

# **Original Article**

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See the Commentary on "Remnant Tumor Margin as Predictive Factor for Its Growth After Incomplete Resection of Cervical Dumbbell-Shaped Schwannomas" via https://doi.org/10.14245/ns.2244202.101.



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# Remnant Tumor Margin as Predictive Factor for Its Growth After Incomplete Resection of Cervical Dumbbell-Shaped Schwannomas

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**Objective:** The purpose of our study was to investigate the risk factors of remnant tumor growth after incomplete resection (IR) of cervical dumbbell-shaped schwannomas (DS). **Methods:** Twenty-one patients with IR of cervical DS with at least 2 years of follow-up were included and were divided into 2 groups: the remnant tumor growth (G) (n = 10) and no growth (NG) (n = 11) groups. The tumor location in the axial plane according to Toyama classification, the location of the remnant tumor margin, and the tumor growth rate (MIB-1 index) index were compared.

**Results:** No significant differences in Toyama classification and MIB-1 index were found. Age was significantly higher in the G group (61.4 years vs. 47.6 years; p = 0.030), but univariate logistic regression analysis revealed little correlation to the growth (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.001–1.166; p = 0.047). Seventeen patients (9 in the G and 8 in the NG group) underwent the posterior one-way approach, and significant differences in the location of the remnant tumor margin were confirmed: within the spinal canal in 1 and 0 case, at the entrance of the intervertebral foramen in 7 and 1 cases, and in the foramen distal from the entrance in 1 and 7 cases, in the G and NG groups, respectively (p = 0.007). The proximal margin was identified as a significant predictor of the growth (OR, 56.0; 95% CI, 2.93–1,072; p = 0.008).

**Conclusion:** Remnant tumors with margins distally away from the entrance of the foramen were less likely to grow after IR of cervical DS.

**Keywords:** Cervical spinal cord tumor, Dumbbell, Schwannoma, Residual tumor, Surgical margin, MIB-1

# INTRODUCTION

The incidence of dumbbell-shaped tumors accounts for 18% of all spinal cord tumors, and among these, 44% occur most commonly in the cervical spine. Spinal schwannoma is the most frequent primary spinal cord tumor of which dumbbell-shaped tumors account for 6%-23%. For spinal dumbbell-shaped schwannomas (DS), the most appropriate surgical approach is always debatable because of the complexity of the proportion of

extraforaminal components. The surgical approaches for spinal DS are roughly classified into 3 groups: anterior/lateral one-way approach, posterior one-way approach, and combined anterior/lateral and posterior approaches. *En-bloc* gross total resection (GTR) is the most desirable procedure and should be performed when possible because the recurrence rate of spinal DS after GTR is low, ranging from 0%<sup>4-6</sup> to 3.2%.<sup>7</sup> However, some procedures for GTR could be extensive and invasive, with high complication rates,<sup>2,8</sup> and the anatomical location of the vertebral

artery (VA) and spinal nerve roots can make achieving GTR safely difficult.<sup>4,9-11</sup> Given these adverse circumstances for GTR, incomplete resection (IR) occasionally needs to be performed and the intraforaminal and extraforaminal components are involuntarily left after posterior one-way surgery. Accordingly, the postoperative behavior of remnant tumors after IR, rather than the recurrence rate of tumors after GTR, should be highlighted, and several studies have investigated it.<sup>4,7,12-15</sup> However, the reported growth rates of remnant tumors ranged widely from 16.7%<sup>15</sup> to 60%,<sup>12,13</sup> and most studies have failed to propose clinical implications to predict remnant tumor growth. Thus, this study investigated remnant tumor growth after IR of cervical DS and identified its predictive factors.

# **MATERIALS AND METHODS**

# 1. Study Design and Subjects

Seventy-six patients with cervical DS who underwent surgery at a single academic institution between 1997 and 2015 were reviewed. Of the 76 patients, 28 underwent IR of cervical DS.

Patients who underwent IR of cervical DS based on the findings of postoperative magnetic resonance imaging (MRI) and those who underwent postoperative MRI at more than 2 time points to investigate remnant tumor growth with a minimum of 2 years of follow-up were included in the study. Finally, 21 patients were enrolled in the study. IR was defined as resection of cervical DS with a remnant tumor at the intraforaminal or extraforaminal area. Patients with and without remnant tumor growth were divided into 2 groups: the growth (G) and no growth (NG) groups, respectively.

