Rapamycin treatment reduced reactive gliosis at the lesion site in a spinal cord ischemia model (Codeluppi et al., 2009). Rapamycin activates autophagy and improves myelination in a demyelinating neuropathy model (Rangaraju et al., 2010). In this study, the inhibition of mTOR by rapamycin during the acute phase of SCI significantly reduced the neural tissue damage and locomotor impairment. Therefore, the administration of rapamycin during the acute phase should induce a cytoprotective effect to reduce the secondary injury of SCI. Further studies may clarify the effect of rapamycin on regulating neuroprotection and neuroregeneration and lead to a novel therapeutic strategy after SCI.

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Author Disclosure Statement

No competing financial interests exist.

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Tumors at the lateral portion of the C1–2 interlaminar space compressing the spinal cord by rotation of the atlantoaxial joint: new aspects of spinal cord compression

Report of 2 cases

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The authors describe 2 patients with C-2 nerve root tumors in whom the lesions were located bilaterally in the lateral portions of the C1–2 interlaminar space and compressed the spinal cord when the atlantoaxial joint was rotated.

The patients were adult men with neurofibromatosis. Each presented with clumsiness of both hands and motor weakness of the extremities accompanied by spastic gait. Magnetic resonance imaging of the cervical spine performed with the neck in the neutral position showed tumors at the bilateral lateral portion of the C1–2 interlaminar space without direct compression of the spinal cord. The spinal cord exhibited an l-shaped deformity at the same level as the tumors in one case and a trapezoidal deformity at the same level as the tumors in the other case. Computed tomography myelography and MRI on rotation of the cervical spine revealed bilateral intracanal protrusion of the tumors compressing the spinal cord from the lateral side. The tumors were successfully excised and occipitocervical fusion was performed.

The tumors were pushed out into the spinal canal from the bilateral lateral portion of the interlaminar spaces due to rotation of the atlantoaxial joint. This was caused by a combination of posteromedial displacement of the lateral mass on the rotational side of the atlas and narrowing of the lateral portion of the interlaminar space on the contralateral side due to the coupling motion of the lateral bending and extension of the atlas. The spinal cord underwent compression from both lateral sides in a one-way rotation. Without sustained spinal cord compression, intermittent long-term dynamic spinal cord compression from both lateral sides should induce a pathognomonic spinal cord deformity and the onset of paralysis. To the authors' knowledge, there have been no reports of the present conditions—that is, the bilateral protrusion of tumors from the bilateral lateral portion of the C1–2 interlaminar spaces into the spinal canal due to atlantoaxial rotation.

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Key Words • **spinal cord tumor** • **dumbbell tumor** • **neurofibromatosis** • **atlantoaxial joint** • **oncology**

Neurofibromatosis is often complicated by multiple spinal cord tumors such as schwannomas and neurofibromas.[1,2,9] The C-2 nerve root frequently arises in such tumors.[7] Spinal cord tumors occupying the spinal canal compress the cord and nerve roots, causing various neurological symptoms.[1,2,7] When patients with spinal cord tumors present with paralysis, tumors directly compressing the spinal cord are clearly observed on MRI. Goel et al.[3] presented a series of 60 patients with C-2 nerve root tumors. Fifty-six of the 60 patients had unilateral C-2 nerve root tumors, whereas 4 patients had bilateral tumors. In 9 patients, including all 4 with bilateral tumors, there was evidence of NF. Bilateral C-2 tumors were often observed in patients with NF. In the present report we describe 2 cases of NF presenting with cervical myelopathy. In both patients, conventional MRI of the cervical spine revealed tumors located at the bilateral lateral portion of the C1–2 interlaminar space that did not compress the spinal cord directly. However, it demonstrated an unusual l-shaped deformity of the spinal cord at the same level as the tumors in one case and a trapezoidal deformity of the spinal cord at the same level as the tumors in the other case. In both cases, CTM and MRI on rotation of the cervical spine revealed bilateral intracanal protrusion of the tumors and direct compression of the spinal cord. To our knowledge, there have been no previous reports of the present conditions.

Abbreviations used in this paper: CTM = CT myelography; JOA = Japanese Orthopaedic Association; NF = neurofibromatosis.

* Drs. Ozawa and Kusakabe contributed equally to this work.

Case Reports

Case 1

History and Examination. In 2002 this 58-year-old man with NF Type 1 began to experience an unstable gait. Since early 2008, he had felt numbness and clumsiness of both hands and gait disturbance that rapidly progressed. He therefore visited our clinic. Neurological examination revealed lower-extremity muscle weakness. Tendon reflexes of the upper and lower extremities were accelerated bilaterally. We established a diagnosis of myelopathy of the upper cervical spine. The patient's JOA score for cervical myelopathy[4] was 8 (combined score of 2, 1, 1, 1, 1, and 2) of a possible 17 points. The symptoms did not change with flexion, extension, or rotation of the neck. Plain lateral radiography of the cervical spine showed no spinal canal stenosis or instability. Midsagittal T2-weighted MRI performed with the patient in the neutral position showed spinal cord swelling with a higher signal intensity region at C1–2. Axial MRI revealed tumors at the bilateral lateral portion of the C1–2 interlaminar space and slight indentation of the dural tube. Although there was adequate subarachnoid space around the spinal cord, the cord exhibited an I-shaped deformity at C1–2 (Fig. 1). The spinal cord was not compressed directly and seemed to show atrophy. We performed MRI and CTM under flexion, extension, and rotation of the cervical spine. The flexion and extension MRI and CTM studies did not show any spinal cord compression. However, the rotation MRI and CTM studies revealed bilateral intracanal protrusion of the tumors compressing the lateral side of the spinal cord (Fig. 2). We considered that the paralysis and spinal cord deformity were caused by protrusion of the tumors from the bilateral lateral portion of the C1–2 interlaminar space into the spinal canal following rotation of the cervical spine.

Operation. We excised the tumors of the C1–2 interlaminar space following resection of the C-1 posterior arch and posterior fusion (occiput–C3) with segmental instrumentation. The tumors seemed to originate from the C-2 nerve root ganglion, and they did not adhere to the dura mater. The tumors were excised in a piecemeal manner. Histologically the tumors were determined to be neurofibromas.

Postoperative Course. At 4 years after surgery, the patient had improved neurologically, and his JOA score had increased to 13. Bone fusion was complete 1 year postoperatively. Magnetic resonance images showed restoration of the spinal cord shape with enlargement of the higher signal intensity region on T2-weighted sequences. Tumors at the bilateral lateral portion of the C1–2 interlaminar space had not recurred (Fig. 3).

Case 2

History and Examination. In early 2008 this 32-year-old man with NF Type 1 experienced numbness and clumsiness in both hands and gait disturbance. He visited our clinic. Neurological examination revealed upper-extremity muscle weakness. The triceps tendon reflex and knee and ankle jerks were accelerated bilaterally. We made a diagnosis of cervical myelopathy in the upper cervical region. The patient's JOA score was 13 (combined score of 3, 3, 1, 2, 1, and 3). The symptoms did not change when the patient moved his neck. Plain lateral radiography showed no unusual findings in the cervical spine. Sagittal T2-weighted

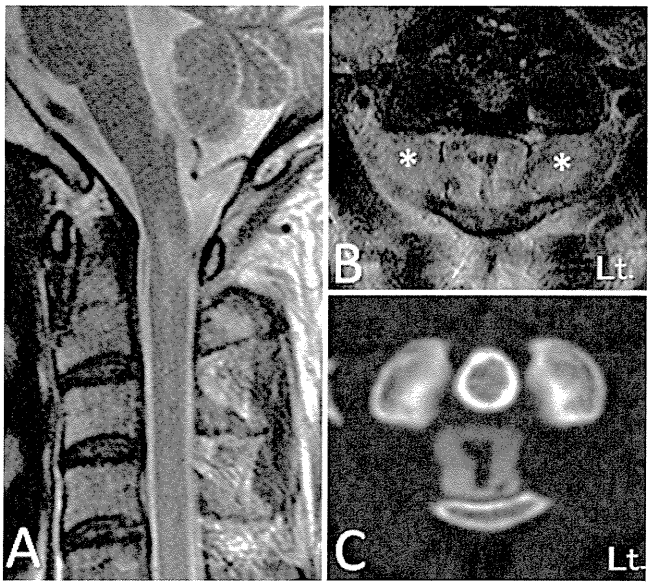

FIG. 1. Case 1. **A:** Sagittal T2-weighted MR image taken in the neutral position showing spinal cord swelling with a higher signal intensity region at C1–2. **B:** Axial T2-weighted MR image at C1–2 showing tumors at the bilateral lateral portion of the C1–2 interlaminar space *(asterisks)* and slight indentations of the dural tube. **B and C:** Axial T2-weighted MRI and CTM studies at C1–2 showing an I-shaped deformity of the spinal cord despite adequate subarachnoid space around the spinal cord.

