

Contrast MRI findings for spinal schwannoma as predictors of tumor proliferation and motor status

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Financial support: None

Conflict of Interest: The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Abstract

Study Design: Retrospective analysis.

Objective: The goal of this study was to examine the relationship of the proliferation potency based on the MIB-1 index and motor status with features of T2-weighted images (T2WI) and contrast T1-weighted images (T1WI) of spinal schwannoma.

Summary of Background Data: Spinal schwannomas account for 55% of spinal tumors, but the relationship of cellular proliferation with MRI findings for spinal schwannoma is unknown.

Methods: The subjects were 48 patients (22 males and 26 females) with spinal schwannoma who were classified into 3 subgroups: iso/homo, high/rim, and hetero/hetero, based on T2WI /contrast T1WI. A retrospective analysis of tumor size and MIB-1 index was performed in the context of these MRI findings. Intraoperative findings and pre- and postoperative motor performance were also examined.

Results: The average tumor size was 32.4 mm (range 10 to 130 mm) and the average MIB-1 index was 3.8% (range 1 to 12). In the three subgroups, there were no significant differences in sex, age, duration of disease, tumor lesion, and dumbbell type. In the hetero/hetero group, the tumor size was significantly greater and the MIB-1 index was significantly higher (both $p < 0.05$), compared with the other two groups. The tumor adherence rate was significantly higher for hetero tumors ($p < 0.05$) and preoperative paralysis was more common in cases with tumor adhesion. The rate of paralysis improvement at 1 month was significantly lower for hetero tumors, but all cases had improved at 6 months.

Conclusions: Contrast T1WI MRI was useful for prediction of the proliferative activity and growth of spinal schwannomas, which are associated with increased tumor size and adhesion. A heterogeneous pattern on contrast T1WI indicated an increase in size and adhesion of the tumor. This pattern reflected the preoperative motor status and postoperative motor recovery.

Key words: Spinal schwannoma, Contrast MRI, Heterogeneous intensity, MIB-1 index, Motor status

Key Points

- Patients with spinal schwannoma were classified into iso/homo, high/rim, and hetero/hetero groups based on MRI findings
- Tumor proliferation potency based on the MIB-1 index was greater in the hetero/hetero group
- The tumor adherence rate was significantly higher for hetero/hetero tumors
- Paralysis improvement at 1 month postoperatively was significantly lower for hetero/hetero tumors
- Contrast T1WI MRI is useful for prediction of the proliferative activity and growth of spinal schwannoma

Mini-Abstract/Précis

The relationship of proliferation of spinal schwannoma with findings on MRI was examined in patients undergoing surgery. Contrast T1WI MRI was useful for prediction of tumor size and adhesion. A hetero/hetero pattern on MRI reflected a poorer preoperative motor status and slower postoperative motor recovery.

Introduction

Spinal schwannomas are common intradural extramedullary spinal tumors that account for 55% of spinal tumors.¹ Schwannomas are mostly benign and are classified as grade I tumors by the World Health Organization. Contrast T1-weighted images (T1WI) in Gd DTPA-enhanced MRI are useful for detection and diagnosis.² In these images, morphologic characteristics are detected as rim enhancement with peripheral, homogenous, and heterogenous features.³ Natural progression of spinal schwannomas includes varying size and tumor growth with mucinous degeneration and microcystic changes in histopathology.⁴ This diversity can be evaluated by contrast MRI, but the relationship between cell proliferation and MRI features has not been evaluated for these tumors. In this study, we examined the relationship of the proliferation potency of spinal schwannomas based on the MIB-1 labeling index with features on T2-weighted images (T2WI) and contrast T1WI. Intraoperative findings and preoperative and postoperative motor performance were also evaluated.

Materials and Methods

Patient Population

The Institutional Review Board of the School of Medicine, University of Nagoya approved this study, and each patient provided informed consent before enrollment. From 2007 to 2014, we identified 48 patients (22 males and 26 females) with a pathological diagnosis including MIB-1 index of spinal schwannoma who underwent tumor resection. Background data for the 48 patients are summarized in Table 1. The mean age at surgery was 48.6 years (range 16-81 years) and the mean disease duration was 17.5 months (range 3-48 months). The tumors were located on the cervical, thoracic, and lumbar spine in 16 patients each, and were of the dumbbell type in 15 cases (31%), with 13% classified as Type 2, 73% as Type 3, and 13% as Type 4 in the Eden classification.

