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Statistical Analysis C
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Manuscript Preparation E
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Patient: Male, 75-year-old
Final Diagnosis: High-grade myxofibrosarcoma involving the spine • malignant fibrosus histiocytoma at the spine
Symptoms: Myelopathy
Clinical Procedure: Hybrid apporach • separation surgery and IMRT
Specialty: Neurosurgery • Orthopedics and Traumatology

Objective: Rare disease

Background: Myxofibrosarcoma involving the spine is a rare and intractable disease. Although wide surgical resection is the mainstay of treatment, it is often difficult to complete marginal *en-bloc* resection due to adjacent neurovascular components in the spine. Separation surgery, a partial resection to achieve circumferential separation and high-dose irradiation such as postoperative intensity-modulated radiation therapy, has received much attention as a new therapy for spinal tumors. However, little evidence regarding separation surgery with intensity-modulated radiation therapy for a spinal myxofibrosarcoma exists.

Case Report: We present a case of a 75-year-old man with progressive myelopathy. Radiological examination revealed severe spinal cord compression due to an unknown widespread multiple tumor in the cervical and thoracic spine. Computed tomography-guided biopsy showed high-grade sarcoma. Positron emission tomography detected no other tumors in the body. Separation surgery was therefore performed with posterior stabilization. Hematoxylin and eosin staining showed storiform cellular infiltrates and pleomorphic cell nuclei. Histopathology identified high-grade myxofibrosarcoma. Postoperative intensity-modulated radiation therapy of 60 Gy in 25 fractions was completed without any adverse effects. The patient had greatly improved neurological function, was capable of walking with a cane, and had no recurrence for at least 1 year after surgery.

Conclusions: We reported a case of an unresectable high-grade myxofibrosarcoma of the spine successfully treated with the combination of separation surgery and postoperative intensity-modulated radiation therapy. This combination therapy is a relatively safe and effective treatment option in patients with impending neurological damage by unresectable sarcomas when total *en-bloc* resection is challenging due to the size, location, or adhesion.

Keywords: Histiocytoma, Malignant Fibrous • Radiotherapy, Intensity-Modulated • Spinal Cord Compression • Spine

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Background

Myxofibrosarcoma is a unique subtype of soft-tissue sarcoma, accounting for 5% of soft-tissue sarcoma diagnoses [1]. Myxofibrosarcoma often arises in the extremities of patients over 60 years of age [1]. Approximately 10% of myxofibrosarcoma is located on the trunk [2] and rarely involves the spine. Histopathologic patterns of myxofibrosarcoma are characterized by a myxoid component of extracellular matrix, pleomorphic spindle cells, and curvilinear blood vessels [2]. Myxofibrosarcoma has a high local recurrence rate, ranging from 16% to 57% [2] and wide surgical resection with or without radiotherapy is the mainstay of treatment if macroscopic complete resection is possible [2-4]. Although myxofibrosarcoma involving the spine is rare [5-9], it is often difficult to complete marginal *en-bloc* resection with a sufficient tumor-free margin due to adjacent neurovascular components. In unresectable sarcoma, neoadjuvant chemotherapy and/or radiotherapy to achieve macroscopic complete resection should be considered [3,4]. However, spinal involvement adjacent to the spinal cord makes it impossible to deliver a sufficient dose of irradiation [10] and sometimes requires urgent/semi-urgent decompression surgery to prevent irreversible neurological dysfunction.

Separation surgery with postoperative intensity-modulated radiation therapy (IMRT), an advanced type of radiotherapy to safely deliver the accurate radiation while minimizing the dose to surrounding normal tissues, has received much attention as a new therapy for spinal tumors, mainly spinal metastases [10,11]. Separation surgery involves resecting epidural tumor lesions from normal dural structures circumferentially (approximately 3 mm margin between the tumor and spinal cord) with no attempt to aggressively remove the whole tumor or vertebral body, capable of applying high-dose irradiation for the target close/adjacent to the spinal cord [10]. However, little evidence regarding this combination approach for a spinal myxofibrosarcoma exists. The aim of this study is to report and discuss a case of a high-grade myxofibrosarcoma involving the spine treated with the combination of separation surgery and postoperative IMRT.