# 2. Clinical and Radiological Evaluation

The patients' clinical characteristics, including age, sex, the spinal segment of the tumor (the nerve root affected by the tumor), the tumor location in the axial plane according to Toyama classification (Fig. 1),  $^{16}$  surgical approaches (posterior oneway, anterior one-way, and combined anteroposterior approaches), and the MIB-1 index were compared between the 2 groups. Extent of tumor resection was defined as subtotal resection (STR; resection of  $\geq 90\%$ ) and partial resection (PR; < 90%)

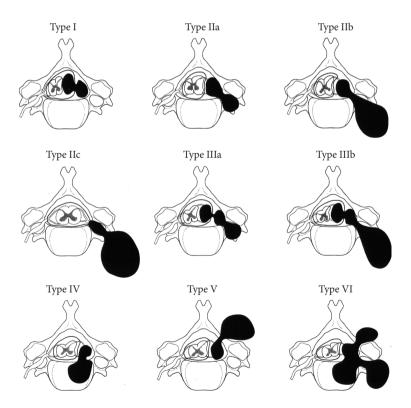


Fig. 1. The location of the dumbbell-shaped tumor in the axial plane by Toyama classification. Type I, intradural and extradural in the spinal canal with the constriction at the dura; type II, extradural with the constriction at the intervertebral foramen; type III, intradural and extradural with 2 constrictions at the dura and the intervertebral foramen; type IV, extradural and intraosseous invading the vertebral body; type V, extradural and extradaminal; and type VI, extradural and multidirectional intraosseous. Types II and III include subtypes according to the degree of extraforaminal spread.

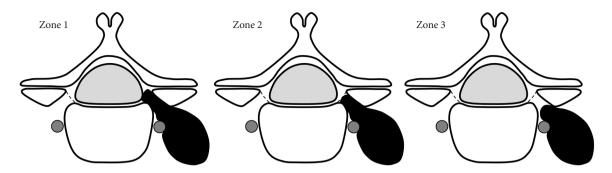


Fig. 2. The anatomical locations of the remnant tumor margins. Zone 1, in the spinal canal; zone 2, at the entrance of the intervertebral foramen, touching the posterolateral corner of the intervertebral disc or vertebral body; and zone 3, in the intervertebral foramen distally away from its entrance. Dotted lines indicate the entrance of the intervertebral foramen.

based on the findings of the axial images of postoperative MRI.<sup>4</sup> Remnant tumor growth was as defined as an increase in size of > 2 mm<sup>7</sup> and its direction was also evaluated using postoperative MRI at more than 2 time points. The anatomical locations of remnant tumor margins were evaluated based on the findings of immediate postoperative axial MRI in 17 patients who underwent posterior one-way surgery, excluding the following 4 patients: 1 patient who underwent anterior one-way surgery, 2 patients who underwent combined anterior and posterior surgeries in the NG group, and 1 patient whose immediate postoperative MRI was not confirmed in the G group. The locations of the remnant tumor margins were categorized into 3 areas as follows: zone 1, remaining in the spinal canal; zone 2, not protruding into the spinal canal but touching the posterolateral corner of the intervertebral disc or the vertebral body at the entrance of the intervertebral foramen; and zone 3, in the intervertebral foramen distally away from the posterolateral corner of the intervertebral disc or the vertebral body at its entrance (Fig. 2). For the occiput (Oc)/C1 and C1/C2 segments, the entrance of the intervertebral foramen was simply defined as the lateral border of the spinal canal (the medial wall of the lateral mass of C1 or the pedicle of C2).

# 3. Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD). The MIB-1 index was presented as median (first to third interquartile). A comparison of each independent variable between the 2 groups was performed using the Mann-Whitney U-test for the MIB-1 index and an independent t-test for other continuous variables. A chi-square test was used to analyze discrete variables. Univariate logistic regression analysis was performed to investigate the correlation of each aforementioned variable with remnant tumor growth. Regrowth-free probability was calculated using the Kaplan-Meier method. A p-value for comparison of regrowth-free probability between patients with surgical margins at zone 3 and those with surgical margins at 1 or 2 was determined by Log-rank test. IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA) was used for all statistical analyses. Probability values of less than 0.05 were used to denote statistical significance.

#### 4. Compliance With Ethical Standards

We certify that all applicable institutional and governmental regulations concerning the ethical use of human participants and the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments were followed during the course of this research. Informed consent was obtained from all individual participants included in the study. This study was approved by the Institutional Review Board (IRB) of Keio University School of Medicine (IRB No. 20110142).