Imaging Studies

All patients underwent serial MRI using T1WI (TR, 400-700 ms; TE, 9-25 ms), fast

spin-echo T2WI (TR, 3000-5000ms; TE, 96-150ms), and contrast (0.1 mmol/kg Gd-DTPA) T1WI sequences. Two board-certified neurosurgeons and two radiologists reviewed all images. The neurosurgeons worked mainly as spine surgeons and interpreted MRIs daily in clinical and research practice. At the time of the interpretation, the neurosurgeons were blinded to information on age, sex, clinical history and symptoms. Each identified the tumor in the 48 patients and assessed its location, size, signal intensity characteristics and enhancement. The reviewers (K.I. and Y.I.) identified and characterized abnormalities by consensus. Tumor size was determined as the average of the sizes measured by the reviewers, and was defined as the craniocaudal lesion diameter on contrast-enhanced MRI sagittal images.

The contrast signal characteristics were classified relative to the spinal cord, based on our previous report.³ T2WI was classified as isointense (iso), homogeneous hyperintense (high), or heterogeneous intense (hetero). Contrast enhancement patterns on contrast T1WI were classified as homogeneous (homo), as rim enhancement when peripheral (rim), or heterogeneous (hetero). Schwannomas were then classified into 3 subgroups: iso/homo, high/rim, and hetero/hetero, based on the characteristics of T2WI/contrast T1WI (Fig. 1).

Neurological Evaluation

Preoperative motor function was evaluated in manual muscle testing (MMT) on the day before the operation. Preoperative motor deficit (PMD) was defined as a decrease of ≥ 1 point in MMT below 4. Improvement of motor deficit (IMD) was defined as an increase of ≥ 1 point in postoperative MMT compared with the preoperative motor status. The paralysis improvement rate was defined as the number of IMD cases / the number of preoperative PMD cases. Postoperative motor status was checked on postoperative (POD) day 1 and POD 2, several times before discharge, and at 1, 3, and 6 months after the operation. Preoperative and postoperative motor status were both determined by doctors other than those who performed the surgery.

Pathological Investigation

Paraffin sections were dewaxed in xylene and 100% alcohol, and rehydrated. Endogenous peroxidase activity was blocked by incubating the slides with 0.5% hydrogen peroxide with methanol for 30 min. Antigen retrieval was performed by autoclaving at 121°C for 10 min. Sections were treated with normal serum diluted 1:10, followed by an anti-MIB-1 primary antibody (Dako Corp.) at 1:200 dilution. Staining using the avidin-biotin-peroxidase complex technique and nuclear staining with hematoxylin were then performed. To calculate the proliferation index, positive cells were counted in three randomly selected grids (25×25 μm) at ×400 magnification, and the results were expressed as a percentage of all cells. Cell counting was performed with minimum variability and later confirmed in a blinded fashion.

Intraoperative Findings

The patient underwent surgery in the prone position. First, laminectomy was performed, and then the dura was dissected delicately to avoid injuring the posterior wall of the tumor and neural tissue. In tumor resection, a case in which the tumor tightly adhered to dura and neural tissue was treated by piece-by-piece resection due to the difficulty of complete en-bloc resection. This type of case was defined as having an adherent tumor.

Statistical Analysis

Analysis was performed using Statistical Program for the Social Sciences ver. 21 (SPSS, Chicago, IL). Data are presented as mean ± SD. Differences between two groups were analyzed by Mann-Whitney U test and Student t-test, and those among three groups by Kruskal-Wallis test. P<0.05 was considered to be significant in all analyses.

Results

Clinical Manifestation

There were no significant differences in sex, age, duration of disease, tumor lesion, and dumbbell type among the iso/homo, high/rim, and hetero/hetero groups (Table 2). Age

distributions of the patients in each group are shown in Figure 2. Patients between 40 and 50 years old made up the largest group.