Case Report

A 75-year-old man reported having 3 months of numbness and muscle weakness of the right fingers. One month later, he visited a nearby clinic because he gradually developed muscle weakness in the right lower limb. He progressively developed gait and urinary disturbance and was then referred to our institution. He had no family history and no past medical history of malignant tumor. His past medical history was diabetes mellitus. Neurological examination revealed hypoesthesia beneath the nipples and muscle weakness with the manual muscle testing level 4 of 5 in the right upper limb and 3 of 5 in the lower extremities. Radiographs showed bilateral winking owl sign at T3 and T4 (**Figure 1**). Magnetic resonance imaging (MRI) (**Figure 2**), computed tomography (CT) (**Figyure 3A-3C**), and positron emission tomography (PET) (**Figure 3D-3G**) disclosed multiple mass lesions at T3 and T4, invading the ribs, pedicles, and vertebrae, resulting in severe spinal cord compression. Epidural tumors extended to the cervical spine. He was

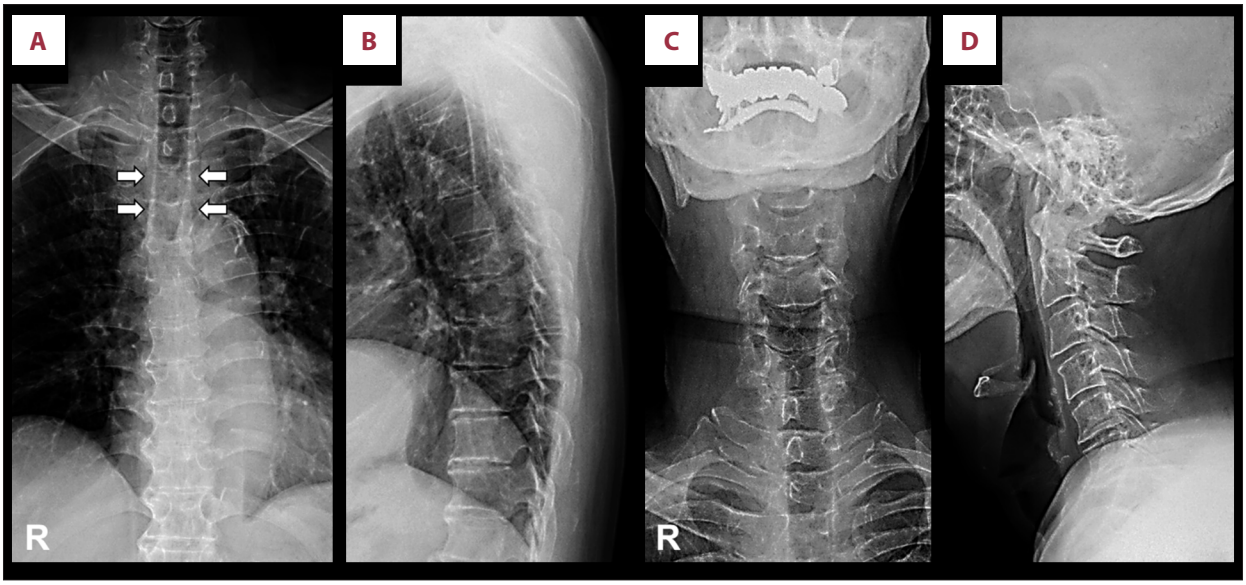

Figure 1. Preoperative radiographs showing osteolytic lesion at T3 and T4. (**A**) A posteroanterior radiograph of thoracic spine with bilateral winking owl sign at T3 and T4 (white arrows). (**B**) A lateral radiograph of thoracic spine. (**C**) A posteroanterior radiograph of cervical spine. (**D**) A lateral radiograph of cervical spine.

