Clinical Features of Recurrent Spinal Cord Tumors

Osahiko Tsuji, Narihito Nagoshi, Satoshi Suzuki, Yohei Takahashi, Satoshi Nori, Mitsuru Yagi, Morio Matsumoto, Masaya Nakamura and Kota Watanabe

Department of Orthopaedic Surgery, Keio University School of Medicine, Tokyo, Japan

Abstract:

Introduction: Only a few reports have described the clinical features of recurrent spinal cord tumors. This study aimed to report the recurrence rates (RRs), radiographic imaging, and pathological features of various histopathological recurrent spinal cord tumors using a large sample size.

Methods: This study adopted the retrospective observational study design using a single-center study setting. We retrospectively reviewed 818 consecutive individuals operated for spinal cord and cauda equina tumors between 2009 and 2018 in a university hospital. We first determined the number of surgeries and then the histopathology, duration to reoperation, number of surgeries, location, degree of tumor resection, and tumor configuration of the recurrent cases.

Results: A total of 99 patients (46 men and 53 women) who underwent multiple surgeries were identified. The mean duration between the primary and second surgeries was 94.8 months. A total of 74 patients underwent surgery twice, 18 patients thrice, and 7 patients 4 or more times. The recurrence sites were broadly distributed over the spine, with mainly intramedullary (47.5%) and dumbbell-shaped (31.3%) tumors. The RRs for each histopathology were as follows: schwannoma, 6.8%; meningioma and ependymoma, 15.9%; hemangioblastoma, 15.8%; and astrocytoma, 38.9%. The RRs after total resection were significantly lower (4.4%) than that after partial resection. Neurofibromatosis-associated schwannomas had a higher RR than sporadic schwannomas ($p<0.001$, odds ratio [OR]=8.54, 95% confidence interval [95% CI]: 3.67-19.93). Among the meningiomas, the RR increased to 43.5% in ventral cases ($p<0.001$, OR=14.36, 95% CI: 3.66-55.29). Within the ependymomas, partial resection ($p<0.001$, OR=2.871, 95% CI: 1.37-6.03) was found to be significantly correlated with recurrence. Dumbbell-shaped schwannomas exhibited a higher RR than non-dumbbell-shaped ones. Furthermore, dumbbell-shaped tumors other than schwannoma had a higher RR than dumbbell-shaped schwannomas ($p<0.001$, OR=16.0, 95% CI: 5.518-46.191).

Conclusions: Aiming for total resection is essential to prevent recurrence. Dumbbell-shaped schwannomas and ventral meningiomas exhibited higher RR requiring revision surgery. As for dumbbell-shaped tumors, spinal surgeons should pay attention to the possibilities of non-schwannoma histopathologies.

Keywords:

recurrent spinal cord tumor, dumbbell-shaped tumor, ventral meningioma, intramedullary ependymoma, spinal astrocytoma

Spine Surg Relat Res 2023; 7(3): 225-234

dx.doi.org/10.22603/ssrr.2022-0136

Introduction

Since Gowers and Horsley first reported the case of spinal cord tumor removal in 1888[1], the therapeutic outcome of spinal cord tumor resection has significantly improved over the past few decades due to the advancement in diagnostic imaging and improvements in microscopic surgical techniques, as well as the introduction of ultrasonic surgical aspirators and intraoperative electrical monitoring[2]. The goal of treatment for spinal cord and cauda equina tumors is to completely remove the lesion without damaging the spinal cord, cauda equina, or spinal nerve roots and exacerbating the patient's neuropathy. However, even today, the treatment of recurrent spinal cord tumor cases is often challenging in the field of spinal surgery. Furthermore, only a few reports have described recurrent spinal cord tumors according to each histology[3-6]. In clinical practice, we encounter many cases in which the tumor recurs and is difficult to treat. Al-

Corresponding author: Narihito Nagoshi, nagoshi@keio.jp

Received: July 1, 2022, Accepted: October 3, 2022, Advance Publication: December 12, 2022

though there have been epidemiological reports from Japan on surgically treated cases of spinal cord tumors in a multicenter study setting (678 cases over 10 years and 118 cases over 3 years)[7,8], due to the rarity of spinal cord tumors, epidemiological reports of spinal cord tumors with large sample sizes focusing on recurrence rates (RRs) are scarce. In this study, we retrospectively reviewed consecutive cases of recurrent spinal cord tumor surgery in a single-center study setting.

Materials and Methods

Subjects

We retrospectively reviewed data for consecutive patients who underwent surgery for spinal cord tumors, cauda equina, and spinal nerve root at our institution between 2009 and 2018. All patients had complete radiography, MRI evaluations from the preoperative assessment, and 2-year follow-up. In this study, 818 patients who underwent tumor resection at our institution were included. With the approval of our institution's ethical board, we retrospectively collected clinical data for each patient from their charts and operative records.

Surgical procedure

All surgeries were performed by an equally skilled surgical team *via* microscopy under general anesthesia and neuromonitoring. Among the 864 surgeries, 852 were performed using a posterior spinal approach. Seven patients underwent tumor resection *via* the anterior spinal approach, and five were treated with a combined anterior and posterior approach. In the case of the posterior approach for cervical or upper thoracic (T1-3), the patient was placed in the so-called Concorde prone position using the Mayfield® head clamp. In the case of the posterior approach for middle-thoracic and lumbar cases, the patient was positioned prone on a spinal frame. Following cervical laminoplasty or thoracic/lumbar laminectomy and/or laminotomy, the tumor was resected under a surgical microscope. For the resection of dumbbell-shaped tumors, the posterior one-way approach was mainly employed in this study. Our basic surgical strategy for a dumbbell-shaped tumor was to first resect the tumor within the spinal canal (both intradural and extradural) posteriorly and then dissect out and resect the tumor in the intervertebral foramen as far outward as possible. If the extradural portion of the dumbbell-shaped tumor located at the foramen was relatively small (e.g., Toyama type 3a), we resected the tumor using the posterior approach[9]. Alternatively, if the extradural portion of the dumbbell-shaped tumor was relatively large (e.g., Toyama type 3b), we resected the tumor posteriorly as far outward as possible to the area in the intervertebral foramen distally away from its entrance, as previously reported[9].