# RESULTS

#### 1. Demographics of Patients

The patients' characteristics are summarized in Table 1, and the details of each case are shown in Table 2. Twenty-one patients (9 males and 12 females) were included in this study. The mean follow-up period was 67.8 ± 43.9 months. None of the patients received postoperative irradiation for the remnant tumors. Among the 21 patients, 10 (47.6%) showed remnant tumor growth and were included in the G group (5 males and 5 females). The remaining 11 patients (52.4%) were included in the NG group (4 males and 7 females). No significant difference in sex was found between the 2 groups. Age at surgery was significantly higher in the G group than in the NG group (61.4 years vs. 47.6 years; p = 0.030). The most frequently involved

Table 1. Patient characteristics

Age (yr)       0.030*         Mean ± SD       61.4 ± 14.6       47.6 ± 12.3         Range       37–83       32–72         Sex       0.665         Male       5       4         Female       6       7         Follow-up period (mo), mean ± SD       61.0 ± 31.8       73.9 ± 53.5       0.515         Affected nerve root (n)       1       0       0       2         2       1       2       2       2       2       2       2       2       2       3       1       1       4       1       1       1       2       2       2       6       0       2       2       2       6       0       2       2       2       6       0       2       2       2       6       0       2       2       2       6       0       2       2       2       2       6       0       2       2        2       6       0       2       2       1       2       2       2       1       2       2       2       1       2        2       2       1       2       2       2       1       2       2       2       2 <th< th=""><th>Characteristic</th><th>G group (n=10)</th><th>NG group (n=11)</th><th>p-value</th></th<>	Characteristic	G group (n=10)	NG group (n=11)	p-value
Mean ± SD       61.4 ± 14.6       47.6 ± 12.3         Range       37-83       32-72         Sex       0.665         Male       5       4         Female       6       7         Follow-up period (mo), mean ± SD       61.0 ± 31.8       73.9 ± 53.5       0.515         Affected nerve root (n)       1       0       0       2       1       2       3       1	Age (yr)			0.030*
Male 5 4 Female 6 7 Follow-up period (mo), mean ± SD  Affected nerve root (n) 7, 1 0,745  1 1 0 0,745  1 1 0 0,745  1 1 1 0 0,745  1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1		$61.4 \pm 14.6$	$47.6 \pm 12.3$	
Male       5       4         Female       6       7         Follow-up period (mo), mean ± SD       61.0 ± 31.8       73.9 ± 53.5       0.515         Affected nerve root (n)       0.745         1       1       0       0         2       1       2       1         3       1       1       1       1         4       1       1       1       1         5       2       2       2       2       6       0       2       2       2       6       0       2       7       3       3       3       8       1       0       0       0       7       5       6       0       0       7       5       6       0       0       7       5       6       0       0       7       5       6       0       0       7       6       1       0       0       0       2       1       0       0        1       1       0       0       1       1       0       1       1       0       1       1       0       1       1       0       1       1       0       1       1       1       0 <td>Range</td> <td>37-83</td> <td>32-72</td> <td></td>	Range	37-83	32-72	
Female       6       7         Follow-up period (mo), mean ± SD       61.0 ± 31.8       73.9 ± 53.5       0.515         Affected nerve root (n)       0.745         1       1       0         2       1       2         3       1       1         4       1       1         5       2       2         6       0       2         7       3       3         8       1       0         1       0       0         2a       0       1         2b       2       1         2c       0       1         3a       3       3         4       0       0         3a       3       3         4       0       0         3a       3       3         4       0       0         5       (1)†       (1)†         6       0       1         Extent of tumor resection (n)       2         Partial resection (≥90%)       9       9         Subtotal resection (≥90%)       9       9         Surgical margin (n)       0.0	Sex			0.665