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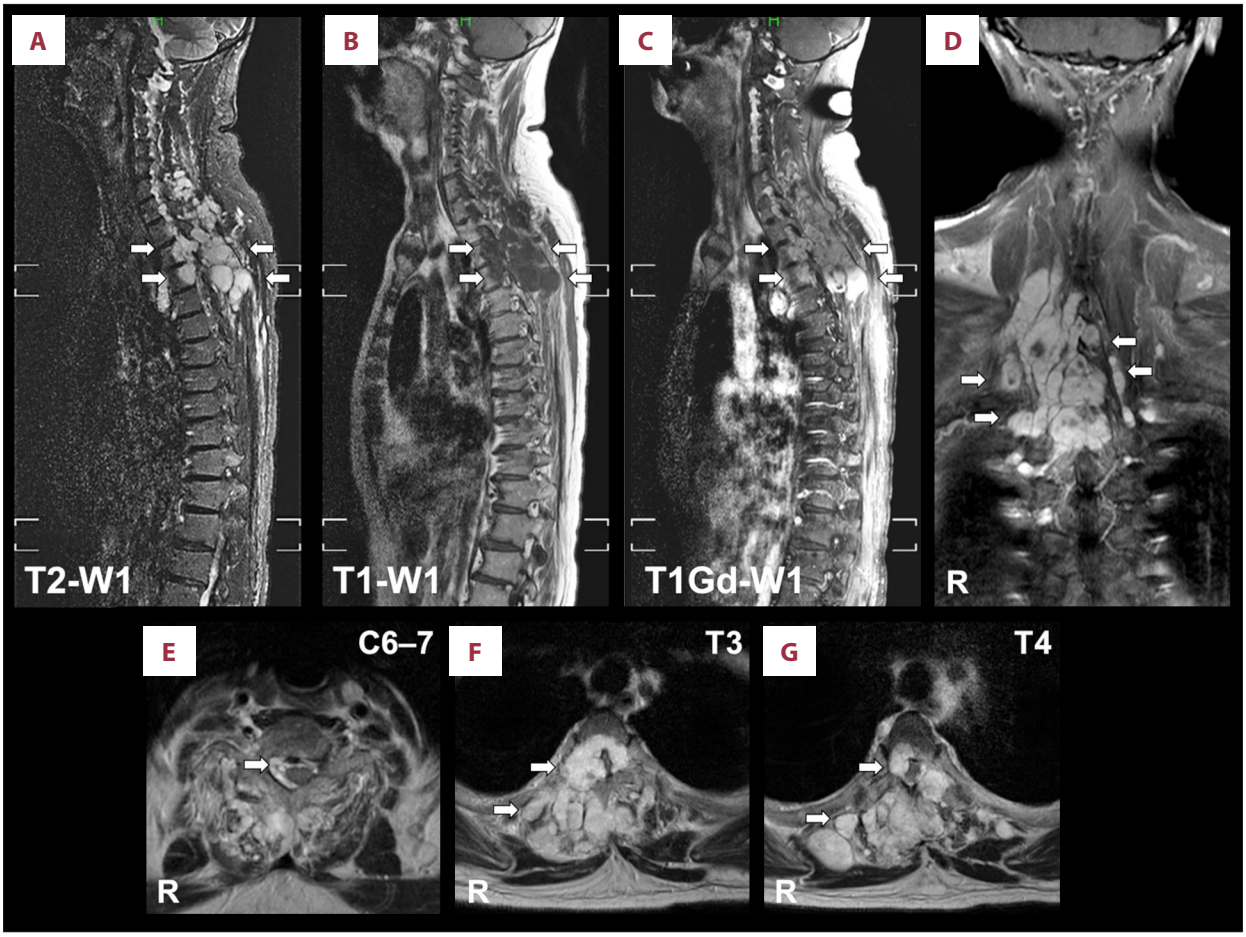

Figure 2. Preoperative magnetic resonance images (MRI) of the spine showing multiple mass lesion at C7-T5 level. (**A, B**) Sagittal T2-weighted (**A**) and T1-weighted (**B**) images showing multiple high-intensity mass lesion at C7-T5 level. (**C**) A sagittal gadolinium-enhanced T1-weighted image showing multiple enhanced mass lesion at C7-T5 level. (**D**) Coronal T2-weighted image showing multiple high-intensity mass lesion. (**E**) An axial T2-weighted image showing an extradural high-intensity mass lesion at the right side of C6/7. (**F, G**) Axial T2-weighted images showing multiple mass lesion at the T3 (**F**) and T4 (**G**) invading rib, vertebrae, and spinal canal with spinal cord compression. White arrows indicate the tumor.

emergently admitted to the hospital. On the same day, percutaneous CT-guided biopsy was performed. It revealed high-grade sarcoma with spindle-shaped tumor cells with nuclear atypia.