MRI Findings

On T2WI, 12 tumors (25%) were isointense, 14 (29%) were homogeneously hyperintense, and 22 (46%) were heterogeneously intense. On contrast T1WI, 22 tumors (46%) showed heterogeneous enhancement, 14 (29%) showed homogeneous enhancement, and 12 (25%) showed ring enhancement. MRI findings on T2WI for all tumors suspected to be schwannomas corresponded with those on contrast T1WI (Table 2).

Tumor Size, and Proliferation Potency

On post-contrast T1WI, the size was 42 ± 24 mm (range 23 to 130 mm) for the 22 hetero tumors, 21 ± 6 mm (range 10 to 45 mm) for the 14 homo tumors, and 29 ± 13 mm (range 16 to 45 mm) for the 12 tumors with ring enhancement. Tumor size was significantly larger in the hetero group ($P < 0.05$) (Table 2).

The MIB-1 index was 5.8 ± 2.5 (range 2 to 12) for the 22 hetero tumors, 2.2 ± 0.8 (range 1 to 5) for the 14 homo tumors, and 2.9 ± 1.4 (range 1 to 5) for the 12 tumors with ring enhancement. The 4 cases with a MIB-1 index $\geq 10\%$ were all in the T1WI hetero group, and the MIB-1 index was significantly higher in this group ($p < 0.05$) (Table 2).

One tumor of size 68 mm gave heterogeneous intense T2WI and post-contrast T1WI, had hypocellular and cystic degeneration characterized as Antoni B, and a MIB-1 index of 10% (Fig. 3). A tumor of size 15 mm showed isointense T2WI and homogeneous intense contrast T1WI, had a compact texture with interwoven bundles of long bipolar spindle cells characterized as Antoni A, and a MIB-1 index of 2% (Fig. 4).

Intraoperative and Postoperative Findings

In intraoperative findings, adherence of the tumor to dura and neural tissue occurred for 12 hetero tumors, 5 homo tumors, and 3 cases with ring enhancement. The tumor adherence rate

was significantly higher for hetero tumors. PMD was present in 9 cases with hetero tumors, 5 with homo tumors, and 3 with ring tumors. The rates of paralysis improvement at 1 month were 22%, 80% and 100% for cases with hetero, homo and ring tumors, respectively, with a significantly lower rate for hetero tumors ($p < 0.05$). Ultimately, there was no worsening of paralysis in any cases and all had improved at 6 months (Table 3).

Discussion

Spinal schwannomas are derived from the nerve sheath and are solitary, well-circumscribed and largely benign neoplasms.^{5,6} Natural progression usually occurs with a slow growth rate of 2.3-5.3% in volume per year^{3,5,7}, and the tumor undergoes necrosis during cell division and develops cystic properties that contribute to the increase in size.³

The monoclonal anti-MIB-1 antibody was raised against a recombinant Ki-67 antigen, and the MIB-1 index has the same sensitivity and specificity as Ki-67 as a marker of proliferation and growth of tumor cells.⁸ Ozawa et al. found a mean MIB-1 index of 6.4% (range 0.9-15.7%) in spinal schwannomas, with a significantly lower index for small tumors and in elderly patients.⁹ Torres-Mora et al. found a MIB-1 index of $< 5\%$ in most schwannomas.¹⁰ In this study, the average MIB-1 index was 3.8% (range 1 to 12%), which is consistent with these reports. Bedavanija et al. suggested that schwannomas with higher proliferative activity (higher MIB-1 index) in the tumor itself have a higher growth rate clinically.¹¹ Fukuda et al. found that tumor volume may be affected by both the actual cellular turnover rate, and by cell death, intratumoral hemorrhage, cystic degeneration, and scarring.¹²

Schwannomas have several growth patterns on MRI, including unchanging, continuous slight growth, and initial slight growth followed by rapid growth.¹³ However, the relationship between the characteristics on contrast T1WI and the MIB-1 index has not been examined previously for spinal schwannomas. This study indicated that the MIB-1 index is significantly higher and the tumor size is significantly larger for tumors with a heterogeneous pattern on contrast T1WI, compared to schwannomas with other patterns. In contrast T1WI, a black geode sign is somewhat specific for an extracranial schwannoma, with the outer rings being