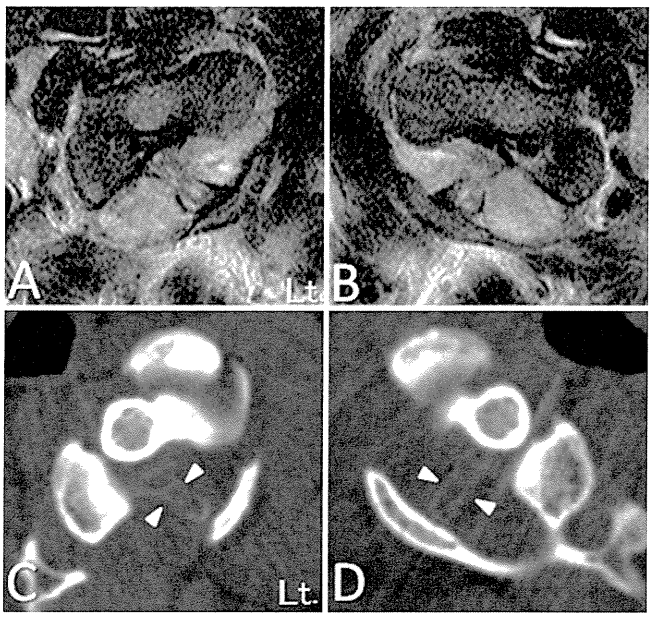

FIG. 2. Case 1. Axial T2-weighted MRI and CTM scans at C1–2 on rotation of the cervical spine revealing bilateral intracanal protrusion of the tumors compressing the lateral side of the spinal cord (rotation to the right **[A and C]** and rotation to the left **[B and D]**). The *arrowheads* show the indentation of the dural tube.

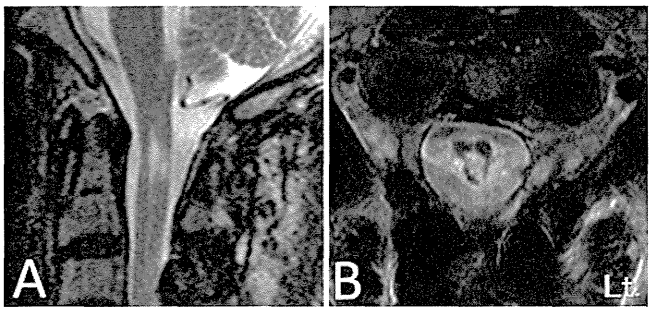

FIG. 3. Case 1. Sagittal **(A)** and axial **(B)** T2-weighted MR images demonstrating restoration of the spinal cord shape and enlargement of the higher signal intensity region 4 years after surgery.

MRI with the patient's neck in the neutral position showed spinal cord swelling and a higher signal intensity region at C1–2. Axial MRI demonstrated tumors in the bilateral lateral portion of the C1–2 interlaminar space and adequate subarachnoid space around the spinal cord. Although the spinal cord was not compressed directly, it showed a trapezoidal deformity at C1–2 (Fig. 4). Both MRI and CTM performed on rotation of the cervical spine revealed bilateral intracanal protrusion of the tumors with direct lateral compression to the spinal cord (Fig. 5). We determined that the patient's paralysis and spinal cord deformity were induced by the protrusion of tumors into the spinal canal.

Operation. We performed tumor excision and occiput–C3 posterior fusion. The tumors seemed to originate from the C-2 nerve root ganglion. Most of the tumors were excised in a piecemeal manner. The histological diagnosis of the tumors was neurofibroma.

Postoperative Course. At 4 years after surgery, the patient showed an excellent neurological improvement, and his JOA score increased to 16. Magnetic resonance imaging demonstrated restoration of the spinal cord shape. The tumors did not recur during follow-up (Fig. 6).

Discussion

We have reported that spinal dumbbell tumors accounted for 18% of all spinal cord tumors.[8] The most frequent originating nerve root is C-2, which passes through the lateral portion of the interlaminar space between the C-1 posterior arch and the C-2 lamina. It is necessary to recognize that tumors located at the bilateral lateral portion of the C1–2 interlaminar space may protrude into the spinal canal on rotation of the cervical spine, even though the tumors are not observed in the spinal canal in the neutral position. On the occasion, the spinal cord is compressed from the lateral side by a protruding tumor, so that the spinal cord shows the characteristic form of an I-shaped elongation in the anteroposterior direction. This is a clue to the diagnosis of this unusual pathological entity.

The lateral atlantoaxial joint consists of the lower articular surface of the lateral mass of the atlas and the upper articular surface of the axis. The rotational range of motion at the atlantoaxial joint is the largest in the spine. In a 3D kinetic analysis of the atlantoaxial joint, the atlas shows the coupling motion of right bending and extension to the axis during left rotation and the coupling motion of left bending and extension to the axis during right rotation.[5] In the present cases, the tumors were in the bilateral lateral portion of the interlaminar space at C1–2. They were pushed out into the spinal canal from the bilateral lateral portion of the interlaminar spaces by the rotation of the cervical spine. This was caused by a combination

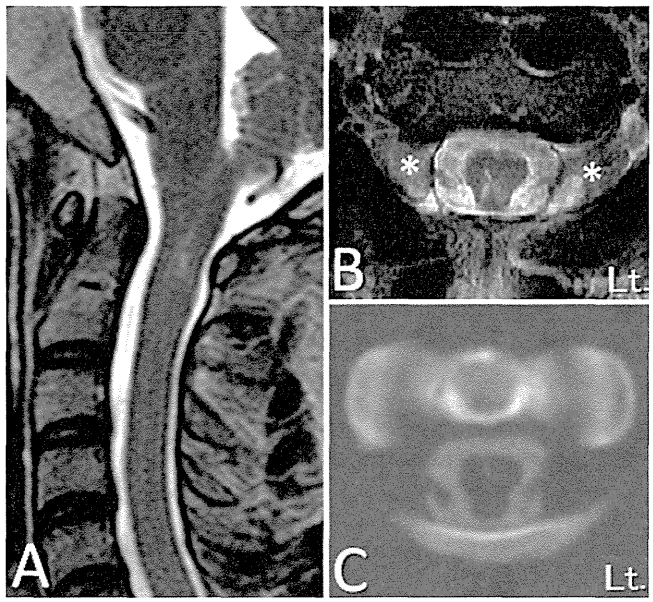

FIG. 4. Case 2. **A:** Sagittal T2-weighted MR image taken in the neutral position showing spinal cord swelling with a higher signal intensity region at C1–2. **B:** Axial T2-weighted MR image at C1–2 demonstrating tumors at the bilateral lateral portion of the C1–2 interlaminar space *(asterisks)*. **B and C:** Axial T2-weighted MRI and CTM scans at C1–2 revealing a trapezoidal deformity of the spinal cord despite adequate subarachnoid space around the spinal cord.

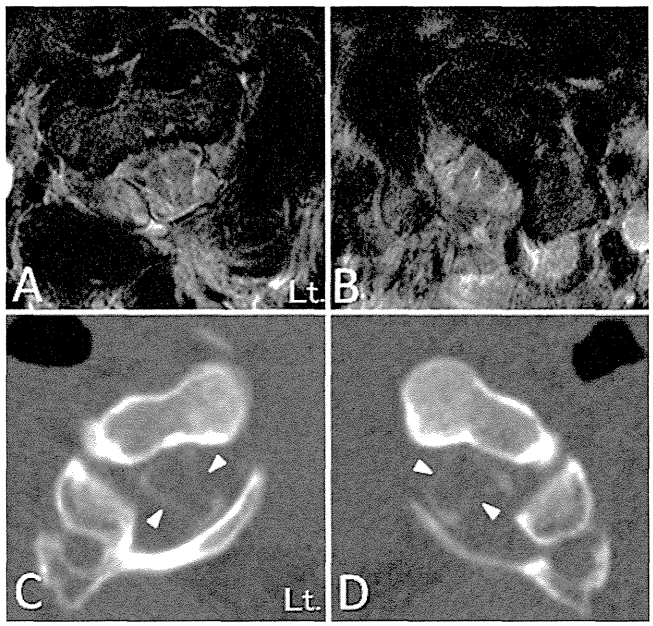

FIG. 5. Case 2. Axial T2-weighted MRI and CTM images at C1–2 on rotation of the cervical spine showing bilateral intracanal protrusion of the tumors compressing the lateral side of the spinal cord (rotation to the right **[A and C]** and rotation to the left **[B and D]**). The *arrowheads* show the indentation of the dural tube.

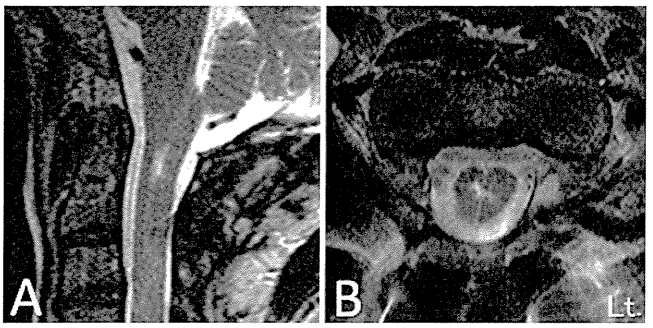

FIG. 6. Case 2. Sagittal (A) and axial (B) T2-weighted MR images demonstrating restoration of the spinal cord shape 4 years after surgery.

of posteromedial displacement of the lateral mass on the rotational side of the atlas and narrowing of the lateral portion of the interlaminar space on the contralateral side due to the coupling motion. In other words, the spinal cord underwent compression from both lateral sides in a one-way rotation. The head and neck are considered to be oriented either to the left or right most of time. Without sustained spinal cord compression, intermittent long-term dynamic spinal cord compression can induce a pathognomonic deformity of the spinal cord and the onset of paralysis. To our knowledge, there have been no reports of the present conditions—that is, bilateral protrusion of tumors into the spinal canal from the bilateral lateral portion of the C1–2 interlaminar spaces due to atlantoaxial rotation.