Follow-up period (mo), mean ± SD       61.0±31.8       73.9±53.5       0.515         Affected nerve root (n)       0.745         1       1       0         2       1       2         3       1       1         4       1       1         5       2       2         6       0       2         7       3       3         8       1       0         1       0       0         2a       0       1         2b       2       1         2c       0       1         2b       2       1         2c       0       1         3a       3       3         4       0       0         3b       3       3         4       0       0         5       (1)†       (1)†         6       0       1         Extent of tumor resection (n)       0       2         Partial resection (< 90%)	Male	5	4	
mean ± SD         Affected nerve root (n)       0.745         1       1       0         2       1       2         3       1       1         4       1       1         5       2       2         6       0       2         7       3       3         8       1       0         Toyama classification (n)       0       0         2a       0       1         2b       2       1         2c       0       1         3a       5       4         3b       3       3         4       0       0         5       (1)†       (1)†         6       0       1         Extent of tumor resection (n)       0.178         Subtotal resection ( $\geq 90\%$ )       0       2         Partial resection ( $< 90\%$ )       9       9         Surgical margin (n)       0.007†         Zone 1       1       0         Zone 2       7       1         Zone 3       1       7         MIB-1 index (%)       0.863	Female	6	7	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		$61.0 \pm 31.8$	$73.9 \pm 53.5$	0.515
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Affected nerve root (n)			0.745
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1	1	0	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	2	1	2	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	3	1	1	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	4	1	1	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	5	2	2	
8 1 0 Toyama classification (n) 0.756  1 0 0 2a 0 1 2b 2 1 2c 0 1 3a 5 4 3b 3 3 4 0 0 5 (1)* (1)* 6 0 1  Extent of tumor resection (n) 0.178  Subtotal resection (≥90%) 0 2 Partial resection (≥90%) 9 9  Surgical margin (n) 0.007†  Zone 1 1 0 Zone 2 7 1 Zone 3 1 7  MIB-1 index (%) 0.863  Median (IQR) 5 (1.75-7.75) 5 (3-10)	6	0	2	
Toyama classification (n) 0.756  1 0 0 2a 0 1 2b 2 1 2c 0 1 3a 5 4 3b 3 3 3 4 0 0 5 (1) $^{\ddagger}$ (1) $^{\ddagger}$ 6 0 1  Extent of tumor resection (n) 0.178  Subtotal resection ( $\geq 90\%$ ) 0 2 Partial resection ( $\leq 90\%$ ) 9 9  Surgical margin (n) 0.007 $^{\dagger}$ Zone 1 1 0 Zone 2 7 1 Zone 3 1 7  MIB-1 index (%) 0.863  Median (IQR) 5 (1.75-7.75) 5 (3-10)	7	3	3	
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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Toyama classification (n)			0.756
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3b 3 3 4 0 0 0 5 (1) $^{\ddagger}$ (1) $^{\ddagger}$ (1) $^{\ddagger}$ 6 0 1   Extent of tumor resection (n) 0.178 Subtotal resection (≥90%) 0 2 Partial resection (<90%) 9 9   Surgical margin (n) 0.007 $^{\dagger}$ Zone 1 1 0   Zone 2 7 1 2   Zone 3 1 7   MIB-1 index (%) 5 (1.75-7.75) 5 (3-10)	2c	0	1	
	3a	5	4	
	3b	3	3	
6 0 1  Extent of tumor resection (n) 0.178  Subtotal resection (≥90%) 0 2  Partial resection (<90%) 9 9  Surgical margin (n) 0.007 $^{\dagger}$ Zone 1 1 0  Zone 2 7 1  Zone 3 1 7  MIB-1 index (%) 0.863  Median (IQR) 5 (1.75-7.75) 5 (3-10)	4	0	0	
Extent of tumor resection (n) 0.178 Subtotal resection (≥90%) 0 2 Partial resection (<90%) 9 9 $0.0007^{\dagger}$ 0.0007 0.00	5	(1) <sup>‡</sup>	$(1)^{\ddagger}$	
Subtotal resection (≥90%)       0       2         Partial resection (<90%)	6	0	1	
Partial resection (<90%) 9 9  Surgical margin (n) 0.007†  Zone 1 1 0  Zone 2 7 1  Zone 3 1 7  MIB-1 index (%) 0.863  Median (IQR) 5 (1.75-7.75) 5 (3-10)	Extent of tumor resection (n	)		0.178
Surgical margin (n)       0.007†         Zone 1       1       0         Zone 2       7       1         Zone 3       1       7         MIB-1 index (%)       0.863         Median (IQR)       5 (1.75-7.75)       5 (3-10)	Subtotal resection (≥90%)	0	2	
Zone 1 1 0  Zone 2 7 1  Zone 3 1 7  MIB-1 index (%) 0.863  Median (IQR) 5 (1.75-7.75) 5 (3-10)	Partial resection (<90%)	9	9	
Zone 2 7 1 Zone 3 1 7 MIB-1 index (%) 0.863 Median (IQR) 5 (1.75-7.75) 5 (3-10)	Surgical margin (n)			$0.007^{\dagger}$
Zone 3 1 7 MIB-1 index (%) 0.863 Median (IQR) 5 (1.75–7.75) 5 (3–10)	Zone 1	1	0	
MIB-1 index (%) 0.863 Median (IQR) 5 (1.75–7.75) 5 (3–10)	Zone 2	7	1	
Median (IQR) 5 (1.75–7.75) 5 (3–10)	Zone 3	1	7	
Median (IQR) 5 (1.75–7.75) 5 (3–10)	MIB-1 index (%)			0.863
		5 (1.75–7.75)	5 (3–10)	
	Range	1–15	1-15	