1 circular and the inner rings having a lobular configuration.¹⁴ However, this pattern was
2 not included in our series.
3

4 Histologically, typical schwannomas are composed of intermixed Antoni A and B
5 components, with cellular arrangements of short bundles and interlacing fascicles defined as
6 Antoni A, and less cellular and organized patterns with more myxoid components as Antoni
7 B.⁵ Ando et al. found that Antoni B tumors have cystic changes and mucus production, and
8 tend to have a higher volume due to the increased cystic portion.³ In general, a relatively high
9 MIB-1 index indicates high proliferation, which could lead to greater differentiation
10 characterized by mucinous degeneration, a microcystic appearance, and necrotic changes
11 classified as Antoni B. These differentiated features histologically were seen in the current
12 study as heterogeneous intense signals on contrast T1WI, consistent with previous reports.
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15 Heterogeneous intense signals on contrast T1WI indicate high proliferation and
16 differentiation. This leads to an increased tumor size that increases vulnerability to
17 continuous compression of the spinal cord. This feature was present in many PMD cases, and
18 tumor adhesion in intraoperative findings was linked to a poor paralysis improvement rate. In
19 surgery for the hetero tumor type, adhesion is a particular concern and requires a careful
20 surgical procedure to prevent postoperative spinal cord damage.
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23 There are several limitations in this study. First, the sample size was relatively small, and
24 an increase in number is desirable for a comparative study, although significant differences
25 were found. Second, retrospective data were used in the study and surgery was not performed
26 based on preoperative Gd contrast images. In the future, improved surgical procedures may
27 be possible with use of these images. Third, motor status was evaluated only using a change
28 of MMT score, but the MIB-1 index and a pathological diagnosis were available in all cases.
29 To our knowledge, this is the first report to examine contrast MRI findings for spinal
30 schwannoma as predictors of tumor proliferation, in addition to evaluation of motor status.
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37 Conclusion

38 The cell proliferative activity of spinal schwannomas differed significantly among three
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groups defined based on MRI patterns. The MIB-1 index was significantly higher and the tumor size was significantly larger for tumors with a heterogeneous pattern on contrast T1WI, due to differentiated features such as mucinous degeneration, microcystic changes, and necrotic changes. We conclude that contrast T1WI MRI is useful for prediction of the proliferative activity and growth of spinal schwannomas, which are associated with increased tumor size and adhesion. A heterogeneous intense pattern on contrast T1WI may indicate a fast growing schwannoma that might be more likely to cause symptoms due to compression of the spinal cord and cauda equina. These patterns reflect the preoperative motor status and postoperative motor recovery. Thus, contrast MRI findings are of relevance in understanding motor performance.

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Table 1. Summary of 48 cases with spinal schwannoma

	Number of patients (n=48)
Sex (M/F)	22/26
Age (y)	48.6 (13-81)
Lesion	
Cervical	16
Thoracic	16
Lumbar	16
Location	
Dumbbell	15
Eden Type 2	2
Type 3	11
Type 4	2
Not Dumbbell	33
Size (mm)	32.4 (10-130)
Total	48

Table 2. Patient and tumor information in each group.

T2WI/ post-contrast T1WI	hetero/hetero n=22	iso/homo n=14	high/ring n=12	p
Patient information				
Sex (M/F)	12/10	4/10	5/7	n.s.
Age (y)	47.4	48.7	52.4	n.s.
Duration period (months)	19.2 (4-72)	18.0 (4-40)	16.6 (3-48)	n.s.
Tumor information				
Lesion (C/T/L)	9/ 6/ 7	4/ 5/ 5	3/ 5/ 4	n.s.
Dumbbell type (n)	7 (31%)	4 (29%)	3 (25%)	n.s.
Tumor diameter (mm)	42 (23-130) *	21 (10-45)	29 (16-45)	*p<0.05
MIB-1 index (%)	5.8 (4-12) *	2.2 (1-5)	2.9 (1-5)	*p<0.05

C: Cervical, T: Thoracic, L: Lumbar

* Tumor diameter and MIB-1 index were significantly greater in the hetero/hetero group
(p<0.05 by Kruskal-Wallis test)

Table 3. Intraoperative adhesion and pre-and postoperative motor status in each group.