Kokubun[6] has reported that 30% of patients with dumbbell tumors originating from C-2 nerve roots present with electric-like shocks extending down the trunk that are triggered by rotation of the neck, and 10% of these patients present with transient muscle weakness of the extremities caused by rotation of the neck. This is considered to be the result of the spinal cord compression enhanced by rotation of the atlantoaxial joint, as observed in the present cases. Although the symptoms did not change on rotation of the neck in our patients, checking for any changes in the symptoms with the neck rotated is a simple examination that can provide important clues when establishing a diagnosis.

The excision of the tumors alone or in combination with atlantoaxial fusion should be performed. Excision of the tumors may be incomplete because of excess bleeding, or the tumors in NF may regenerate over many years. Some improvement of the paralysis over the long term would be expected by adding atlantoaxial fusion. There are several methods available for atlantoaxial fusion. Posterior fusion techniques including the use of Gallie wires, Brooks wires, and Halifax interlaminar clamps were unfeasible because of C-1 posterior arch resection necessary to excise the tumors. We thought that the Magerl screw technique and the posterior C-1 lateral mass–C2 pedicle screw fixation technique were also not feasible because of the bone erosion of the atlas and the upper part of the axis. Therefore, we chose occipitocervical fusion to maintain the frail spinal cord in complete repose for an extended period. Both patients showed an excellent improvement after surgery. On the other hand, we must take the difficulty of reoperation into consideration when the residual tumors grow and paralysis recurs.

Conclusions

We described 2 cases of C-2 nerve root tumors located in the bilateral lateral portion of the C1–2 interlaminar space and compressing the spinal cord on rotation of the cervical spine. It is important to recognize that tumors in the bilateral lateral portion of the C1–2 interlaminar space can protrude into the spinal canal by rotation of the atlantoaxial joint, even though the spinal cord is not compressed in the neutral position.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Ozawa, Kusakabe, Aizawa, Nakamura. Acquisition of data: Ozawa, Kusakabe. Analysis and interpretation of data: Ozawa, Kusakabe. Drafting the article: Ozawa, Kusakabe. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ozawa. Study supervision: Ozawa, Kusakabe, Ishii, Itoi.

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CLINICAL CASE SERIES

Neuroprotective Therapy Using Granulocyte Colony–Stimulating Factor for Patients With Worsening Symptoms of Thoracic Myelopathy

A Multicenter Prospective Controlled Trial

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Study Design. An open-labeled multicenter prospective controlled clinical trial.

Objective. To confirm the feasibility of granulocyte colony–stimulating factor (G-CSF) administration for patients with thoracic myelopathy.

Summary of Background Data. Although G-CSF is best known as an important cytokine commonly used to treat neutropenia, it also has nonhematopoietic functions. Previous experimental studies have shown that G-CSF can enhance tissue regeneration of several organs, such as the heart and the brain. We previously reported that G-CSF promotes functional recovery after spinal cord injury in rodents. On the basis of those findings, we started a clinical trial of neuroprotective therapy, using G-CSF for patients with worsening symptoms of thoracic myelopathy.

Methods. Patients whose Japanese Orthopaedic Association (JOA) score for thoracic myelopathy had decreased 2 points or more during a recent 1-month period were eligible for entry. After giving informed consent, patients were assigned to G-CSF and control groups. The G-CSF group (n = 10) received G-CSF 10 μg/kg per day intravenously for 5 consecutive days. The control group (n = 14) received similar treatments as the G-CSF group except for G-CSF administration. The primary outcome was JOA recovery rate at 1 month after G-CSF administration or initial treatment.

Results. There was greater improvement in neurological functioning between baseline and 1-month follow-up in the G-CSF group (JOA recovery rate: 29.1 ± 20.5%) than in the control group (JOA recovery rate: 1.1 ± 4.2%) ($P < 0.01$). No serious adverse events occurred during or after the G-CSF administration.

Conclusion. The results provide evidence that G-CSF administration caused neurological recovery in patients with worsening symptoms of thoracic compression myelopathy.

Key words: neuroprotective therapy, granulocyte colony–stimulating factor, thoracic myelopathy, clinical trial. **Spine 2012;37:1475–1478**

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Granulocyte colony–stimulating factor (G-CSF) is a 19.6 kDa glycoprotein. It is best known as a growth factor for hematopoietic progenitor cells and is commonly used to treat neutropenia and to mobilize peripheral blood-derived hematopoietic stem cells for transplantation.[1] Several experimental studies have indicated that G-CSF also has nonhematopoietic functions and can enhance the tissue regeneration of several organs such as the heart and the brain.[2,3] We previously reported that G-CSF promotes functional recovery after spinal cord injury in rodents.[4–6]

On the basis of the experimental results described earlier, we hypothesized that administration of G-CSF can effect neurological recovery in patients with progressive compression

myelopathy and started a phase I/IIa clinical trial of G-CSF neuroprotective therapy.[7] In this study, we conducted a multicenter prospective controlled clinical trial (phase IIb) to assess the feasibility of the G-CSF therapy for patients with worsening symptoms of thoracic compression myelopathy.

MATERIALS AND METHODS

This clinical trial was designed as an open-labeled multicenter prospective controlled study and was performed with the approval of the institutional review board of each participating institute. Since April 2010, we recruited patients 20 to 85 years of age, in whom the Japanese Orthopaedic Association (JOA) score (full score = 11 points) decreased 2 points or more during a recent 1-month period.[7]

We assigned patients to a G-CSF group and a control group. Patients in the G-CSF group were given G-CSF 10 μg/kg per day intravenously for 5 consecutive days. Patients in the control group were enrolled in similar treatments as the G-CSF group except for the G-CSF administration. To evaluate neurological improvement resulting from neuroprotective therapy with G-CSF, we planned to follow patients in both groups without surgical treatment for 1 month after G-CSF administration or initial treatment and to provide them with equivalent conservative treatment, such as bed rest. When patients were given informed consent documents, we explained our plans regarding the time of surgery, and we administered G-CSF only to those patients who agreed with the protocol.[7] The G-CSF therapy was performed only in the institute to which the corresponding author (MY) belonged. At the other institutes, patients were treated without G-CSF administration.

The primary outcome was the JOA recovery rate at 1 month after G-CSF administration or initial treatment. We evaluated the patients' severity of myelopathy using the JOA score.[7] Then, we evaluated their motor and sensory functions by determining scores for muscle power and pain sensation according to the American Spinal Injury Association score.[7] In this study, 2 orthopedic spine surgeons specializing in thoracic spine surgery evaluated patients' neurological status independently after G-CSF administration and then mean data were calculated. In addition, we analyzed hematological data from the treated patients.

Statistical analyses were performed using a Mann-Whitney *U* test and a Fisher exact probability test. A *P* value less than 0.05 was considered statistically significant. Results are presented as means ± standard deviation of the mean.

RESULTS

Patient Data

Between April 2010 and October 2010, 24 patients (10 patients in the G-CSF group and 14 patients in the control group) were enrolled and examined for 1 month. Patient data for both groups are summarized in Table 1. In the control group, many patients had the most stenotic level at the lower thoracic spine (T9–T12), although no statistical difference was observed in the distribution of the most stenotic level between the G-CSF and control groups. No statistical difference was observed between groups regarding the spinal canal occupation ratio by heterotopic ossification or vertebral spurs at the most stenotic level.

TABLE 1. G-CSF and Control Group Patient Data

	G-CSF	Control
No. of patients	10	14
Sex		
Male	9	11
Female	1	3
Age, *M* ± SD (range), yr	49.7 ± 8.9 (32–74)	53.1 ± 10.6 (22–72)
Diagnosis		
Thoracic OPLL	5	4
Thoracic OLF	2	6
Thoracic spondylotic myelopathy	3	4
Most stenotic level		
Upper thoracic (T1–T4)	4	4
Middle thoracic (T5–T8)	4	2
Lower thoracic (T9–T12)	2	8
Surgical procedure		
Posterior decompression	5	10
Posterior decompression with instrumented fusion	5	4

G-CSF indicates granulocyte colony–stimulating factor; OPLL, ossification of posterior longitudinal ligament; OLF, ossification of ligamentum flavum.

Neurological Recovery

The JOA score immediately before G-CSF administration or initial treatment was 3.8 ± 1.3 in the G-CSF group and 4.1 ± 1.4 in the control group, showing no statistical difference between groups (Table 2). There was greater improvement in neurological functioning between baseline and 1-month follow-up in the G-CSF group (JOA recovery rate: 29.1 ± 20.5%) than in the control group (JOA recovery rate: 1.1 ± 4.2%) ($P < 0.01$) (Table 2).

Regarding the muscle power score, greater improvement between baseline and 1-month follow-up was observed in the G-CSF group (improvement of muscle power score: 2.8 ± 2.8) than in the control group (improvement of muscle power score: 1.6 ± 5.3) ($P < 0.05$) (Table 2).