G group, patients with remnant tumor growth; NG group, patients without remnant tumor growth; SD, standard deviation; IQR, interquartile range.

nerve root was C7 (3 patients in each group), followed by C5 (2 patients in each group). According to Toyamas classification, the most frequent location of the tumor was type IIIa (intradural, extradural, and foraminal) (5 patients in the G group and 4 patients in the NG group), followed by type IIIb (intradural, extradural, and paravertebral) (3 patients in each group).

#### 2. MIB-1 Index

The median MIB-1 index values were 5 (1.75–7.75) and 5 (3–10) in the G and NG groups, respectively. No significant difference in the MIB-1 index values was found between the 2 groups (p = 0.863) (Table 1).

#### 3. Remnant Tumor Margin and Its Growth

During the period when the patients in this study underwent operations in our institution, the posterior one-way approach was mainly adopted for the resection of cervical DS. The anterior one-way approach was performed in one patient with Toyama type IIc (foraminal and paravertebral) (case 18 in Table 2) to only resect the paravertebral portion. The combined anterior and posterior approaches were performed in 2 patients: one with Toyama type VI, where the interosseous portion of the tumor in the affected vertebral body was removed using the anterior approach (case 14 in Table 2), and the other with Toyama type IIIb, where the extraforaminal portion was removed using the anterior approach because of the surgeon's discretion (case 12 in Table 2). With these 3 exceptions, the posterior one-way approach was performed in the remaining 18 patients (10 in the G group and 8 in the NG group). In all these 18 cases, the intraforaminal portion of the tumor was resected as much as possible within the capsule and the extraforaminal portion was left intentionally. No significant difference was found in the percentage of STR and PR between the 2 groups (p = 0.178) (Table 1). Among the 10 patients in the G group, the directions of the remnant tumor growth were bidirectional both extraforaminally and into the spinal canal in 8 patients and unidirectional into the spinal canal in 2 patients. Extraforaminal unidirectional growth was not observed. The remnant tumors grew into the spinal canal to compress the dura without spinal cord compression in 4 patients and to compress the spinal cord in 6 patients. Reoperation was necessary in one patient because of spinal cord compression with neurologic deterioration. A significant difference in the anatomical location of the remnant tumor margin was observed between the 2 groups: zone 1, 1 and 0 patient; zone 2, 7 and 1 patients; and zone 3, 1 and 7 patients in the G and NG groups, respectively (p = 0.007) (Table 1).

<sup>\*</sup>p<0.05, statistically significance using the independent t-test.  $^{\dagger}$ p<0.05, statistically significance using the chi-square test for independence.  $^{\ddagger}$ Number in the paragraphs indicates type III+V.

Group	Case No.	Sex	Age (yr)	Follow-up period (mo)	Affected nerve root	Toyama classification	Surgical approach	Extent of tumor resection	Remnant tumor Mar- gin (zone)	MIB-1 index (%)	Regrowth direction
G	1	F	49	106	4	IIIb	P	PR	2	1	SC+EF
	2	F	66	112	5	IIIa	P	PR	2	5	SC+EF
	3	M	83	50	5	IIb	P	PR	1	5	SC+EF
	4	F	69	96	8	IIIb	P	PR	2	15	SC+EF
	5	F	53	24	2	IIb	P	PR	2	5	SC+EF
	6	M	75	32	3	IIIa	P	PR	2	5	SC
	7	M	37	51	1	IIIa+V	P	PR	3	2	SC+EF
	8	M	61	47	7	IIIb	P	PR	2	10	SC+EF
	9	M	74	55	7	IIIa	P	PR	2	1	SC
	10	F	47	37	7	IIIa	P	Unknown	Unknown	7	SC
NG	11	M	45	193	5	IIa	P	PR	3	15	-
	12	M	62	96	7	IIIb	A+P	PR	NA	5	-
	13	F	32	122	5	IIIb	P	PR	3	5	-
	14	F	56	125	6	VI	A+P	PR	NA	1	-
	15	M	48	55	2	IIIa+V	P	PR	3	10	-
	16	F	41	34	6	IIIa	P	PR	3	3	-
	17	F	72	24	4	IIIa	P	STR	2	5	-
	18	F	43	33	7	IIc	A	STR	NA	5	-
	19	M	32	55	3	IIIa	P	PR	3	2	-
	20	F	40	41	2	IIa	P	PR	3	5	-

Table 2. Details of the preoperative and postoperative characteristics of the tumor

P, posterior one-way approach; A, anterior one-way approach; A+P, combined anterior and posterior approaches; PR, partial resection; STR, subtotal resection; NA, not applicable because case 12 and 14 underwent the combined anterior and posterior approach and case 18 underwent the anterior one-way approach; SC, spinal canal; EF, extraforaminal direction.