Data collection

In addition to age, gender, and number of surgeries, we investigated the histopathology and location of the resected tumor of all the participants. Then, we investigated multiple operated cases with recurrent tumors and examined the interval between primary and secondary surgeries, the spinal locations of the recurrent tumors, and the tumor configuration on cross-sectional MRI images. Malignant tumors were defined based on the World Health Organization (WHO) classification: WHO grade I tumors were defined as "benign"; grade II, "intermediate"; and grade III/IV, "malignant." The age of the participants enrolled was classified by decade. The spinal location of the tumors was determined based on their rostro-caudal barycenter in sagittal MRI images as follows: the center of the tumor location at the Oc-C 2 level was defined as upper-cervical, C3-6 as cervical, C7-T3 as cervicothoracic[10], T3-10 as thoracic, T11-L2 as thoracolumbar, L3-5 as lumbar, and S1-3 as sacral. Recurrent spinal cord tumors were defined as tumors occurring at the same spinal level with the same histological diagnosis as that at the initial surgery. RR was defined as the ratio of the number of patients who underwent reoperation due to tumor recurrence to the total number of patients operated on at our institute during the same period[3]. The extent of tumor resection was defined as follows according to the previous reports[11,12]: gross total resection (GTR) as no visual evidence of remaining tumor on the surgical field of the operating microscope, near total resection (NTR) as <10% residual tumor mass following surgery, and subtotal resection (STR) as removal of 50%-90% of tumor tissue at the end of surgery. We compared the RRs based on the achievement of the GTR and partial resection (NTR/STR). Especially for cases of meningioma, tumor localization was classified into dorsal (including lateral) and ventral types depending on the localization of the dural attachment, as previously reported[13]. We also investigated a breakdown of Simpson grade for meningioma resection[13]. Furthermore, among recurrent dumbbell-shaped tumors, we examined the histopathology in detail and compared the RRs of dumbbell-shaped schwannomas with that of tumors other than schwannomas.

Statistical analysis

Data were expressed as mean±standard deviations (SD) unless otherwise indicated. We conducted statistical analyses using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as means± SD and categorical variables as percentages. A univariable analysis (Mann-Whitney U test for continuous variables and chi-squared test for categorical variables) was conducted to explore the factors associated with tumor recurrence by estimating the odds ratio (OR) and the 95% confidence interval (95% CI). A p-value less than 0.05 was considered statistically significant.

Table 1. Details of Cases with Surgically Treated Spinal Cord Tumors.

Patients	n=818
Gender (no. of cases)	male: 424; female: 394
Age	50.3±17.4 (range 1–89)
Tumor location (no. of cases)	upper-cervical: 77; cervical: 160; cervicothoracic: 97; thoracic: 170; thoracolumbar: 162; lumbar: 110; sacral: 42
Tumor configuration (no. of cases)	intramedullary: 288; intradural-extramedullary: 383; extradural: 20; dumbbell-shaped: 127

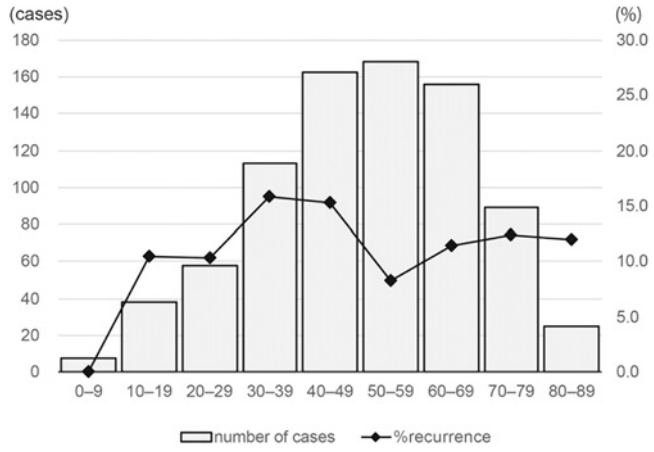

Figure 1. Age distribution of enrolled individuals with spinal cord tumors and recurrence rate of each decade.

Results

Demographics and morphologies of enrolled patients with spinal cord tumors

Table 1 presents the demographics of 818 individuals who had 864 surgically treated tumors. The patients enrolled in this study had a male preponderance consisting of 424 (51.8%) men and 394 (48.2%) women, with ages ranging from 1 to 89 years (mean age, 50.3±17.4; median, 51 years; interquartile range, 39-63). When stratifying the age of the patients by decade, those aged 40-60 years were predominant (Fig. 1). The tumor location evaluated by spinal vertebral level was distributed without significant deviation (Fig. 2). Regarding tumor configuration, 288 patients (35.2%) had intramedullary, 383 (46.8%) intradural extramedullary, 20 (2.5%) extradural, and 127 (15.5%) dumbbell-shaped tumors (Table 1).