T2WI/post-contrast T1WI	hetero/hetero n=22	iso/homo n=14	high/ring n=12	P
Intraoperative findings				
With adhesions (n)	12*	3	2	P<0.05
Motor status				
PMD (n)	9	5	3	
IMD at 1 month (n)	2	4	3	
Improvement rate at 1 month (%)	22*	80	100	P<0.05
IMD at 6 months (n)	9	5	3	
Improvement rate at 6 months (%)	100	100	100	

PMD: Preoperative motor deficit, defined as a decrease of ≥ 1 point in MMT below 4

IMD: Improvement of motor deficit, defined as an increase of ≥ 1 point in MMT compared with the preoperative motor status

Improvement rate is defined as the number of IMD cases / the number of PMD cases

* Adhesion, motor status, and improvement rate were significantly greater in the hetero/hetero group ($p<0.05$ by Kruskal-Wallis test)

Figure Legends

Figure 1. Sagittal images in T2WI/contrast T1WI. A: hetero/hetero images, B: iso/homo images, C: high/ring of enhancement images.

Figure 2. Age distribution of patients in the hetero/ hetero (stripes), iso/homo (gray), and high/ring (black) groups.

Figure 3. A: Tumor with heterogeneous intensity on T2WI. B: Tumor with heterogeneous intensity on post-contrast T1WI. C: Hypocellular and cystic degeneration, characterized as Antoni B with hematoxylin-eosin staining ($\times 400$). D: 10% MIB-1 index showing staining of positive cells ($\times 400$).

Figure 4. A: Tumor with an isointense signal on T2WI. B: Tumor with homogeneous intensity on post-contrast T1WI. C: Compact texture with interwoven bundles of long bipolar spindle cells, characterized as Antoni A with hematoxylin-eosin staining ($\times 400$). D: 2% MIB-1 index showing staining of positive cells ($\times 400$).

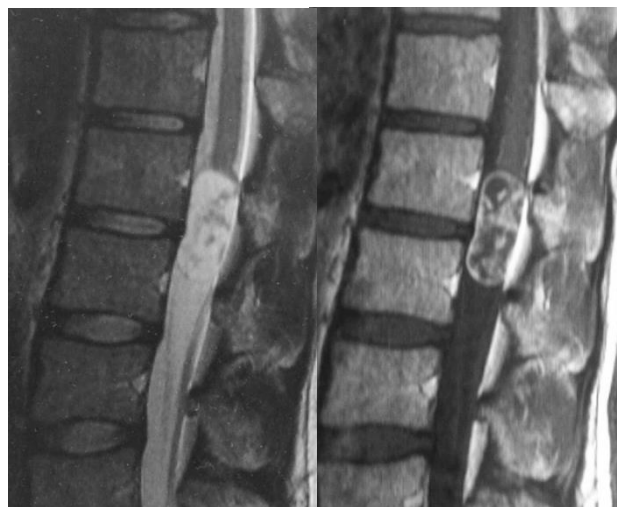
Figure1

T2WI/ contrast T1WI

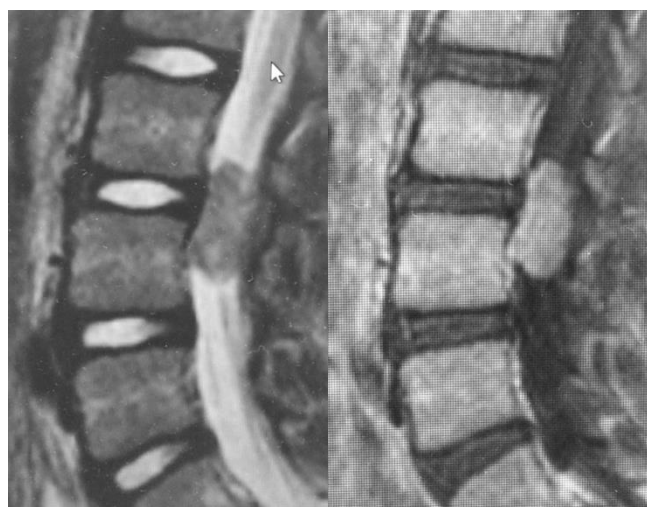
hetero/hetero

iso/ homo

high/ring



(A)