There was also greater improvement in the pain sensation score between baseline and 1-month follow-up in the G-CSF

TABLE 2. Neurological Recovery

	G-CSF $M \pm SD$ (range)	Control $M \pm SD$ (range)	P
JOA score			
Immediately before treatment	3.8 ± 1.3 (1–5.5)	4.1 ± 1.4 (1.5–6.0)	0.501
One month after treatment	5.7 ± 2.4 (1.0–9.0)	4.3 ± 1.3 (2.5–6.0)	0.061
Recovery rate	29.1 ± 20.5 (0.0–63.6)	1.1 ± 4.2 (0.0–15.8)	<0.01
Muscle power score			
Immediately before treatment	41.9 ± 7.8 (22–50)	37.0 ± 15.5 (0–50)	0.884
One month after treatment	44.7 ± 7.6 (25–50)	38.6 ± 12.6 (20–50)	0.241
Increase of muscle power score	2.8 ± 2.8 (0–9)	1.6 ± 5.3 (0–20)	<0.05
Pain sensation score			
Immediately before treatment	68.3 ± 9. 7 (59–78)	74.1 ± 9.8 (60–92)	0.364
One month after treatment	74. 7 ± 10.4 (62–88)	74.9 ± 8.9 (64–92)	0.578
Increase of pain sensation score	6.4 ± 5.5 (1–17)	1.0 ± 3.2 (0–12)	<0.01

Recovery rate = (postoperative score − preoperative score/full score − preoperative score) × 100 (%).

Muscle power score (motor: 0–50 points) and pain sensation (pin prick: 0–98 points) score were defined according to the American Spinal Injury Association score.

G-CSF indicates granulocyte colony–stimulating factor; JOA score, Japan Orthopaedic Association score (thoracic myelopathy: 0–11 points).

group (improvement of the pain sensation score: 6.4 ± 5.5) than in the control group (improvement of the pain sensation score: 1.0 ± 3.2) ($P < 0.01$) (Table 2).

Blood Data and Adverse Events

In the G-CSF group, white blood cell count immediately before G-CSF administration was 7.3 ± 1.6 (× 10^3/mm^3). During the administration, it increased up to 36.7 ± 9.4 (× 10^3/mm^3), ranging from 19.2 to 50.3 (× 10^3/mm^3) (Table 3). G-CSF mobilized cells of the neutrophil lineage, but lymphocytes were not affected (Table 3). G-CSF also caused an increase of monocytes. There was no significant change in inflammation during G-CSF administration, as indicated by C-reactive protein levels (Table 3).

In this series, there was no patient who showed bone pain or hepatic dysfunction after the G-CSF administration. No other severe adverse event occurred during or after the administration.

DISCUSSION

To date, 3 clinical trials of G-CSF administration for neurological disorders have been reported; 2 for amyotrophic lateral sclerosis[8,9] and 1 for cerebral infarction.[10] Zhang *et al*[8] reported that the progression of amyotrophic lateral sclerosis symptoms was inhibited by G-CSF administration, although they did not use controls. Neffussy *et al*[9] performed a controlled study, but they showed no significant difference in the progression of amyotrophic lateral sclerosis symptoms between their G-CSF-treated group and controls. A single clinical trial with G-CSF administration for cerebral infarction has been reported by Shyu *et al.*[10] They reported that neurological symptoms were significantly improved by G-CSF administration.

In this study, we conducted the first clinical trial using G-CSF for patients with worsening symptoms of thoracic

TABLE 3. Hematological Data Before and After G-CSF Administration

	Baseline $M \pm SD$ (range)	Peak Value After G-CSF Administration $M \pm SD$ (range)*	P
WBC, ×10^3/mm^3	7.3 ± 1.6 (5.0–10.3)	36.7 ± 9.4 (19.2–50.3)	<0.01
Neutrophils, ×10^3/mm^3	4.6 ± 1.4 (2.1–6.9)	30.6 ± 6.7 (16.6–40.5)	<0.01
Lymphocytes, ×10^3/mm^3	2.1 ± 0.4 (1.5–2.5)	2.4 ± 0.7 (1.5–3.2)	0.29
Monocytes, ×10^3/mm^3	0.4 ± 0.2 (0.2–0.8)	1.9 ± 0.9 (0.7–2.8)	<0.01
CRP, mg/dL	0.1 ± 0.1 (0.0–0.3)	0.3 ± 0.2 (0.1–0.6)	0.08

**Highest level between the first and seventh day after G-CSF administration.*

G-CSF indicates granulocyte colony–stimulating factor; WBC, white blood cell; CRP, C-reactive protein.

compression myelopathy. One month after G-CSF administration, mean recovery rate of JOA score was 29.1%. In contrast, it was 1.1% in the control group at 1 month after initial treatment. In addition, we observed that both motor power and pain sensation scores significantly increased in the G-CSF group compared with the control group at 1 month after treatment. No surgical treatment was performed in patients of either group during the month after G-CSF administration or initial treatment, and they were equally provided conservative treatment such as bed rest. Thus, the present results strongly suggest that G-CSF administration exhibited a neuroprotective effect for the injured spinal cord in patients with worsening symptoms of thoracic myelopathy and improved the myelopathy.

To the best of our knowledge, there has been no other medical treatment that has provided reliable evidence for improvement of thoracic myelopathy. This study provides evidence that G-CSF neuroprotective therapy may be useful as a medical treatment of patients with worsening symptoms of thoracic compression myelopathy. The G-CSF therapy may be especially useful for patients in whom the treatment of complications other than myelopathy needs to be given priority and thus requires a long waiting period before surgery.

In our present trial, no severe side effects occurred. Thus, we suggest that the dose (10 μg/kg per d), duration (5 consecutive days), and route (intravenous administration) of G-CSF administration used in this study are principally safe for the treatment of patients with thoracic myelopathy.

The biggest limitation of this study was that the trial was performed as an open-labeled study and the selection of patients to the G-CSF group and the control group was not randomized. We cannot deny the possibility that a placebo effect of injection may participate in the improvement of neurological symptoms. To increase the level of evidence, in the next stage the study design should be a randomized, double-blind placebo-controlled study. By conducting a phase IIb clinical trial in a large number of patients with the study design described earlier, we will be able to reach a better conclusion regarding the effectiveness of G-CSF neuroprotective therapy for patients with worsening symptoms of thoracic compression myelopathy.

➢ Key Points

- ❑ A multicenter prospective controlled clinical trial was performed to confirm the feasibility of G-CSF administration for patients with worsening symptoms of thoracic myelopathy.
- ❑ For 10 patients with progressive myelopathy, G-CSF (10 μg/kg per day) was intravenously administered for 5 consecutive days.
- ❑ The administration of G-CSF caused neurological recovery in the patients.

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Spine
SURGERY

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Radiographical Risk Factors for Major Intraoperative Blood Loss During Laminoplasty in Patients With Ossification of the Posterior Longitudinal Ligament

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Study Design. A retrospective multi-institutional study.

Objective. To clarify the distribution of intraoperative blood loss during cervical laminoplasty for ossification of the posterior longitudinal ligament (OPLL), and to identify the radiographical risk factors for the occurrence of major blood loss in patients with OPLL undergoing laminoplasty.

Summary of Background Data. The incidence of major intraoperative blood loss during laminoplasty for OPLL is unknown.

Methods. All patients who underwent cervical laminoplasty for OPLL between April 2005 and March 2008 at 27 institutions across Japan were included in this analysis. We investigated the patients' characteristics and surgical data, and compared the radiographical characteristics of OPLL in patients with and without major blood loss.

Results. The estimated intraoperative blood loss was reported for 545 patients (429 male and 116 female; mean age, 62.7 yr). The mean intraoperative blood loss was 223 g (median, 130 g; range, minimal to 3350 g). Excluding 1 patient with intraoperative vertebral artery injury, major blood loss greater than 500 g was reported in 45 patients (8.3%). Patients with major blood loss were more likely to have neurological complications (5/45 *vs.* 12/499) and a longer hospital stay (29.5 d *vs.* 28.8 d) in comparison with those without major blood loss. The occupying ratio of OPLL was greater in the major blood loss group (48.3% *vs.* 42.2%; $P = 0.02$). A multivariate analysis revealed an occupying ratio of 60% or greater to be associated with an increased risk of major intraoperative blood loss (odds ratio, 2.4; 95% confidence interval, 1.1–5.3).

Conclusion. Laminoplasty for OPLL is associated with a risk of major intraoperative blood loss, which can potentially give rise to devastating postoperative complications. An occupying ratio of 60% or greater is a risk factor for major blood loss during laminoplasty in patients with OPLL.

Key words: laminoplasty, ossification of the posterior longitudinal ligament, major intraoperative blood loss. **Spine 2012;37: E1588–E1593**

Laminoplasty has been widely used for the treatment of cervical compressive myelopathy since its development in the 1970s, and its efficacy is well established in the literature.[1] It is generally considered to be a relatively less invasive procedure and can be safely applied to the elderly population.[2–11] The reported intraoperative blood loss in laminoplasty for cervical spondylotic myelopathy (CSM) ranges from 43 to 608 g, with many cases being less than 100 g,[8,9,11] and blood transfusion is generally not necessary.