Imaging and clinical features of the recurrent cases

Table 2 presents the comparison results between the cases with recurrent tumors (R(+) group) and those without recurrence (R(−) group). Of the 818 enrolled individuals, 99 had tumor recurrence. Of these patients, 41 had undergone primary surgery at another hospital. The mean duration between the primary and second surgeries was 94.8±109.7 months (median, 60 months; interquartile range, 14-143). A total of 74 patients underwent surgery twice, 18 underwent surgery three times, and 7 underwent four or more times. No significant gender preference was observed between the R(+) [341 women and 378 men] and R(−) [53 women and 46 men] groups. When stratifying the age of the patients at the time of primary surgery by intervals of 10 years, there was a unimodal peak in patients in their 40s to 60s (Fig. 1). The RR in each age group was approximately 10%-15%, and no significant difference was observed in the RRs between the age groups (Fig. 1, Table 2). Although there were no significant differences in the RRs of tumors located at various spinal levels, significant differences were observed in the RRs when considering tumor configuration (Table 2): dumbbell-shaped spinal cord tumors exhibited significantly higher RRs. Concerning the degree of tumor resection, GTR was achieved in 597 cases, NTR in 61 cases, and STR in 160 cases. The RRs for each degree of tumor resection were 4.4% for GTR, 31.1% for NTR, and 33.8% for STR, respectively (Table 2): as a natural consequence, the RR was significantly lower in those with GTR ($p<0.001$). The RRs in relation to the grade of malignancy were 9.7% in benign, 15.9% in intermediate, and 56.3% in malignant tumors with statistically significant differences in RRs by grade (Table 2).

Pathological features of the recurrent cases

Table 3 presents the recurrence rate for each histopathology. The RRs of spinal schwannomas and meningiomas, accounting for most extramedullary spinal intradural tumors, were 7.6% and 15.6%, respectively. When focusing on schwannomas, patients with neurofibromatosis (neurofibromatosis type 1 or 2 or schwannomatosis) exhibited a significantly higher recurrence rate than those with sporadic spinal schwannomas ($p<0.001$, [OR]=8.54, 95% confidence interval [95% CI]: 3.67-19.93). Regarding the degree of tumor resection, among 344 patients with spinal schwannomas, 281 underwent GTR and 63 partial resections (NTR/STR). As a corollary, the RR was significantly lower in patients with GTR (2.5%) than in those who underwent partial resection (28.6%) ($p<0.001$). Analysis of the degree of tumor resection as a function of tumor configuration revealed that there was significantly less GTR in dumbbell-shaped schwannoma. The GTR achievement rate was significantly higher in those with non-dumbbell-shaped schwannoma, whereas in those with non-dumbbell- and dumbbell-shaped schwannomas, the rates were 92.9% (n=239) and 56.2%, re-

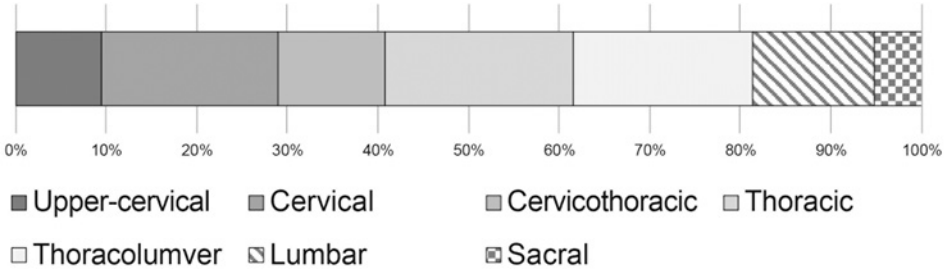

Figure 2. Location of tumors at the initial surgery (n=818).

Table 2. Comparison between Recurrent and Non-recurrent Cases.

Variables	R (–)	R (+)	p value
number of cases	719	99	–
gender (%male)	52.6	46.5	0.254
	Recurrence rate (%)		
Age (no. of cases)			0.557
0–9 (8)	0.0		
10–19 (38)	10.5		
20–29 (58)	10.3		
30–39 (113)	15.9		
40–49 (163)	15.3		
50–59 (168)	8.3		
60–69 (156)	11.5		
70–79 (89)	12.4		
80–89 (25)	12.0		
Tumor location (no. of cases)			0.136
upper cervical (77)	14.3		
cervical (160)	16.9		
cervicothoracic (97)	15.5		
thoracic (170)	7.6		
thoracolumbar (162)	11.1		
lumbar (110)	9.1		
sacral (42)	11.9		
Tumor configuration (no. of cases)			<0.001
intramedullary (288)	14.2		
intradural-extramedullary (383)	7.0		
extradural (20)	0.0		
dumbbell-shaped (127)	24.4		
Degree of tumor resection (no. of cases)			<0.001
GTR (597)	4.4		
NTR (61)	31.1		
STR (160)	33.8		
Tumor malignancy (no. of cases)			<0.001
benign [WHO grade I] (698)	9.7		
intermediate [WHO grade II] (88)	15.9		
malignant [WHO grade III/IV] (32)	56.3		

spectively (n=105) (p<0.001).

Among spinal meningiomas, when classifying the meningeal origin site on the axial section view, the ventral type had a significantly higher rate of recurrence than the dorsal/lateral type (p<0.001, OR=14.36, 95% CI: 3.66-55.29). As for the Simpson grade for meningioma resection, 51 patients achieved Simpson grade I, 22 grade II, 8 grade III, and 1 grade IV. The RRs for each Simpson grade were as follows: 1.96% for grade I (1 case), 13.6% for grade II (3 cases), 100% for grade III (8 cases), and 100% for grade IV (1 case) (Table 4a). In the case of meningiomas with ventral location, the breakdown of Simpson grade and RRs was as follows: 9 cases achieved grade I (RR=11.1%), 6 grade II (RR=16.7%), 7 grade III (RR=100%), and 1 grade IV (RR=

Table 3. Recurrence Rate for Each Histopathology.

