead only have pain (mMG score I).¹⁾ In the earlier stages of disease, the tumor is deep within the spinal cord and cannot be identified from the appearance of the spinal cord. For this reason, early operation cannot avoid the risk of cord traction and manipulation,

leading to the inevitable impairment of the normal spinal cord. When the tumor has reached a medium volume and is closer to the posterior surface of spinal cord, the contour of the spinal cord may still be recognized; therefore, the risk of surgical damage to the surrounding functional cord (dorsal column function) is reduced.³⁵⁾ Further study of the natural history of intramedullary ependymoma is required to demonstrate the relationship between the tumor growth curve and the increasing severity of symptoms and to identify a critical point of accelerated deterioration of neurological function, which will provide valuable information for the surgical decision-making process.

In our series, four patients rejected operation primarily due to the surgical risk; unfortunately, all four patients showed neurological function deterioration, and after finally undergoing surgery, their neurological statuses were unable to return to their initial status. Postponing surgery may play a role in transforming asymptomatic patients into symptomatic ones due to the continuous tumor growth, which results in the worsening of symptoms. We suggest that surgery be performed as early as possible after diagnosis to help the patient before symptoms are aggravated, but careful consideration of surgery should be taken for patients who lack neurological deficits.^{12,34)}

Clinical outcomes

In the early postoperative course, 9–67% of patients experienced neurological status aggravation.^{12,14,16,26)} Evaluating the mMG at discharge, the improvement, stabilization, and deterioration rates were 5.3%, 57.9%, and 36.8% (14 patients), respectively. Five (35.7%) of the 14 patients improved to their baseline within 1 month, which was comparable to another series, and the recovery rate might benefit from aggressive postoperative rehabilitation and steroid treatment for postoperative edema.^{7,14,35)} Postoperative neurological decline was associated with a poor preoperative status, which indicates that reduced preoperative neurological function does not respond well to the operation perioperatively.

Postoperative symptoms (e.g., paresthesia, motor, or walking dysfunction) began to improve within 1 month with improvement continuing during the postoperative follow-up, which in part parallels the experience of other research groups.^{14,17,23)} At the most recent evaluation, the majority of the postoperative symptoms improved to a normal or near-normal level. The improvements in the postoperative paresthesia and walking deficits over time were associated with their absence as preoperative symptoms.^{26,34)} To minimize these dysfunctions, it is imperative to perform the myelotomy along the

midline, which we would identify from anatomic landmarks, ultrasonography, or dorsal cord mapping.

The clinical improvement was significant within the first 1 year and maintained during follow-up and at the final evaluation; compared to the preoperative status, 60.5%, 21.1%, and 18.4% of patients presented with stable, improved, and worsened mMGs, respectively, which was in accordance with previously published studies.^{12,14,23} Karikari et al.²² reported that 20% of patients improved, 69% remained the same, and 10.9% worsened. During the observation period, 7.9% of the tumors recurred and the P/R-free survival rate at 10 years was 92.0%. Others reported 48–75% P/R-free survival rate at 10 years, which was quite different from our results; this might be due to small number (three cases) of patients with WHO Grade III tumors in our series and the regrowth inhibition after devascularization of the residual tumors.^{3,16,28} Two of the three patients rejected surgery after P/R and died within 1 year, which decreased the overall survival rate from 100% at 3 years to 93.7% at 10 years.

Prognostic variables

Poor preoperative status is a significant predictor of poor outcomes.^{6,8,12,15,16,21,22,29} Patients with worse preoperative functional statuses had fewer opportunities for neurological improvement.⁹ Our study also indicated that a good preoperative status (mMG I) is a favorable predictor, as has been previously reported in other studies.^{16,26} Bansal et al.⁴ concluded that the preoperative neurological condition was the strongest predicting factor of the functional outcome beyond the histological differentiation of the intramedullary tumors. Furthermore, early diagnosis and operation have been suggested to be vital for positive outcomes.^{4,8} It has been postulated that once the normal plasticity of the spinal cord is impaired, surgery offers few advantages with regard to functional improvement. Additionally, operations and radiotherapy can increase impairment to the medulla and spine.

Tumor boundary has been considered a prognostic factor in previously published studies. The existence of a subarachnoid space guarantees safety in aggressive resection, en bloc resection, and the avoidance of a residual tumor.^{5,14} A multivariate regression analysis supported the significant effect of a well-defined boundary on favorable postoperative neurological function, and we found that an ill-defined boundary with tight adhesion between the lesion and normal tissue increases the difficulty of surgery, whereas a distinct boundary contributes to complete resection. An attempt at complete removal without a well-defined plane would inevitably lead

to relatively poor prognosis.

Limitations of the present study

The limitations of the present study are as follows: (1) this was a single-center study with a relatively small number of patients; (2) this was a nonrandomized trial lacking a control group and was unable to compare the outcomes between patients who did or did not undergo operation; and (3) the study included 38 cases that were limited to the histology of ependymoma and with the lesion location in the medullocervical regions alone. Because of the small number of patients, we did not analyze the effect of complete resection, histology, and postoperative radiotherapy on the outcomes.

Conclusions

The primary predictors of a good outcome after surgery are a good preoperative status and a well-defined tumor boundary. Patients lacking preoperative paresthesia or walking deficits have favorable functional improvement in these two symptoms postoperatively. Half of the patients with perioperative neurological decline improve to baseline within 3 months, and nearly half of all patients have a full- or part-time job within 1 year. Surgical risks depend on the tumor size and disease stage, and patients should be informed of these risks. The goal of surgery is to stabilize the preoperative neurological function. Operation is recommended for all patients with IME, including patients with minimal neurological signs, and should be performed as soon as possible once the diagnosis has been made and before neurological function further deteriorates.

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Conflicts of Interest Disclosure

The authors declare no conflict of interest. No work resembling the enclosed article has been published or is being submitted for publication elsewhere and this study has not been presented in any conference or seminar. We identify that no financial interests or

affiliations with institutions, organization, or companies are mentioned or have impacts on the views expressed in the article. Meanwhile, in the study, there is no reproducing pre-published information or material. The study was not an experimental study on animals or human subjects. The Beijing Tiantan Hospital Research Ethics Committee approved this study. It is neither a randomized controlled trial nor a systematic review nor meta-analysis.

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