(B)



(C)

Figure2

Cases

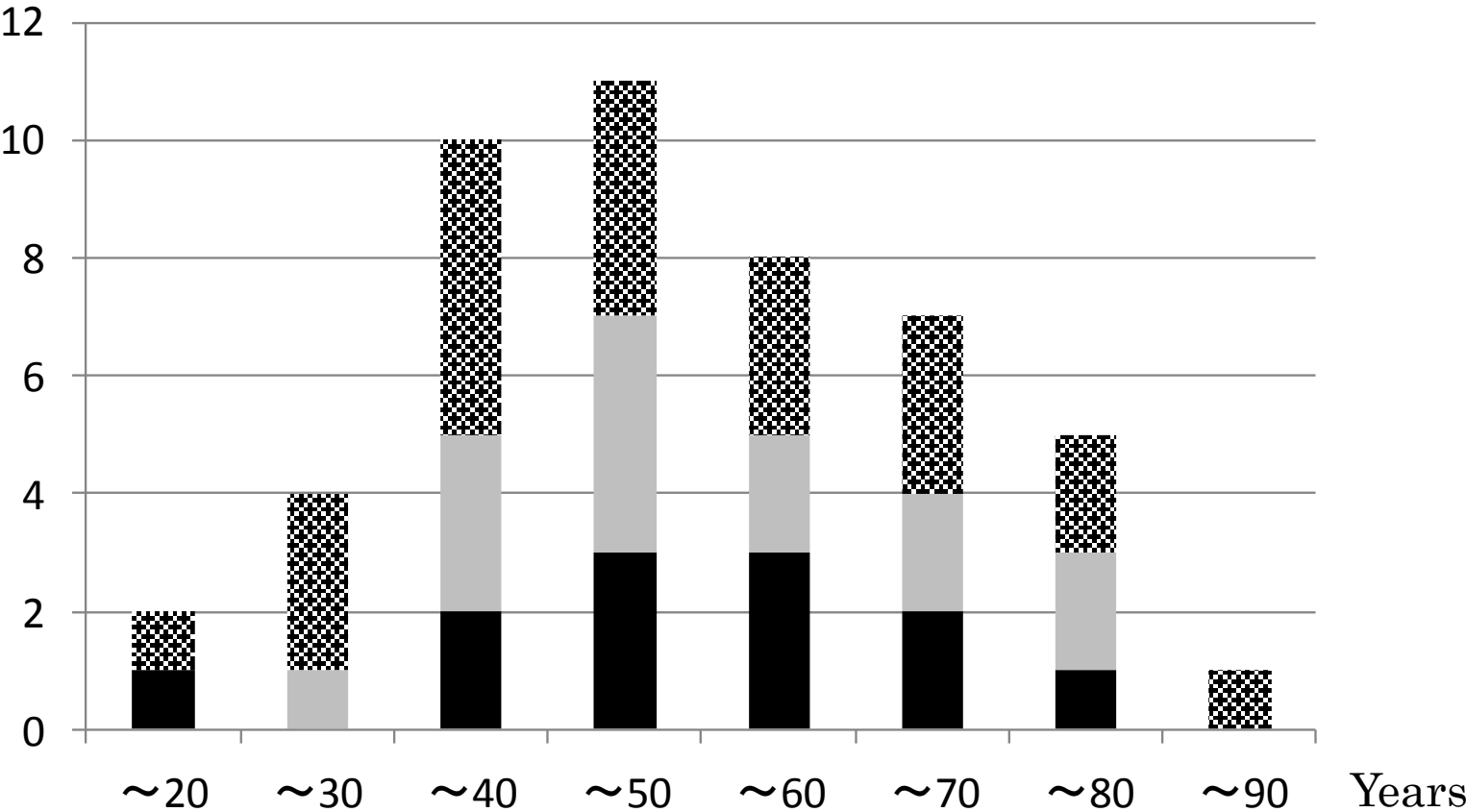


Figure 3