Variables (no. of cases)	Recurrence rate (%)
Schwannoma/Neurofibroma (344)	7.6
Sporadic (303)	4.6
Neurofibromatosis (41)	29.3†
Meningioma (82)	15.6
Dorsal/Lateral (59)	5.1
Ventral (23)	43.5 ‡
Ependymoma (107)	15.9
WHO grade I (33)	15.2
WHO grade II (74)	16.2
Astrocytoma (36)	38.9
Low-grade (24)	37.5
High-grade (12)	41.7
Hemangioblastoma (38)	15.8
Sporadic (31)	9.7
vHL (7)	42.9§
Cavernous hemangioma (62)	3.2
Spinal lipoma (33)	12.1
True spinal lipoma (11)	18.2
With spinal dysraphism (22)	9.1
SFT/Hemangiopericytoma (10)	50.0
Intramedullary cystic lesion (18)	5.6
MPNST (3)	100.0
Chordoma (3)	100.0
Ganglioneuroma (6)	50.0
Miscellaneous (76)	3.9

†: p<0.001, reference=sporadic, ‡: p<0.001, reference=dorsal/lateral, §: p<0.05, reference=sporadic, vHL: von Hippel-Lindau disease, SFT: solitary fibrous tumor, MPNST: malignant peripheral nerve sheath tumor

Table 4. Recurrence Rates and Simpson Grade for Meningioma.

a. Recurrence rate and Simpson grade of a total of 82 cases with meningioma. Higher Simpson-grade exhibited significantly higher RR (p<0.001).

Simpson grade	R (−)	R (+)	RR
I	50	1	1.96
II	19	3	13.6
III	0	8	100.0
IV	0	1	100.0

b. Recurrence rate and Simpson grade of ventrally located meningioma (n=23).

Simpson grade	R (−)	R (+)	RR
I	8	1	11.1
II	5	1	16.7
III	0	7	100.0
IV	0	1	100.0

c. Recurrence rate and Simpson grade of dorsally/laterally located meningioma (n=59).

Simpson grade	R (−)	R (+)	RR
I	42	0	0.0
II	14	2	12.5
III	0	1	100.0
IV	–	–	

R: recurrence, RR: recurrence rate.

100%) (Table 4b). The ventral location of meningioma compelled initial surgeons to resect the tumors partially (p< 0.001), and the grade III and IV partial resection consequently led to significantly higher RRs (Table 4c).

Regarding intramedullary tumors, especially gliomas, the RRs of ependymoma and astrocytoma were 15.9% and 38.9%, respectively. Based on the classification of central nervous system tumors by the WHO, we divided the enrolled patients with gliomas into two subgroups: ependymomas of WHO grades I (25 patients with myxopapillary ependymomas and 8 patients with subependymomas) and II and astrocytomas of low-grade (grades I and II) and high-grade (grade III and IV). In addition, we compared the RRs of each subtype. As a result, no significant difference was observed in RR in these subtype comparisons (Table 3). Among 107 patients with ependymomas, 81 (75.7%) underwent GTR, 7 (6.5%) NTR, and 19 (17.8%) STR. When comparing the degree of tumor resection between WHO grade I and II ependymomas, the ratio of GTR in patients with grade II ependymomas tended to be higher than that in patients with grade I ependymomas (63.6% in grade I and 81.1% in grade II, p=0.052). Notably, all eight cases of subependymoma (WHO grade I) underwent STR in the primary surgery owing to their indistinct boundary with the surrounding normal cord. Univariable analysis was conducted using age, gender, WHO grade, and degree of resection (GTR or partial resection) to search for factors associated with ependymoma recurrence, and only the degree of tumor resection (partial resection) was a statistically significant factor associated with recurrence (p<0.001, OR=2.871, 95% CI: 1.37-6.03).

As for spinal astrocytoma, 36 patients with astrocytoma were enrolled in this study, of which 24 had low-grade (WHO grade I/II) and 12 had high-grade (grade III/IV), as presented in Table 3. Regarding the degree of tumor resection for astrocytoma, 13 patients (36.1%) underwent GTR, 6 (16.7%) NTR, and 17 (47.2%) STR. Although we conducted univariable analysis with the presence of recurrence as the objective variable and age/gender/GTR/high-grade as explanatory variables, none of these factors were statistically significant (p=0.597 for age, 0.270 for gender, 0.968 for GTR, and 0.809 for high-grade). Focusing on the patients with high-grade astrocytoma (n=12), all underwent STR as a result. Consequently, the rate of GTR was significantly higher in those with low-grade astrocytoma (54.2%) than in those with high-grade astrocytoma (0%) (p=0.001). In 10 out of 12 patients with high-grade astrocytoma, we performed chemoradiotherapy using temozolomide and/or

bevacizumab as postoperative adjuvant therapy. One patient with grade IV cervical glioblastoma who did not receive chemoradiotherapy died before postoperative adjuvant therapy. Of 10 patients treated with adjuvant chemoradiotherapy, 3 had also undergone cordotomy at the upper thoracic level, and the remaining spinal cord and nerve root below the transected site were completely resected, including the dura mater and the basis of the nerve roots. Among three patients with cordotomy, only one survived for 7 years. However, the remaining 11 cases with high-grade astrocytoma with or without cordotomy died from intracranial dissemination of tumor within 2 years following primary surgery.