However, in laminoplasty for patients with ossification of the posterior longitudinal ligament (OPLL), even experienced surgeons occasionally encounter unexpected major blood loss.[12,13] Major intraoperative blood loss in spine surgery can necessitate a transfusion, which has been reported to be associated with an increased risk for disease transmission and surgical site infection,[14,15] and major blood loss also potentially causes multiple end-organ damage, including visual loss[16] and spinal cord ischemia.[17] Despite its clinical significance, intraoperative blood loss in laminoplasty for OPLL has not yet been sufficiently investigated.

The objective of the present study was to clarify the distribution of intraoperative blood loss in cervical laminoplasty for OPLL, and to identify the radiographical risk factors for the occurrence of major blood loss.

MATERIALS AND METHODS

To investigate the neurological complications in laminoplasty for cervical OPLL, the Research Group for Ossification of

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the Spinal Ligament sponsored by the Japanese Ministry of Health, Labour, and Welfare conducted a multi-institutional retrospective survey in January 2009. The incidence of neurological deficits was already reported in 2011,[18] and we used the same data set, and reanalyzed it in the present study, focusing on the intraoperative blood loss. All patients who underwent cervical laminoplasty for OPLL between April 2005 and March 2008 at 27 institutions to which members of the research group belonged were reviewed. These institutions are all university hospitals and national medical centers, and the diagnoses, surgical indications, and OPLL surgeries were all performed by the experienced senior spine surgeons who belonged to this research group. Patients who underwent laminoplasty in 3 vertebrae or more down to T1 were included in the analysis. The number of surgically treated vertebrae was counted, with a partial laminectomy being counted as 0.5 vertebra. The patients with laminoplasty below T2 or simultaneous anterior surgery and those with a traumatic spinal cord injury within 3 weeks before surgery were excluded.

We investigated the patients' characteristics, the surgical data (laminoplasty type, number of surgically treated vertebrae, length of the operation, and estimated intraoperative blood loss), and the preoperative radiographical characteristics of the OPLL (size of the OPLL [number of vertebrae involved], OPLL type, occupying ratio, Cobb angle between C2 and C7 [cervical lordotic angle; C2–C7 angle], and the presence of a high intensity area on T2 magnetic resonance imaging). The hospital stay and the presence of neurological deterioration within 2 weeks postoperatively were also investigated. On the basis of the distribution of intraoperative blood loss on the box-and-whisker plot, we defined an estimated intraoperative blood loss greater than 500 g as major blood loss (Figure 1). We compared the patients' characteristics, their surgical data, and the radiographical characteristics of OPLL in the patients with major blood loss and the control group. We also surveyed whether it was possible to determine the risk factors for major blood loss within the radiographical characteristics by a multivariate analysis.

All analyses were carried out using the IBM SPSS Statistics software program, version 19 (SPSS, Inc., Somers, NY). For the comparisons of the parameters between the groups, the chi-square test was used for categorical data, and the Mann-Whitney *U* test was used for continuous variables. Spearman rank correlation coefficient was calculated to analyze the correlation between the variables. The risk-factor analysis was conducted by a multivariate logistic regression analysis. For all statistical tests, $P < 0.05$ was considered to be significant.

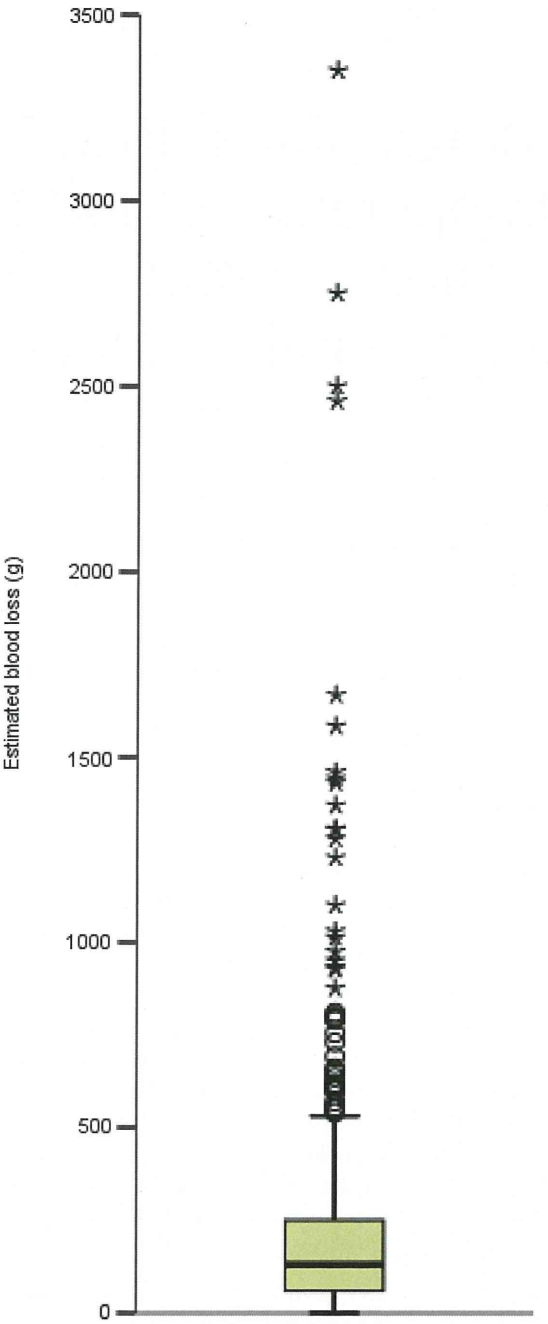

Figure 1. The distribution of intraoperative blood loss during cervical laminoplasty for ossification of the posterior longitudinal ligament. Circles indicate outliers; stars, extreme outliers.

RESULTS

This study identified 574 eligible patients. The estimated intraoperative blood loss was reported for 545 patients (429 male and 116 female). The mean age of the patients was 62.7 ± 9.9 years (range, 30–86 yr). Twenty-four percent of the patients had diabetes mellitus and 30.8% had hypertension. No patient had any kind of coagulopathy that could have potentially affected the intraoperative hemostasis. A total of 286 patients (52.5%) underwent double-door laminoplasty and 234 patients (42.9%) had open-door laminoplasty. Other types of expansive laminoplasties were performed in 25 patients (4.6%). The mean number of the surgically treated vertebrae was 5.0 ± 0.8 (range, 3–8). The mean length of the operation was 156 ± 70 minutes (range, 43–573 min), and the mean intraoperative blood loss was 223 ± 330 g (median, 130 g; range, minimal to 3350 g) (Figure 1). The mean hospital stay was 28.9 ± 18.9 days (range, 5–199 d). Neurological deterioration in the lower limbs within 2 weeks postoperatively was reported in 3.3% of the patients, and

neurological deterioration in the upper limbs was reported in 6.7% including proximal paresis (C5 palsy) in 4.4%.

Major intraoperative blood loss greater than 500 g was reported in 46 patients. One of those patients was complicated by a vertebral artery injury while making a trough for double-door laminoplasty, and the intraoperative blood loss was 1460 g. Excluding this patient, 8.3% (45 of 544 patients) had major blood loss during uneventfully completed laminoplasty, and only these patients were included in further analyses. The incidence of major blood loss in double-door laminoplasty was 4.2%, whereas it was 12.0% in subjects who underwent open-door laminoplasty. The prevalence of diabetes and hypertension was not significantly different from the major blood loss group and the control group (diabetes mellitus, 17.8% *vs.* 24.7%, $P = 0.30$; hypertension, 40.0% *vs.* 29.9%; $P = 0.16$). The surgical data were compared in the 2 groups, and the mean numbers of surgically treated vertebrae were 5.1 ± 1.0 and 5.0 ± 0.8 ($P = 0.68$), and the mean lengths of the operations were 240 ± 112 and 149 ± 59 minutes ($P < 0.001$), respectively. The mean hospital stays were 29.5 ± 14.4 and 28.8 ± 19.1 days, respectively, and had a tendency to be longer in the major blood loss group ($P = 0.16$). Patients with major blood loss were more likely to have neurological deterioration in the lower limbs (5/45 *vs.* 12/499) and C5 palsy (5/43 *vs.* 19/496) than those without major blood loss.