IIIb

7

P

PR

3

10

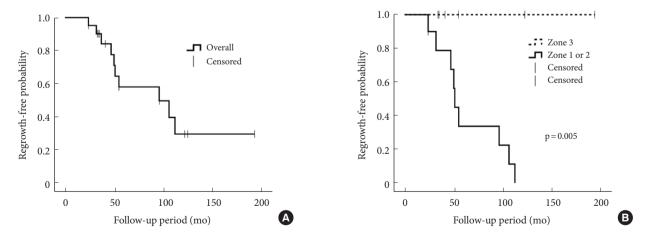


Fig. 3. Kaplan-Meier curves of regrowth-free probability. Overall patients (A) and comparison between the patients with surgical margins at zone 3 and those with surgical margins at zone 1 or 2 (B).

The mean regrowth-free period was 106 months (95% confidence interval [CI], 73–139 months). The regrowth-free proba-

bility at 2, 5, and 10 years was 95.2%, 58.3%, and 30.0%, respectively (Fig. 3A). There was significant difference in the regrowth-free

21

F

53

35

probability between patients with surgical margins at zone 3 and those with surgical margins at zone 1 or 2 (Fig. 3B) (p = 0.005).

#### 4. Univariate Logistic Regression Analysis

The anatomical location of the remnant tumor margin and age showed a significant correlation to remnant tumor growth, whereas the other variables did not. The proximal tumor margin at zone 1 or 2 had a higher risk of remnant tumor growth (odds ratio [OR], 56.0; 95% CI, 2.93–1,072; p=0.008) than higher age (OR, 1.08; 95% CI, 1.001–1.166; p=0.047).

# 5. Case Presentation 1

A 74-year-old male with Toyama type IIIa schwannoma derived from the right C7 nerve root (Fig. 4A) underwent hemilaminectomy, followed by PR of the tumor (complete resection of the intracanalicular portion and IR of the intraforaminal por-

tion within the capsule) (case 9 in Table 2). The remnant tumor margin was located on the posterolateral corner of the vertebral body, the entrance of the intervertebral foramen, on the immediate postoperative MRI (Fig. 4B, arrow), which was classified as zone 2. The unidirectional growth of the remnant tumor into the spinal canal was confirmed 11 months after surgery (Fig. 4C, arrow) and expanded further to compress the spinal cord 54 months after surgery (Fig. 4D). The patient has shown no neurologic deterioration and has been followed up without reoperation. The MIB-1 index was 1%.

# 6. Case Presentation 2

A 32-year-old male with Toyama type IIIa schwannoma derived from the left C3 nerve root (Fig. 5A) also underwent hemilaminectomy, followed by PR of the tumor (complete resection of the intracanalicular portion and IR of the intraforaminal por-

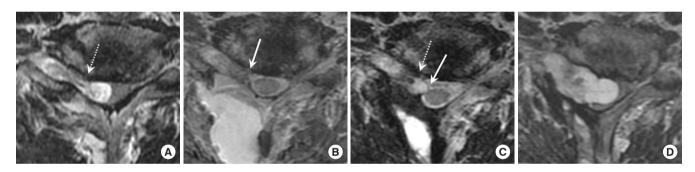


Fig. 4. T2 axial magnetic resonance images of the foraminal remnant tumor with postoperative growth. (A) Toyama type IIIa (case 9 in Table 2). (A, C) Dotted arrows indicate the posterolateral corner of the vertebral body defined as the entrance of the intervertebral foramen. The remnant tumor margin was on the corner (B, arrow). The tumor growth 11 months (C, arrow) and 54 months (D) after surgery.