Regarding another major type of intramedullary tumor, vascular tumor, the RRs of hemangioblastoma and cavernous hemangioma were 15.8% and 3.2%, respectively. For vascular tumors, such as hemangioblastoma and cavernous hemangioma, the basic surgical strategy is to resect the tumor as a single mass rather than piece by piece. All cases with cavernous hemangioma (n=62) underwent GTR, and 33 out of 38 patients (86.8%) with hemangioblastoma underwent GTR. Among 30 patients with sporadic hemangioblastoma, 28 (93.3%) underwent GTR, and 2 (6.7%) underwent STR as a result. All two cases with STR eventually exhibited recurrence. Consequently, the RR was relatively low in the vascular tumors following GTR (15.8% in hemangioblastoma and 3.2% in cavernous hemangioma). We divided the patients with spinal hemangioblastoma into sporadic and von Hippel-Lindau disease (vHL) groups and found that those with vHL exhibited a significantly higher RR than those with sporadic hemangioblastomas (p=0.030, OR=7.0, 95% CI:1.178-43.355). The RRs for the other remaining histopathologic tumors with relatively lower incidence rate were as follows: spinal cord lipoma, 12.1%; solitary fibrous tumor (SFT)/hemangiopericytoma (HPC), 50.0%; intramedullary cystic lesions, 5.6%; malignant peripheral nerve sheath tumor (MPNST), 100%; chordoma, 100%; ganglioneuroma, 50.0%; and miscellaneous histopathology, 3.9% (Table 3).

Concerning spinal cord lipoma, all patients with spinal cord lipoma underwent partial resection (STR) and duroplasty. Among 33 patients with spinal cord lipoma, 22 (66.7%) were associated with spinal dysraphism, and 11 (33.3%) were without spinal dysraphism (true spinal cord lipoma) (Table 3). A total of four patients had recurrence, and there was no significant difference in the RRs between patients with and without spinal dysraphism (p=0.451). Two recurrent cases with true spinal cord lipoma exhibited local adhesive arachnoiditis at the primary surgical site, and two cases underwent spinal shortening surgery at the upper lumbar level for the recurrent tethered cord syndrome following filum terminale resection.

Recurrence rate of dumbbell-shaped tumors

Table 5a presents the RRs of dumbbell-shaped schwannomas. Compared with non-dumbbell-shaped schwannomas, the dumbbell-shaped ones exhibited a significantly higher RR (14.3% vs. 4.2%, p=0.003, OR=3.455, 95% CI: 1.554-7.677) in the univariable analysis. Focusing on dumbbell-shaped tumors as a whole regardless of histopathology (n=127), 31 patients with dumbbell-shaped tumor had a recurrence comprising 15 schwannomas and 16 non-schwannomas (Table 5b). The detailed histopathology of the 16 non-schwannoma recurrent dumbbell-shaped tumor cases was as follows: three meningioma/ganglioneuroma/chordoma/SFT(HPC), two MPNST, and one hemangioblastoma and sarcoma (Fig. 3). Non-schwannoma dumbbell-shaped tumor cases showed a significantly higher RR than dumbbell-shaped schwannoma cases (Table 5b, p<0.001, OR =16.0, 95% CI: 5.518-46.191). The six remaining cases of dumbbell-shaped non-schwannoma without recurrence were

Table 5. Recurrence Rates of Dumbbell-shaped Tumors.

a. Recurrence rates of spinal schwannomas (n=344) in dumbbell- and non-dumbbell-shaped configurations.

Variables (no. of cases)	Recurrence rate (%)
Dumbbell (105)	14.3*
Non-dumbbell (239)	4.2

b. Recurrence rates for dumbbell-shaped tumors of all histopathologies (n=127).

Variables (no. of cases)	Recurrence rate (%)
Schwannoma (105)	14.3
Other than schwannoma (22)	72.7†

*: p=0.003, reference=non-dumbbell,

†: p<0.001, reference=schwannoma.

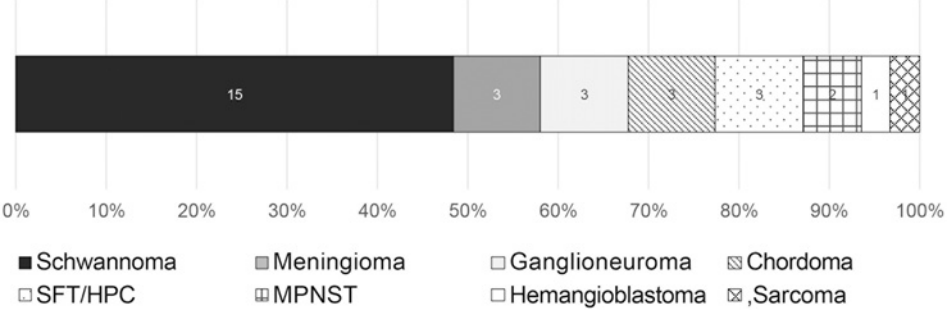

Figure 3. Detailed histopathology of the recurrent dumbbell-shaped tumors (n=31).

meningioma, ganglioneuroma, cavernous hemangioma, SFT, metastasizing leiomyoma, and multiple endocrine neoplasia type 1.

Discussion

This study characterized the RRs of spinal cord and cauda equina tumors, including intra- and extramedullary locations with various histopathologies. In addition, it identified the factors associated with recurrence within schwannomas, meningiomas, hemangioblastomas, and dumbbell-shaped tumors. Inferring the relationship between tumor recurrence and genetic background, such as neurofibromatosis or vHL, is feasible, and these genetic backgrounds were identified as significant factors in this study (Table 3). To date, our study consisted of one of the largest sample-sized case series with spinal cord tumors in single-center settings worldwide. However, enrolling surgically treated cases could cause selection bias. Similar to previous reports from Japan, our results indicated that schwannomas were the most common and had a preponderance within intradural extramedullary tumors compared with meningiomas[7,8], whereas in the United States, the frequencies of spinal meningiomas and schwannomas were almost comparable, with a slightly higher incidence of meningiomas[14].