Since macroscopic complete resection was impossible, neoadjuvant chemotherapy and radiotherapy were considered. However, radiotherapy including IMRT was also difficult because the tumor expansion was adjacent to the spinal cord. Chemotherapy and particle therapy was not applicable because of a poor performance status of 4. However, the lack of metastatic lesions in PET indicated a relatively long-term survival. We thus performed separation surgery after 2 weeks of waiting. Following embolization of bilateral T3 and T4 segmental arteries, epidural tumors at the cervical and thoracic spine were circumferentially removed to create a safe margin between the tumors and spinal cord (**Figure 4A, 4B**). The majority of tumors invading the vertebral body were not resected due to the risks for bleeding and neurological damage. Macroscopic observation demonstrated multiple mass lesions and rich myxoid and intratumor hemorrhage (**Figure 4C, 4D**). Hematoxylin and eosin staining sections demonstrated a storiform pattern of spindle-shaped tumor cells with mucus and pleomorphic cellular infiltrates with pleomorphic cell nuclei (**Figure 4E, 4F**). Immunohistochemical staining for cytokeratin AE1/AE3, cytokeratin CAM 5.2, S100 protein, SRY-box 10 (SOX10), CD34, αSMA, desmin, brachyury, trimethylation of histone H3 at lysine 27 (H3K27me3), and Ki-67 were performed. These markers were negative except for H3K27me3. Spindle-cell carcinomas, melanoma, malignant peripheral nerve sheath tumor, and leiomyosarcoma were excluded and this tumor was diagnosed as a high-grade myxofibrosarcoma. Posterior decompression and stabilization with the instrumentation from C7 to T7 was completed without any trouble (**Figure 5**). The operation time was 336 min. The blood loss was 2360 ml. Postoperative IMRT for

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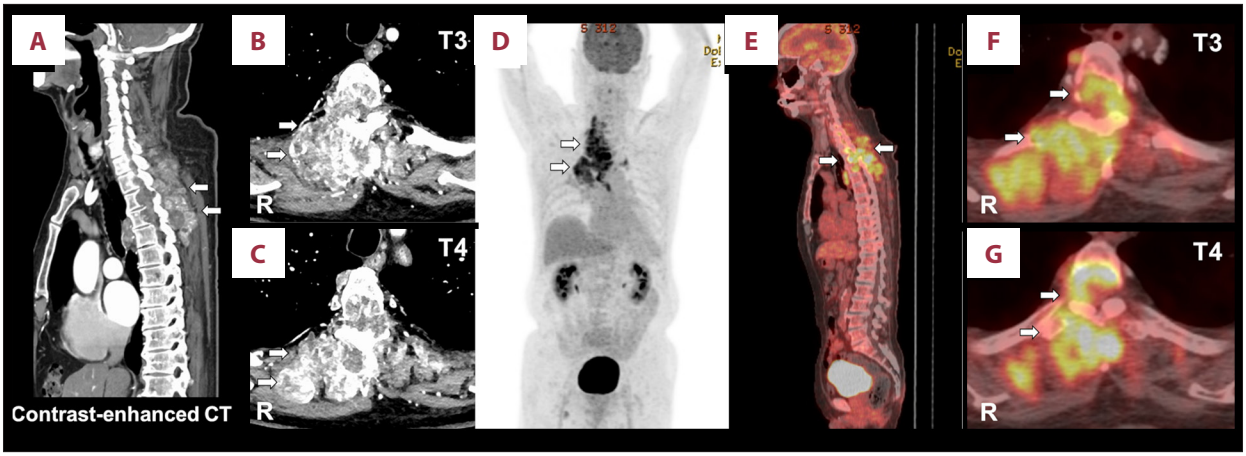