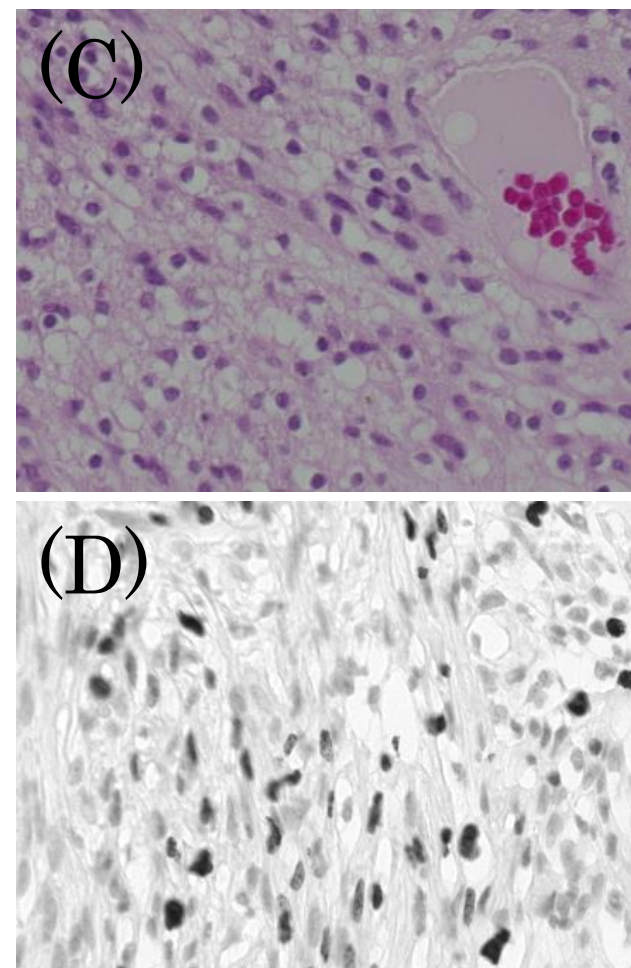
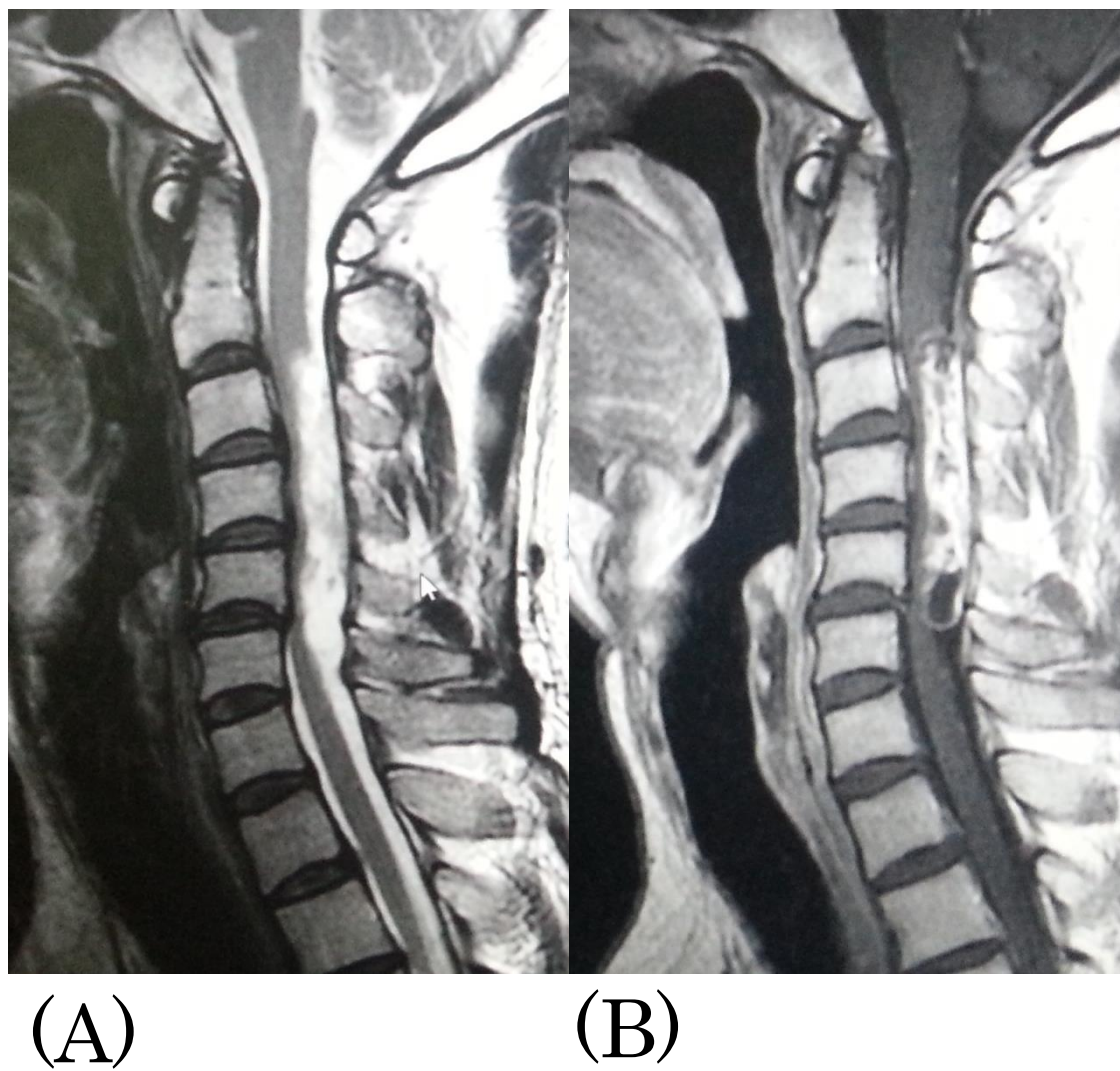