Previous reports evaluated surgical outcomes according to each histopathology. Regarding schwannomas, Safaee et al. retrospectively investigated a total of 221 spinal nerve sheath tumors, including schwannoma, neurofibroma, and MPNST, in 199 patients with neurofibromatosis. They reported that, as expected, the extent of tumor resection (GTR) was associated with a lower RR[15]. Li et al. reported the clinical features of spinal schwannomas in 65 patients with schwannomatosis compared with 831 with solitary schwannomas and 102 with NF-2, concluding that NF-2 exhibited more aggressive clinical behaviors requiring multiple surgeries than solitary and schwannomatosis[16]. These findings are consistent with our results indicating that spinal schwannomas associated with neurofibromatosis (NF-1, 2, and schwannomatosis) had a higher RR than sporadic schwannomas (solitary) (Table 3). Our data implied that for sporadic spinal schwannoma cases, achieving GTR as much as possible might be important to prevent recurrence.

As for meningiomas, this study demonstrated that ventral location resulted in higher RRs than dorsal/lateral location ($p<0.001$). Nakamura et al. evaluated a total of 68 cases of spinal meningioma with a mean of 12 years postoperative follow-up. They concluded that Simpson grade I resection should be selected to avoid recurrence, whereas ventral location compelled surgeons to confine Simpson grade II resection that led to recurrence in long-term follow-up[13]. Recently, Maiuri et al. evaluated recurrent and non-recurrent meningiomas (6 cases of recurrent spinal meningioma compared with 50 non-recurrent cases) and demonstrated that higher MIB-1 indices and arachnoid invasion were risk factors for the recurrence of spinal meningiomas, whereas tumor location and extent of dural resection (Simpson grade I or II) were not significant[17]. In the case of ventral meningiomas, our results may only reflect the technical difficulties in achieving Simpson grade I resection. Future analysis of long-term follow-up with a larger sample size focusing only on spinal meningioma cases is warranted.

Regarding intramedullary spinal cord tumors, which are rarer than intradural extramedullary tumors, most previous studies demonstrated surgical outcomes of intramedullary spinal cord tumors consisting of approximately 100 to 200 cases of various histopathological types. Karikari et al. showed surgical outcomes of 102 intramedullary tumors with a mean follow-up of 41.8 months[4]. According to this report, of 55 patients with ependymoma (WHO grade 2), 90.9% underwent GTR and 7.1% had recurrence. Among 21 cases of spinal astrocytoma, 14.3% underwent GTR, and 47.7% had recurrence. On the other hand, in the case of 12 patients with hemangioblastoma, 91.7% achieved GTR, and there was no recurrence within their follow-up duration. The authors concluded that tumor histopathology was the most important predictor of postoperative neurological outcome, as it was related to resectability and recurrence[4]. Similarly, Klekamp et al. evaluated a total of 225 cases with spinal intramedullary tumors of various histopathologies and conducted a detailed analysis of the risk factors for surgical morbidity with a mean follow-up of 41 months[5]. This study reported that in long-term follow-up, the RRs for ependymomas and low-grade astrocytomas were significantly correlated with the extent of tumor resection (GTR)[5]. Moreover, Tsuji et al. reported that achieving GTR was one of the independent prognostic factors for ambulation ability[12]. We also exhibited that GTR achievement was negatively correlated with the RRs of ependymoma with statistical significance. In this study, we analyzed a total of 288 cases of intramedullary tumors and evaluated the RRs. Based on the hypothesis that high-grade tumors would have a high RR, we evaluated glioma cases (ependymomas and astrocytomas) and compared the RRs between low and high malignant grades. However, contrary to our expectations, the RR in high-grade glioma was not significantly higher than that in low-grade glioma (Table 3, 15.3% for grade 1 ependymoma and 16.2% for grade 2, 37.5% for grade 1/2 astrocytoma, and 41.7% for grade 3/4). Among the patients with WHO grade I ependymoma, all eight patients with subependymoma underwent STR due to the obscure boundary between the tumor and normal cord, similar to previous reports[18,19]. As Yuh et al. reported, to reduce the risk of neurological deficit following surgery for subependymoma, an intentional STR was an alternative option based on their benign nature[19]. Especially with regard to the myxopapillary ependymomas (n=25), the capsular violation detected in intraoperative findings has been reported as a factor strongly associated with recurrence[20,21]. Thorough assessment of the clinical outcome and the relevance of adjuvant radiotherapy for the myxopapillary ependymomas with capsular violation need to be investigated in future study.

Concerning the degree of tumor resection for astrocytoma, all patients with high-grade astrocytoma (n=12) underwent STR as a result. Although we performed additional cordotomy and adjuvant chemoradiotherapy, the prognosis of high-grade astrocytoma was quite poor. Recently, Nagoshi et al. reported that similar to our results, neither chemoradiotherapy nor cordotomy for high-grade astrocytoma could improve the overall survival rate[22]. To date, there is still no certainty about the best practices for high-grade astrocytoma treatment owing to its rarity and extremely poor prognosis. Further detailed molecular analysis combined with extensive resection and adjuvant chemotherapy would be desirable in a large, nationwide sample size to investigate the prognostic factors for high-grade spinal astrocytoma.