Next, the preoperative radiographical characteristics of OPLL were compared in the 2 groups (Table 1). The occupying ratio was greater in the major blood loss group (48.3% *vs.* 42.2%, $P = 0.02$). We further stratified the patients by laminoplasty types to compare the occupying ratio between patients with or without major blood loss. In the double-door laminoplasty group (n = 234), the occupying ratio was significantly greater in patients with major blood loss than in the control group (53.5% *vs.* 42.4%, $P = 0.007$). Also in the open-door laminoplasty group (n = 285), the occupying ratio was greater in patients with major blood loss, although it did not reach statistical significance (44.3% *vs.* 41.7%, $P = 0.36$). We performed a scatterplot analysis focusing on the relationship between intraoperative blood loss and the occupying ratio (Figure 2), but no strong correlation was found ($r = 0.13$, $P = 0.002$). However, among those with a high occupying ratio of 60% or greater, major blood loss was reported in 16.7% (10 of 60 patients), whereas it was reported in only 6.9% of those with an occupying ratio less than 60%. These radiographical parameters were surveyed for a risk-factor analysis. The patient age, sex, size of OPLL, OPLL type, and an occupying ratio of 60% or greater were used for the independent variables. A total of 515 patients in whom all these parameters were available were included in this analysis. By the stepwise multivariate logistic regression analysis, an occupying ratio of 60% or greater was the only

TABLE 1. Comparisons of the Radiographical Characteristics of OPLL According to the Occurrence of Major Intraoperative Blood Loss (Blood Loss > 500 g)

Estimated Blood Loss (g)	Total (n = 544)	>500 g (n = 45)	≤500 g (n = 499)	*P*
Sex (male/female)	428/116	39/6	389/110	0.17
Age (yr)	62.7 ± 9.8	60.6 ± 10.1	62.9 ± 9.8	0.10
Size of OPLL (vertebrae)	3.7 ± 1.5 (n = 536)	3.9 ± 1.4 (n = 43)	3.6 ± 1.5 (n = 493)	0.23
OPLL type				0.14
Continuous	103 (19.9%)	13 (31.7%)	90 (18.9%)	
Segmental	134 (25.9%)	10 (24.4%)	124 (26.1%)	
Mixed	257 (49.7%)	18 (43.9%)	239 (50.2%)	
Local	23 (4.4%)	0 (0.0%)	23 (4.8%)	
Not specified	27	4	23	
Occupying ratio (%)	42.7 ± 13.2 (n = 535)	48.3 ± 13.4 (n = 43)	42.2 ± 13.1 (n = 492)	0.02
C2–C7 angle (°)	12.2 ± 10.5 (n = 534)	12.5 ± 9.8 (n = 43)	12.2 ± 10.6 (n = 491)	0.93
High-intensity area on T2 magnetic resonance imaging				0.51
+	383 (72.4%)	33 (76.7%)	350 (72.0%)	
−	146 (28.0%)	10 (23.3%)	136 (28.0%)	
Not available	15	2	13	

All parameters were compared in the major blood loss group and the control group.

OPLL indicates ossification of the posterior longitudinal ligament.

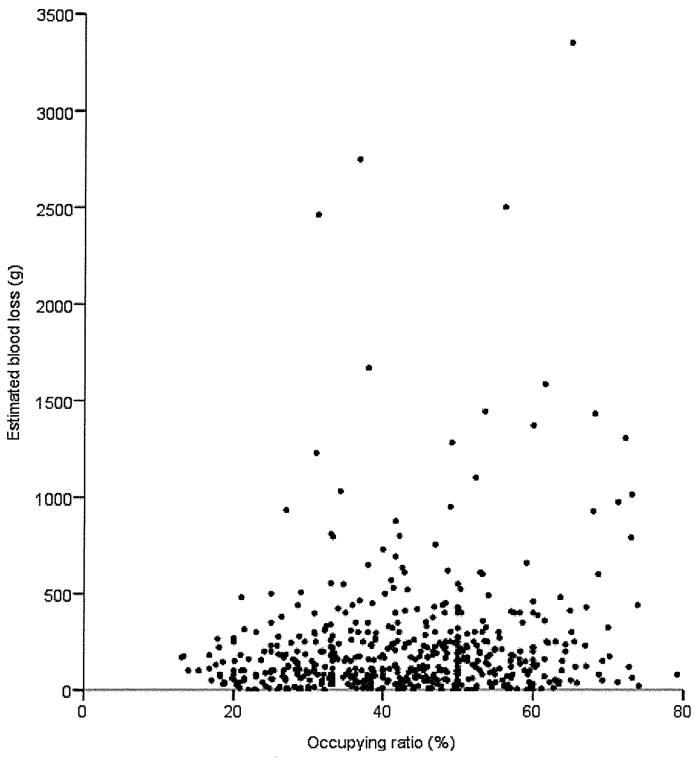

Figure 2. The scatter diagram of intraoperative blood loss and occupying ratio of ossification of the posterior longitudinal ligament.

variable that remained significant (odds ratio, 2.4; 95% confidence interval, 1.1–5.3; $P = 0.03$).

DISCUSSION

We have investigated the distribution of intraoperative blood loss during laminoplasty for OPLL, and major blood loss greater than 500 g was reported in 8.3% of the patients. Major blood loss was associated with an increased risk of postoperative neurological deterioration and a longer hospital stay. An occupying ratio of 60% or greater was the only clear risk factor among the preoperative radiographical characteristics of OPLL for major intraoperative blood loss.

In the present study, the mean intraoperative blood loss was 223 g and the median was 130 g. There have been several studies that reported the intraoperative blood loss in cervical laminoplasty for CSM.[2–11] The mean blood loss ranged from 43 to 608 g, but many of the cases lost less than 100 g.[8,9,11] On the contrary, only a few studies have reported the intraoperative blood loss in laminoplasty for OPLL, with the amounts ranging from 119 to 493 g.[3,6,7,19,20] The results of the present study for the mean blood loss correlate with these reports. Three previous reports compared the amount of blood loss in OPLL and CSM,[3,6,7] and 2 of them indicated that the blood loss was greater in the OPLL group.[3,6] It is necessary to keep in mind that in these studies of small surgical populations, the rare cases of major blood loss may not be reflected in the average. The present study is the first report that mentions the distribution of intraoperative blood loss during laminoplasty for OPLL based on the analysis of the largest number of surgical subjects in multiple institutions. The fact that the maximum blood loss was more than 3000 g, with all operations performed by experienced surgeons in the federal research study group, is worth attention.

Major intraoperative blood loss is important because it is known to be associated with multiple postoperative complications.[14–17,21] Major blood loss during spine surgery can cause inadvertent hypotension and jeopardize the spinal circulatory system, which may potentially result in postoperative neurological deterioration. There has been no study that has discussed the risk factors for major blood loss in spine surgery. Defining major intraoperative blood loss is somewhat challenging. There have been a few published risk-factor analyses of intraoperative blood loss in liver surgery, but their definitions of major blood loss varied among the studies, including 1500 g and the 25th percentile of the population.[22,23] Because there is no established definition of significant intraoperative blood loss during spine surgery[24] and whether a transfusion was performed was not known in the present study, we defined 500 g as the cutoff, because blood loss of greater than approximately 500 g was recognized as an outlier on the box-and-whisker plot (Figure 1). Patients with major blood loss above this cutoff were more likely to have neurological deterioration than those without major blood loss in the present study, although this association could be complicated by the difference in the occupying ratio between the 2 groups. The association between intraoperative hypotension and spinal cord damage has not been proven,[17] but some of these complications could have been avoided by careful preoperative planning including the preparation of blood transfusion.

We attempted to identify the risk factors for major blood loss in the preoperative radiographical characteristics of OPLL. The surgical procedure used for laminoplasty is the same, regardless of the morphology of the OPLL, besides the longitudinal exposure of the surgical field and the number of expanded vertebrae being larger according to the size of OPLL. Therefore, the size of the OPLL was expected to be a risk factor, but interestingly it was not significantly larger in the group that experienced major blood loss. On the contrary, a high occupying ratio of 60% or greater was found to be a clear risk factor for major blood loss. An occupying ratio of 60% or greater is also known to be a risk factor for the development of myelopathy,[25] and we used this value as the cutoff in this observational study instead of performing the receiver operating characteristic curve analysis. When laminoplasty is performed in patients with OPLL with a high occupying ratio, we recommend that a blood transfusion should be prepared preoperatively in case of major blood loss. The patients should also be well informed about this possible complication.

Although the occurrence of abnormal intraoperative bleeding during laminoplasty for OPLL has been historically reported,[26] the episodes have been reported only anecdotally because of its relative rarity, and the precise frequency and the pathology of major blood loss in laminoplasty remain unknown. Some authors have hypothesized that the bleeding tendency in patients with OPLL is caused by the abnormality of angiogenesis associated with ectopic bone formation,[6] whereas other authors showed that intraoperative blood loss

during cervical laminoplasty correlates with the vertebral intraosseous pressure, which is considered to be identical to the epidural venous pressure.[5] The abnormal distention of the epidural venous plexus was also reported by close intraoperative observation during laminoplasty.[26] In the present article, we found that a high occupying ratio was a risk factor for major blood loss. Thus, we speculate that the thick OPLL obstructs local epidural venous drainage *via* Batson plexus, thereby changing the local circulation pattern.

There are some limitations to this study that should be kept in mind when interpreting the results. First, whether a transfusion was performed or not was not reported in the study. Some of the complications related to spine surgery are known to be associated with transfusion. We used 500 g as the cutoff for major blood loss and showed that blood loss of greater than this value was associated with a poor postoperative outcome, but what percentage of the subjects in the major blood loss group consequently needed a blood transfusion is unknown. Second, it is possible that the study population had some selection bias. We chose to use the population selected in the national survey, and all the diagnoses and surgeries were done by experienced surgeons in university hospitals or national medical centers. Therefore, the demographical data of these patients might have been different from those of the population in which laminoplasty for OPLL is generally indicated. On the contrary, the accuracy of diagnosis and surgical skill were of guaranteed quality, and the episodes of major blood loss may be encountered more frequently in other institutions or when surgeries are performed by less experienced surgeons. Third, it is unclear where and when in the surgical procedure major blood loss occurred. The relatively larger amount of bleeding could have continued throughout the procedure; from the incision to the closure of the wound, or the massive bleeding could have occurred only in association with the manipulation of the lamina and extradural tissue. A high occupying ratio was found to be a risk factor for major blood loss; therefore, the massive bleeding may have occurred during the opening of the lamina on the distended epidural venous plexus. Further studies that include close intraoperative observations are warranted to prove this. Finally, given that the incidence of major blood loss was 16.7% even with a high occupying ratio, it is speculated that major intraoperative blood loss is multifactorial. The patients' characteristics, including their comorbidities (cardiovascular diseases, history of anticoagulation, *etc.*) and surgeons' factors (preferred methods for the procedure, experience, *etc.*) can affect the incidence of major blood loss. For example, intraoperative blood loss has been reported to be greater in open-door laminoplasty than in double-door laminoplasty,[27] possibly because epidural venous plexus is more developed laterally than in the middle of the spinal canal, and it can be more easily damaged during the manipulation of the lamina. The present study also reported major blood loss more frequently in the open-door laminoplasty group, and it may be partly associated with this anatomical factor. Among these potential risk factors, we have focused on the radiographical characteristics of OPLL in the study, which can be objectively assessed preoperatively. Further studies are warranted to identify risk factors other than the radiographical characteristics.