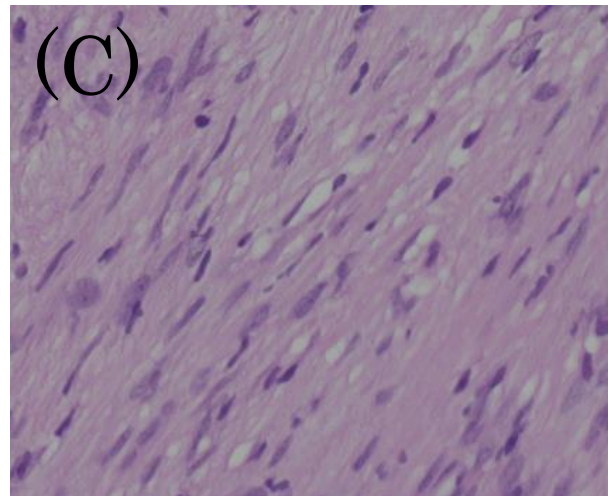
Figure 4



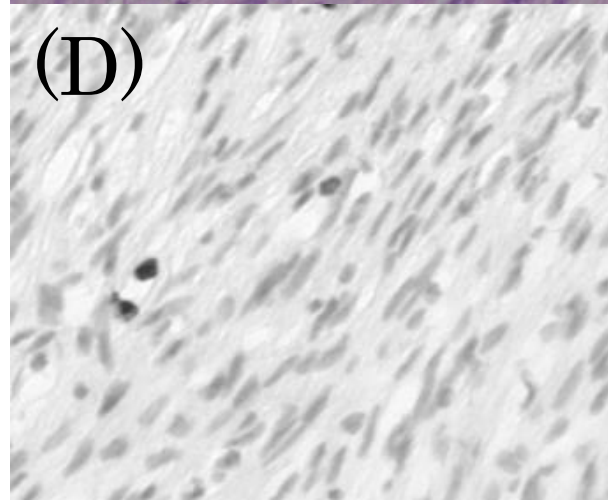
(A)



(B)



(C)



(D)