Regarding the malignant tumors, all three patients with MPNST, diagnosed *via* CT-guided biopsy, received preoperative chemotherapy using adriamycin and ifosfamide, and surgical resection (all underwent STR as a result) was performed after a maximum of three courses of chemotherapy with imaging evaluation. After surgery, reoperation, chemotherapy, and radiation therapy were performed depending on the condition of each patient and the presence of metastatic recurrence. However, the 2-year survival rate was 0%, and all patients died due to intracranial dissemination of tumor cells. As for chordoma, all patients who underwent partial resection (STR) of the tumor located at the cervical level and who received heavy ion beam radiotherapy for the remaining tumor postoperatively survived at least 2 years during the follow-up period. However, the precise 5-year survival rate for final prognosis was unknown as all patients were transferred to other institutions for heavy ion therapy.

As previously reported, total resection should be attempted to prevent the recurrence of dumbbell-shaped schwannomas[6]. This study demonstrated that dumbbell-shaped schwannomas had a significantly higher RR than non-dumbbell-shaped ones (Table 5a). In the case of dumbbell-shaped spinal tumors, because most of them are composed of schwannomas/neurofibromas, an algorithm has been proposed to diagnose dumbbell-shaped tumors as schwannomas according to their morphology on MRI[23]. However, our results indicated that a total of 22 of 127 cases of dumbbell-shaped tumors were diagnosed as other than schwannoma, and these dumbbell-shaped tumors other than schwannomas had significantly higher RR than dumbbell-shaped schwannomas (Table 5b). Thus, our results indicated that even for dumbbell-shaped tumors, a surgical plan must be developed for total removal in the primary surgery. Furthermore, it should be noted that there are other types of dumbbell-shaped tumors in addition to schwannomas. On the preoperative imaging evaluation, a new scoring system for the differential diagnosis of malignant and benign spinal dumbbell-shaped tumors was also advocated[24].

For dumbbell-shaped schwannomas, to resect the Eden type 1 and 2 dumbbell-shaped schwannomas, the posterior one-way approach was mainly employed for the resection of intradural portions in this study. On the other hand, in cases where total resection could be highly hazardous, STR was an alternative practical choice that yielded a favorable long-term outcome with a lower MIB-1 index[6]. Among the cases with Eden type 2 schwannomas, some exhibited larger intra- and extra-foraminal portions of tumors, resulting in partial resection. Furthermore, the location of the tumor around the vertebral artery may compel the surgeons to complete surgery in partial resection. Recently, Kitamura et al. elucidated a predictive factor of remnant tumor growth following partial resection of cervical dumbbell-shaped schwannoma using the posterior one-way approach[9]. They reported that the MIB-1 index exhibited no significant difference between patients with and without remnant tumor growth, contrary to the previous report[6], and that remnant schwannomas with margins distally away from the entrance of the foramen were less likely to grow following incomplete resection[9]. In the present study, there was a lack of data on the size of the extra-spinal canal (extra-foraminal) component of the dumbbell-shaped schwannoma to what extent it could be totally removed from the posterior one-way approach, and the enrolled spinal schwannomas were distributed from the cervical to the sacral spinal levels. Henceforth, the validity of the posterior one-way or anterior-posterior combined approach for spinal dumbbell-shaped schwannomas to achieve GTR needs to be investigated in future studies.

The rarity of highly malignant spinal cord tumors (e.g., chordoma, MPNST) might require careful interpretation of our results due to the difficulty in performing statistical analysis using such a small number of cases. In addition, more detailed research of each histopathology focusing on recurrence is considered mandatory. Even with these limitations, it is quite significant to report the RR of spinal cord tumors of heterogeneous histopathologies using the largest sample size after excision due to their scarcity.

This study has potential limitations that need to be discussed. First, this was a single-center retrospective study enrolling only surgically treated spinal cord tumor cases with possible selection bias, which unavoidably confined the level of evidence even though this study had the largest sample size. Second, surgical outcomes, especially for ambulatory abilities, were also not included in this study. In the near future, a detailed analysis of the configuration and postoperative outcome of each tumor histopathology will be required. Third, we were not able to determine whether the recurrence was due to the oncological characteristics of each tumor cell or the regrowth of the tumor tissues intentionally left to preserve the spinal cord. As for meningiomas, ventral location requires highly technical difficulty and consequently complicates GTRs[25].

In conclusion, we evaluated the imaging and pathological characteristics of recurrent spinal cord tumors. Of the 818 cases of spinal cord tumor surgery between 2009 and 2018, 99 (47 intramedullary) had reoperation. GTR resulted in significantly lower RRs than NTR/STR. In addition to cases with genetic background (neurofibromatosis or vHL), particular attention should be paid to initial surgery for

dumbbell-shaped tumors and ventrally originating meningiomas due to a higher RR. The surgeons should formulate an elaborate surgical plan at primary surgery to achieve GTR for dumbbell-shaped tumors and meningiomas located ventrally. Furthermore, when treating dumbbell-shaped tumors, spinal surgeons should pay attention to the possibility of histology other than schwannomas.

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

Sources of Funding: No funds were received in support of this work. There were no relevant financial activities outside the submitted work.

Acknowledgement: We would like to express our utmost respect to the great predecessor surgeons in our department, Dr. Kiyoshi Hirabayashi and Dr. Yoshiaki Toyama. We salute our former colleague surgeons in our department, Dr. Kazuhiro Chiba, Dr. Masahiko Watanabe, Dr. Yuto Ogawa, Dr. Ken Ishii, Dr. Takashi Tsuji, Dr. Naobumi Hosogane, Dr. Akio Iwanami, Dr. Tomohiro Hikata, and Dr. Nobuyuki Fujita. The authors also thank Ms. Makiko Miyazaki, Ms. Satomi Nagai, Ms. Yukari Yamanishi, and Ms. Kie Wakita for their assistance. The final draft of this manuscript was edited by Francois Renault-Mihara (ClearBioEditing).