Fig. 5. T2 axial magnetic resonance images of the foraminal remnant tumor with no postoperative growth. (A-C) The dotted arrows and solid arrows indicate the posterolateral corner of the vertebral body defined as the entrance of the intervertebral foramen and the remnant tumor margin, respectively. (A) Toyama type IIIa (case 19 in Table 2). (B) The remnant tumor margin was in the foramen (arrow) distally away from the posterolateral corner of the intervertebral disc (dotted arrow). (C) No obvious evidence of tumor growth 55 months after surgery.

tion within the capsule) (case 19 in Table 2). The remnant tumor margin was in the intervertebral foramen (Fig. 5B, arrow) distally away from the posterolateral corner of the vertebral body (Fig. 5A–C, dotted arrow), which was classified as zone 3. The growth was not observed until the final follow-up MRI 55 months after surgery (Fig. 5C). The MIB-1 index was 2%.

# **DISCUSSION**

In this study, we examined the growth of remnant tumors after IR of cervical DS and investigated its predictive factors. Our findings revealed that the anatomical location of the remnant tumor margin was the most significant predictor of remnant tumor growth. This result suggests that remnant tumors with its surgical margin distally away from the entrance of the intervertebral foramen were less likely to grow into the spinal canal even when the extraforaminal components are involuntarily left after a posterior one-way surgery.

Reportedly, the occurrence rate of remnant tumor growth after IR ranged from 16.7% to 60%.4,12-15 Ryu recently performed quantitative analyses of remnant tumor sizes after IR of cervical DS in 31 patients.<sup>7</sup> Seven (Eden type II or III<sup>17</sup>) of the 31 cases (22.6%) showed remnant tumor growth during the mean follow-up period of 16 months, and among the 7 cases, 2 underwent reoperations because of the newly developed symptoms caused by the growth. In this series, no significant differences in age, sex, tumor location by Eden classification, and preoperative and postoperative tumor sizes were found between patients with and without remnant tumor growth. This study revealed that frequent postoperative MRI follow-up is important but it could not indicate the predictive factors for the growth of remnant tumors, which could help us plan the surgical and postoperative strategies. To summarize the results of studies in addition to Ryu's study, detailed information, including the spinal segment of the tumor (cervical, thoracic, or lumbar), surgical approaches (posterior, anterior, or combined), remnant tumor margin (intradurally, extraforaminally, or interosseously), directions of remnant tumor growth (into the spinal canal or extraforaminally), and MIB-1 index, was not fully provided. Therefore, knowing the long-term behavior of remnant tumors after IR of cervical DS and the kind of factor that would have the most significant impact on the remnant tumor growth is still difficult.

In this study, 10 of the 21 patients (47.6%) showed remnant tumor growth during the mean follow-up period of 61 months. The directions of the residual tumor growth were bidirectional

both extraforaminally and into the spinal canal in 8 patients and unidirectional into the spinal canal in 2 patients. Note that the growth was directed at least into the spinal canal in all patients, whereas 11 of the 21 patients (NG group, 52.4%) showed no growth during the mean follow-up period of 74 months. This obvious difference in the fate of the remnant tumors between the 2 groups prompted us to investigate the predictive factors of their growth.

As far as we investigated, the MIB-1 index is the only one factor used as a prognostic marker of remnant tumor growth after IR of spinal DS. Sohn reported that the average MIB-1 index was significantly higher in patients with remnant tumor growth  $(6.3\% \pm 5.6\%)$  than in those without growth  $(2.0\% \pm 1.6\%)$ . <sup>14</sup> In addition, Nakamura indicated the clinical significance of the MIB-1 index and proposed that additional resection using the anterior approach should be considered when the MIB-1 index is high (>5%) to remove the remnant tumor after IR during the initial posterior-approach operation.<sup>4</sup> However, these studies only showed a descriptive indication regarding the possibility of reoperation after remnant tumor growth. Therefore, the current study performed quantitative and statistical analyses to identify the predictors of remnant tumor growth, but our findings indicate that the MIB-1 index has no association with remnant tumor growth.