CONCLUSION

Laminoplasty for OPLL is associated with a risk of major intraoperative blood loss, which can potentially give rise to devastating postoperative complications. A multivariate analysis showed that patients with a high occupying ratio of 60% or greater were at a 2.4-fold higher risk of major intraoperative blood loss greater than 500 g. When we choose to perform laminoplasty for OPLL with a high occupying ratio, a sufficient transfusion should therefore be prepared preoperatively with extreme care.

➢ Key Points

- ❑ This is the retrospective multi-institutional study investigating the distribution of intraoperative blood loss in laminoplasty for cervical OPLL in 545 patients.
- ❑ Major intraoperative blood loss greater than 500 g during uneventfully completed laminoplasty was reported in 45 patients (8.3%), and it was associated with an increased risk of postoperative neurological deterioration and a longer hospital stay.
- ❑ Patients with a high occupying ratio (≥60%) were at a 2.4-fold higher risk of major intraoperative blood loss than those with a lower occupying ratio.

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ORTHOPAEDIC SURGERY

Neurological recovery after posterior decompression surgery for anterior dural compression in paralytic spinal metastasis

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Abstract
Purpose Paralysis in spinal metastasis is often caused by anterior dural compression, and anterior approach has been frequently chosen for decompression despite its dreadful complications. On the other hand, the effectiveness of posterior indirect decompression has not specifically established. The objective of the present study was to investigate the anatomical patterns of dural compression, and to clarify the effectiveness of posterior surgery for anterior lesions.
Methods We retrospectively analyzed the anatomical patterns of spinal metastasis on MRI images and the neurological recovery in the paralytic patients who underwent posterior decompression and fusion surgery with intraoperative radiation therapy. The recovery rate was compared between those with an anterior or circumferential dural compression (A+), who were indirectly decompressed, and those with a posterior and/or lateral dural compression (A−), who were directly decompressed.
Results A total of 135 cases were included in the study, and 81.5% had anterior dural compression (A+). In the A+ group, 88.2% of preoperatively non-ambulatory cases regained the gait. Full recovery was achieved in 50% of preoperatively ambulatory cases. These rates were not significantly different from those in the A− group. The rate of gait regain was diminished in the surgeries of the middle thoracic spine (T5-8).
Conclusions Most spinal metastases cause paralysis by anterior compression; however, the result of posterior indirect decompression was similar to that of posterior direct decompression, although kyphosis negatively affected the result. Anterior decompression might not always be necessary for soft tumor compression as long as the adjuvant therapy is effective for the local control.

Keywords Spinal metastasis · Paralysis · Posterior decompression surgery · Anterior compression

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Introduction

Increasing numbers of patients with metastatic spinal tumor are currently being encountered in the clinical setting. With the amazing progress of the treatment of tumors and the improvement of prognosis, the treatment of paralysis due to spinal metastasis is an emerging challenge for all spine surgeons. Since the dural sac is often compressed anteriorly by the tumor mass, some surgeons believe that anterior surgery is superior to posterior surgery for accomplishing decompression [1, 2]. Anterior surgery, however, has some definite drawbacks in its potentially mortal complications including respiratory impairment and major vessel damage [3]. These complications may potentially preclude surgical intervention for patients in an advanced stage. Moreover, not all anterior compressive lesions necessitate an anterior direct decompression. For example, good neurological results have been reported with posterior surgery for patients with paralysis due to burst fracture [4, 5].

Although some authors have reported favorable outcomes following posterior surgery for paralytic spinal metastasis [6–8], their studied population numbers are limited and the detailed clinical results according to the morphological patterns of metastasis were not reported. Therefore, the results of posterior decompression for anterior compression have not been specifically established. We have performed posterior decompression surgery for paralytic spinal metastasis, even with anterior compressive lesion, believing that posterior indirect decompression is satisfactory as long as local control of the anterior lesion is guaranteed. For the local control of the tumor, we use intraoperative radiation therapy (IORT), which allows for direct high-dose irradiation to the residual tumor and avoids damage to the spinal cord with the use of a lead shield [9]. In the present study, we investigated the anatomical and morphological characteristics of the dural compression by the spinal metastasis and compared the result of posterior decompression surgery for various patterns of metastasis to clarify the effectiveness of posterior surgery for anterior lesion.

Materials and methods

We retrospectively analyzed the data of 205 patients with metastatic tumor in the cervical, thoracic or lumbar vertebrae who underwent posterior decompression surgery between November 1992 and December 2008.

Surgical indication and procedure

Surgery was indicated in those patients with paralysis due to spinal metastasis who presented with neurological impairment and had an expected survival period of more than 6 months, and whose general condition was good enough to be a candidate for a surgery under general anesthesia. Preoperative embolization of the tumors' blood vessels was performed for hypervascular tumors, such as metastases from renal and thyroid cancer. We performed a wide laminectomy by a posterior approach to decompress the dural sac. For extradural tumors in the spinal canal, we only resected the dorsal portion to the equator as much as possible. We did not, however, resect ventrally located extradural tumors to avoid massive bleeding and spinal cord damage. Thus, the metastases that were associated with anterior dural compression were indirectly decompressed by our procedure. Thorough direct decompression was accomplished in those with posterior and/or lateral dural compressions. Instrumentation was also performed in almost all patients, mainly by a 2 above and 2 below pedicle screw fixation, with a few exceptions of those with limited prognosis or activity of daily living and increased risk of surgical site infection. For those with tumors of low radiosensitivity, preoperative or postoperative external radiation therapy was applied additionally.

Intraoperative radiation therapy

For all patients, intraoperative irradiation was applied for the residual lesions in the pedicles and vertebral body. After decompression was achieved, a lead plate was set on the lamina to shield the spinal cord. The patient was transferred to the irradiation room and electron beam irradiation was then administered. The electron energy was determined such that the most ventral region of the tumor would receive at least 40% of the dose. The delivered dose was 20–30 Gy, which biologically corresponds to approximately 45–70 Gy of fractionated external irradiation. Electron beams show marked scatter, spreading from behind the shielded central spinal cord region to reach the posterior region of the vertebral body located directly anterior to the spinal cord (Fig 1).

Statistical analysis

The patients who were followed for more than 3 months after the surgery were included in the study. The details of the surgical procedure (operation time, estimated blood loss, use of instrumentation, use of external radiation therapy, and primary tumor) were investigated. The operated level was categorized into cervical, thoracic (upper: T1-4, middle: T5-8 and lower: T9-12) and lumbar. The most involved spinal level was adopted for the surgeries involving multiple vertebrae.

Preoperative axial MRI images were used to locate the metastatic lesions in the vertebra as well as the primary compression site of the dural sac in the spinal canal. Lesions in the vertebral body, the pedicles and the posterior elements were defined as "anterior", "lateral" and "posterior", respectively. The anatomical existence of the metastasis was classified into seven categories (three locations and their combinations). The primary compression site of the dural sac was defined in the same way, but we added "circumferential" compression instead of "anterior, lateral and posterior" (Fig. 2). The neurological recovery was compared between the group with anterior or circumferential dural compression (A+ group), which was indirectly decompressed, and the group with posterior and/or lateral compression (A− group), treated with direct decompression. The recovery rate was further surveyed according to the involved spinal level.