Author Contributions: OT designed the study and wrote the initial draft of the manuscript.

MM, MN, and KW were responsible for designing the study protocol and recruiting participants.

SS, YT, SN, NN, and MY contributed to the analysis and interpretation of data and assisted in the preparation of the manuscript.

NN was responsible for all working related to this submission as corresponding author. Also, all authors approved the final version manuscript and agreed to be accountable for all aspects of the work.

Ethics Approval and Informed Consent: The study protocol was conducted in accordance with the Declaration of Helsinki and in compliance with the ethical guidelines for medical and health research involving human subjects and approved by the ethics committee of our institute (approval number 20110222). Informed consent was obtained in the form of opt-out on the website. Those who rejected were excluded.

References

1. Gowers WR, Horsley V. A case of tumour of the spinal cord. removal; recovery. Med Chir Trans. 1888;71:377-430 11.
2. Hussain I, Parker WE, Barzilai O, et al. Surgical management of intramedullary spinal cord tumors. Neurosurg Clin N Am. 2020; 31:237-49.
3. Asazuma T, Toyama Y, Watanabe M, et al. Clinical features associated with recurrence of tumours of the spinal cord and cauda equina. Spinal Cord. 2003;41:85-9.
4. Karikari IO, Nimjee SM, Hodges TR, et al. Impact of tumor histology on resectability and neurological outcome in primary intramedullary spinal cord tumors: a single-center experience with 102 patients. Neurosurgery. 2011;68:188-97; discussion 97.
5. Klekamp J. Treatment of intramedullary tumors: analysis of surgical morbidity and long-term results. J Neurosurg Spine. 2013;19: 12-26.
6. Nakamura M, Iwanami A, Tsuji O, et al. Long-term surgical outcomes of cervical dumbbell neurinomas. J Orthop Sci. 2013;18:8-13.
7. Hirano K, Imagama S, Sato K, et al. Primary spinal cord tumors: review of 678 surgically treated patients in Japan. A multicenter study. Eur Spine J. 2012;21:2019-26.
8. Ozawa H, Aizawa T, Kanno H, et al. Epidemiology of surgically treated primary spinal cord tumors in Miyagi, Japan. Neuroepidemiology. 2013;41:156-60.
9. Kitamura K, Nagoshi N, Tsuji O, et al. Remnant tumor margin as predictive factor for its growth after incomplete resection of cervical dumbbell-shaped schwannomas. Neurospine. 2022;19:32-40.
10. Wang VY, Chou D. The cervicothoracic junction. Neurosurg Clin N Am. 2007;18:365-71.
11. Kumar R, Banerjee S. Management and functional outcome of intramedullary spinal cord tumors: a prospective clinical study. Asian J Neurosurg. 2014;9:177-81.
12. Tsuji O, Nagoshi N, Ishii R, et al. Poor prognostic factors for surgical treatment of spinal intramedullary ependymoma (World Health Organization Grade II). Asian Spine J. 2020;14:821-8.
13. Nakamura M, Tsuji O, Fujiyoshi K, et al. Long-term surgical outcomes of spinal meningiomas. Spine (Phila Pa 1976). 2012;37:E 617-23.
14. Duong LM, McCarthy BJ, McLendon RE, et al. Descriptive epidemiology of malignant and nonmalignant primary spinal cord, spinal meninges, and cauda equina tumors, United States, 2004-2007. Cancer. 2012;118:4220-7.
15. Safaee M, Parsa AT, Barbaro NM, et al. Association of tumor location, extent of resection, and neurofibromatosis status with clinical outcomes for 221 spinal nerve sheath tumors. Neurosurg Focus. 2015;39:E5.
16. Li P, Zhao F, Zhang J, et al. Clinical features of spinal schwannomas in 65 patients with schwannomatosis compared with 831 with solitary schwannomas and 102 with neurofibromatosis Type 2: a retrospective study at a single institution. J Neurosurg Spine. 2016;24:145-54.
17. Maiuri F, Del Basso De Caro M, de Divitiis O, et al. Recurrence of spinal meningiomas: analysis of the risk factors. Br J Neurosurg. 2020;34:569-74.
18. Wu Z, Iwanami A, Yasuda A, et al. Intramedullary cervicothoracic subependymoma: report of three cases and review of the literature. J Orthop Sci. 2015;20:927-34.
19. Yuh WT, Chung CK, Park SH, et al. Spinal cord subependymoma surgery: a multi-institutional experience. J Korean Neurosurg Soc. 2018;61:233-42.
20. Klekamp J. Spinal ependymomas. Part 2: Ependymomas of the filum terminale. Neurosurg Focus. 2015;39:E7.
21. Nakamura M, Ishii K, Watanabe K, et al. Long-term surgical outcomes for myxopapillary ependymomas of the cauda equina. Spine. 2009;34:E756-60.
22. Nagoshi N, Tsuji O, Suzuki S, et al. Clinical outcomes and a therapeutic indication of intramedullary spinal cord astrocytoma. Spinal Cord. 2022;60:216-22.
23. Iwata E, Shigematsu H, Yamamoto Y, et al. Preliminary algorithm

for differential diagnosis between spinal meningioma and schwannoma using plain magnetic resonance imaging. J Orthop Sci. 2018;23:408-13.
24. Matsumoto Y, Harimaya K, Kawaguchi K, et al. Dumbbell scoring system: a new method for the differential diagnosis of malignant and benign spinal dumbbell tumors. Spine. 2016;41:E1230-6.
25. Lonjon N, Russo V, Barbarisi M, et al. Spinal cervical meningiomas: the challenge posed by ventral location. World Neurosurg. 2016;89:464-73.