Fukuda et al.<sup>18</sup> reported that the thickness of the remnant tumor after IR of vestibular schwannoma (VS) using the lateral suboccipital approach, which was defined as the maximum diameter of the remnant tumor on the same side of the internal acoustic canal (IAC) with the brainstem and cerebellum, was positively related to its growth toward the brainstem and cerebellum. Another recent study reported that remnant VS locations other than IAC had greater risk of remnant VS regrowth than those in IAC.<sup>19</sup> On the basis of this finding, we hypothesized that remnant tumor growth into the spinal canal could be affected by the anatomical location of the remnant tumor margin relative to the border dividing the spinal canal and intervertebral foramen. The posterolateral corner of the intervertebral disc or the vertebral body was defined as an anatomical landmark indicating the border, and accordingly, the proximal margin at the corner or within the spinal canal, compared with the distal margin in the intervertebral foramen away from the corner, was identified as a significant predictor of remnant tumor growth (OR, 56.0; 95% CI, 2.93-1,072; p=0.008). These findings suggest that the proximal margin on the verge of the spinal canal and intervertebral foramen leaves a greater chance for a remnant tumor to grow into the spinal canal. This anatomical implication could help us establish a surgical strategy preoperatively and decide the final surgical margin intraoperatively to lower the risk of remnant tumor growth. However, at the same time, we should know that posterior one-way approach to resect the intra- and extraforaminal portion of the tumor distally from the entrance of the foramen might increase the risk to injure VA behind the tumor since VA cannot be controlled posteriorly.9 Additionally, the remnant tumor margin on the postoperative MRI does not necessarily reflect the intraoperative surgical margin, especially when IR was performed within the capsule because the fluid or hematoma filling the cavity after tumor resection can make the margin unclear on MRI. Regardless of whether the surgical margins on MRI contain only capsule or tumor cells, the residual capsule itself could increase the risk of remnant tumor growth because the cleavage between the capsule and tumor cells is indistinct in spinal schwannomas.<sup>20</sup> The diagnostic accuracy of the remnant tumor margin based on MRI findings needs to be further examined by mutually comparing intraoperative findings with postoperative MRI findings.

Though we revealed that the G group had a significantly higher age than the NG group (61.4 years vs. 47.6 years; p = 0.04), higher age had a smaller influence on remnant tumor growth (OR, 1.08; 95% CI, 1.001–1.166; p = 0.047) than the remnant tumor margin, and previous studies have not described significant correlations between age and remnant tumor growth. However, these findings at least support the importance of frequent MRI follow-up in elderly patients as well, especially when the remnant tumor margin is proximal. We unfortunately failed to explain the higher age in the G group, and this should be considered a limitation of this study.

Another limitation of this study is the small sample size and possible sample bias. Multivariate logistic regression analysis was not performed to investigate the independent predictors of remnant tumor growth because of the small sample size, and the univariate analysis performed in this study cannot exclude possible confounding factors. Additionally, another limitation of this study is the lack of quantitative analyses of preoperative and postoperative tumor size. Previous studies measured tumor size as the longest diameter of the tumor on axial MRI<sup>7,11,14,21</sup> and reported that preoperative and postoperative tumor sizes were not significant risk factors for remnant tumor growth.<sup>7,14</sup> However, discrepancies between measurements of tumor size only on axial MRI and the actual 3-dimensional tumor size were much concerned. Novel methods should be applied to evaluate the actual tumor size in the future studies. Finally, we failed to explain why the remnant tumor growth to extraforaminal direction, not only into the spinal canal, was rarely observed when the surgical margins were at zone 3. This mechanism cannot be cleared by the current study as well as by previous studies, and should be multifactorial (e.g., remnant tumor margin, MIB-1 index, remnant tumor size). Another potential factor might be the vascularity of cervical DS. Surgical devascularization of VS reportedly could lead to necrosis of the remnant tumor and reduce the chance of regrowth after IR.<sup>22</sup> Similar mechanism might be applied to cervical DS. Cervical spinal arterial branches arise mainly from the VA, continue as radicular arteries passing through the intervertebral foramen, and then penetrate the dura to supply the nerve root and spinal cord as a major source of blood.<sup>23,24</sup> Cervical DS which has intracanalicular portion, all types other than type IIC by Toyama classification, might be mainly vascularized in the spinal canal. Therefore, resection of cervical DS distally away from the entrance of the intervertebral foramen by a posterior approach might devascularize the remnant tumor and inhibit its regrowth both into the spinal canal and to the extraforaminal direction. However, no study as yet has investigated the vascularity of cervical DS and this hypothesis needs to be further examined.

# **CONCLUSION**

To the best of our knowledge, this is the first study to provide a predictive factor of remnant tumor growth after IR of cervical DS using the posterior one-way approach. No significant difference in the MIB-1 index was found between patients with and without remnant tumor growth contrary to other studies. The entrance of the intervertebral foramen, defined as the posterolateral corner of the intervertebral disc or the vertebral body, could be used as an anatomical landmark to help us know the surgical margin to lower the risk of the remnant tumor growth into the spinal canal.

# **NOTES**

Conflict of Interest: The authors have nothing to disclose.

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