All analyses were carried out using IBM SPSS Statistics Version 19 (SPSS, Inc., Somers, NY, USA). The Chi square test was used to analyze the difference in the categorical data between the two groups and Student's t test or

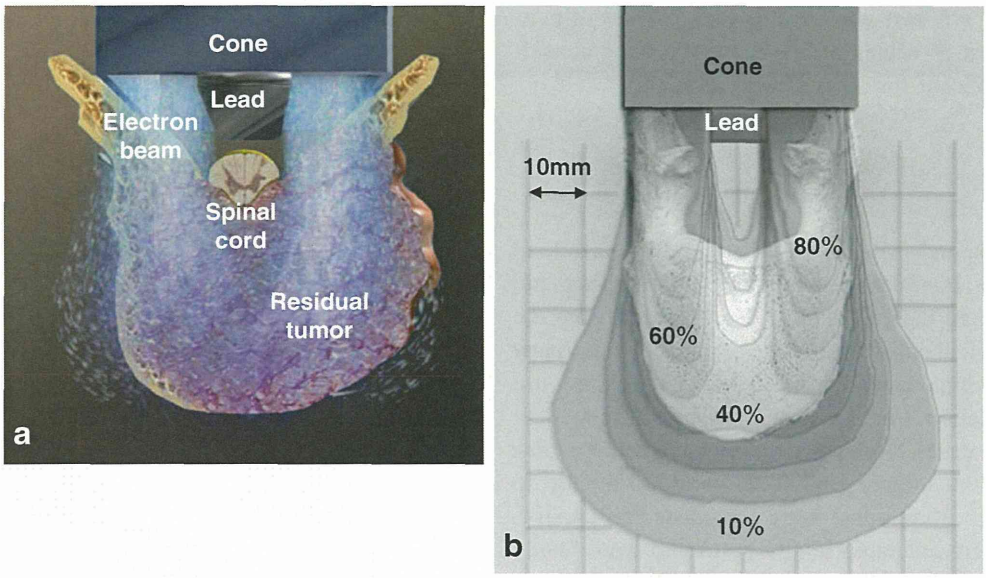

Fig. 1 Intraoperative radiation therapy (**a** schema of irradiation, **b** isodose curves of dose distribution [9]) The permission to use this figure was obtained from Wolters Kluwer Health via Rightslink by Copyright Clearance Center on December 31 2011. License number is 2819330625001

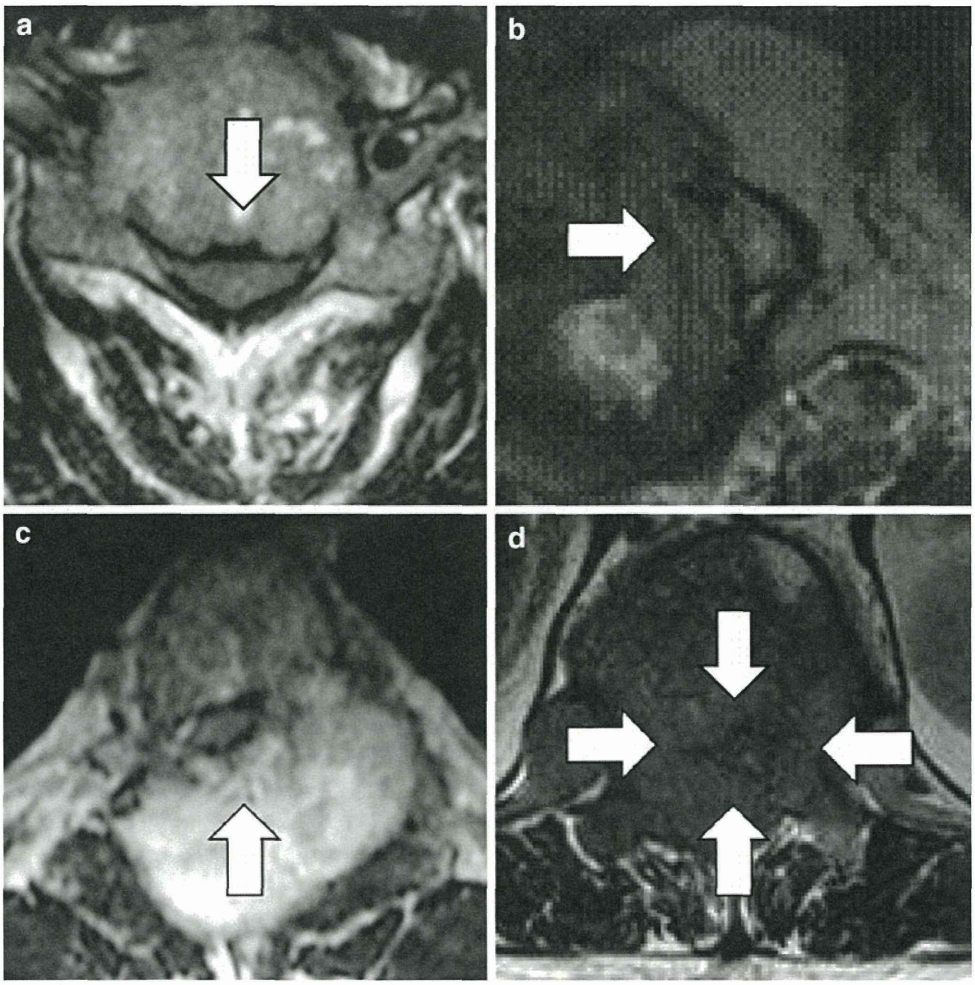

Fig. 2 Anatomical patterns of dural compression (**a** anterior, **b** lateral, **c** posterior, **d** circumferential)

Mann–Whitney's U test was used in the analyses of continuous variables. P values of less than 0.05 were considered to be significant for all statistical tests.

Results

A total of 233 spinal metastases surgeries were performed in 205 patients. Fourteen patients had two surgeries and seven patients had three surgeries. We excluded from the analysis 14 surgical cases with local recurrence in the same or adjacent vertebrae and 43 cases in which we did not use the instrumentation for various reasons. Among the remaining 176 cases, 156 cases followed for more than 3 months after the surgery (follow up period: 3 months to 9.5 years, mean: 30 months) were included. Preoperative MRI images were available in 135 cases and were finally included in our analysis.

The anatomical location of the metastasis is summarized in Fig. 3. Metastasis was positioned anteriorly in 129 patients (95.6%), laterally in 94 patients (69.6%) and posteriorly in 90 patients (66.7%). Figure 4 shows the location of the primary dural compression. The patients with posterior and/or lateral dural compression accounted for 18.5% (A−). The remaining 81.5% had anterior dural compression (A+) and were indirectly decompressed by posterior decompression surgery.

Patient demographic data are shown in Table 1. The neurological status of 93 cases (68.9%) were Frankel C or worse, namely not ambulatory, and the remaining 42 cases

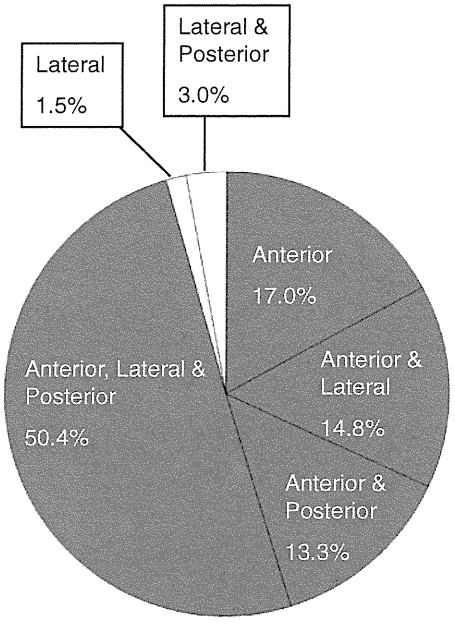

Fig. 3 Locations of metastases in a vertebra. Metastasis was present anteriorly in 95.6% of cases

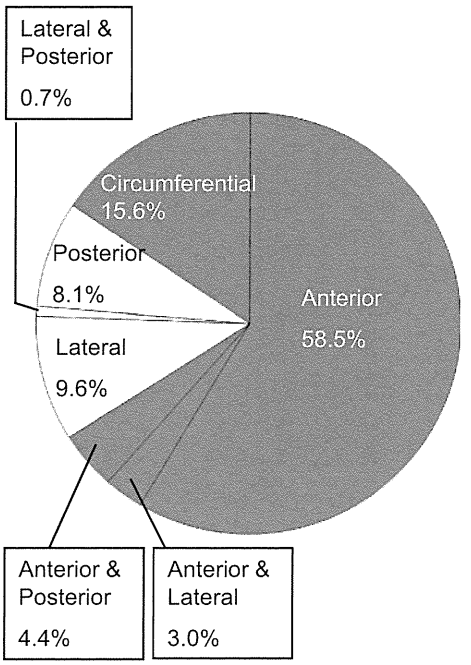

Fig. 4 Primary dural compression site. Anterior or circumferential dural compression was present in 81.5% of cases

(31.1%) were ambulatory with some neurological impairment (Frankel D). Metastases in the thoracic spine accounted for 65.9% of the cases. As the primary tumor, breast cancer accounted for the biggest proportion (21.5%), followed by colon cancer (13.3%), kidney cancer (12.6%) and thyroid cancer (11.1%). There were no significant differences between the two groups in gender, age, preoperative neurological status, operated spinal level, operation time, estimated blood loss and the rate of additional external radiation therapy.

Overall, 92.6% (125/135) of the cases were ambulatory and 27.4% (37/135) showed full recovery with no neurological impairment postoperatively (Table 2). In the A+ group, 76 cases were not ambulatory preoperatively and 67 of them (88.2%) regained the gait postoperatively. Full recovery was achieved in 50% (17/34) of preoperatively ambulatory cases. On the other hand, in the A− group, 17 cases were not ambulatory preoperatively and 16 of them (94.1%) regained the gait postoperatively. Full recovery was achieved in 50% (4/8) of preoperatively ambulatory cases. Neither the rate of gait regain nor the rate of full recovery was significantly different between the two groups ($P = 0.47$ and $P = 1.00$, respectively). The rate of neurological recovery of at least one Frankel's grade was 80.0% in both groups. Among the non-ambulatory cases in the A+ group, surgeries in the cervical spine had a most remarkable rate of gait regain (100%) and those in the thoracic spine were the worst (85.5%). More specifically,