Figure 3. Preoperative contrast-enhanced computed tomography (CT) images (**A-C**) and positron emission tomography (PET) images (**D-G**) of the spine indicating multiple mass lesion at C7-T5 level. (**A**) A right-sagittal CT image showing vertebral body osteolysis and partly enhanced mass lesion at T3 and T4. (**B, C**) Axial CT images showing partly enhanced mass lesion invading rib, vertebrae, and spinal canal at T3 (**B**) and T4 (**C**). (**D**) A coronal PET image showing 18-labeled fluorodeoxyglucose accumulation. (**E**) A sagittal PET image showing 18-labeled fluorodeoxyglucose accumulation. (**F, G**) Axial PET images showing 18-labeled fluorodeoxyglucose accumulation at T3 (**F**) and T4 (**G**). White arrows indicate the tumor.

the residual tumor at the cervical and thoracic spine (60 Gy in 25 fraction) and tumor thrombus in the azygous vein (45 Gy in 15 fraction) was performed 3 weeks after surgery. No adverse effects of radiotherapy were observed. The patient had rapid recovery from myelopathy, became able to walk with a cane 3 months postoperatively, had an improved performance status up to 2, and maintained activities of daily living. At postoperative 16 months, he died from pneumonia, although MRI and PET presented no local recurrence (**Figure 6**).

Discussion

This case report suggested that the combination of separation surgery and postoperative IMRT can be a useful option in patients with impending neurological damage caused by an unresectable sarcoma.

Historically, myxofibrosarcoma was described as a type of malignant fibrous histiocytoma. Malignant fibrous histiocytoma belongs to the heterogeneous group of fibrohistiocytic tumors, including the pleomorphic, myxoid, giant cell, inflammatory, and angiomatoid variants. Malignant fibrous histiocytoma occurs mostly in the soft tissues of the extremities, sometimes in the trunk (approximately 10% [2]), and rarely in the spine [5-9,12]. By 2015, 32 cases of malignant fibrous histiocytoma in the spine had been reported [12]. However, myxofibrosarcoma has gradually been recognized as a distinct histotype, and in 2002 the World Health Organization (WHO) classified the myxoid variant of malignant fibrous histiocytoma with a predominant myxoid component (>50%) as myxofibrosarcoma [2]. Malignant fibrous histiocytoma was renamed undifferentiated pleomorphic sarcoma and was defined as a diagnosis of exclusion in 2002 [2]. Malignant fibrous histiocytoma arising within the spine is quite rare [5-9,12], and myxofibrosarcoma involving the spine is even rarer.

When macroscopic complete resection of a sarcoma involving the spine is possible, *en-bloc* resection is ideal despite high invasiveness and risks for neurological deterioration and bleeding [12], because wide surgical resection with a sufficient margin and postoperative radiotherapy is the standard treatment for a resectable sarcoma [3,4]. With recent progresses in radiotherapy such as IMRT, current evidence suggests the greater efficacy of postoperative IMRT for local control after macroscopic complete resection compared to conventional radiotherapy [13,14]. Although the rate of local recurrence had been reported to range from 16% to 57% [2], Wang et al showed a 5-year local control rate of 81.6% in patients with soft-tissue sarcomas in the trunk after surgical resection and IMRT [13]. Cosper et al reported a 3-year local control rate of 84% in patients with soft-tissue sarcoma in the retroperitoneum [14]. However, almost all of these reported cases were resectable and a positive margin was a risk factor for local recurrence [13,14]. A retrospective study of 27 patients with unresectable paraspinal chordomas and sarcomas demonstrated a local recurrence rate of 35% at 2 years after surgery and IMRT [15]. Taken together, these findings show that an unresectable sarcoma has still a high propensity for local recurrence.

Additionally, clinical outcomes of incomplete resection of malignant fibrous histiocytoma involving the spine are poorer compared to that in the extremities [8,9]. According to a retrospective study in 2011, the median survival of 7 patients with debulking surgery for unresectable malignant fibrous

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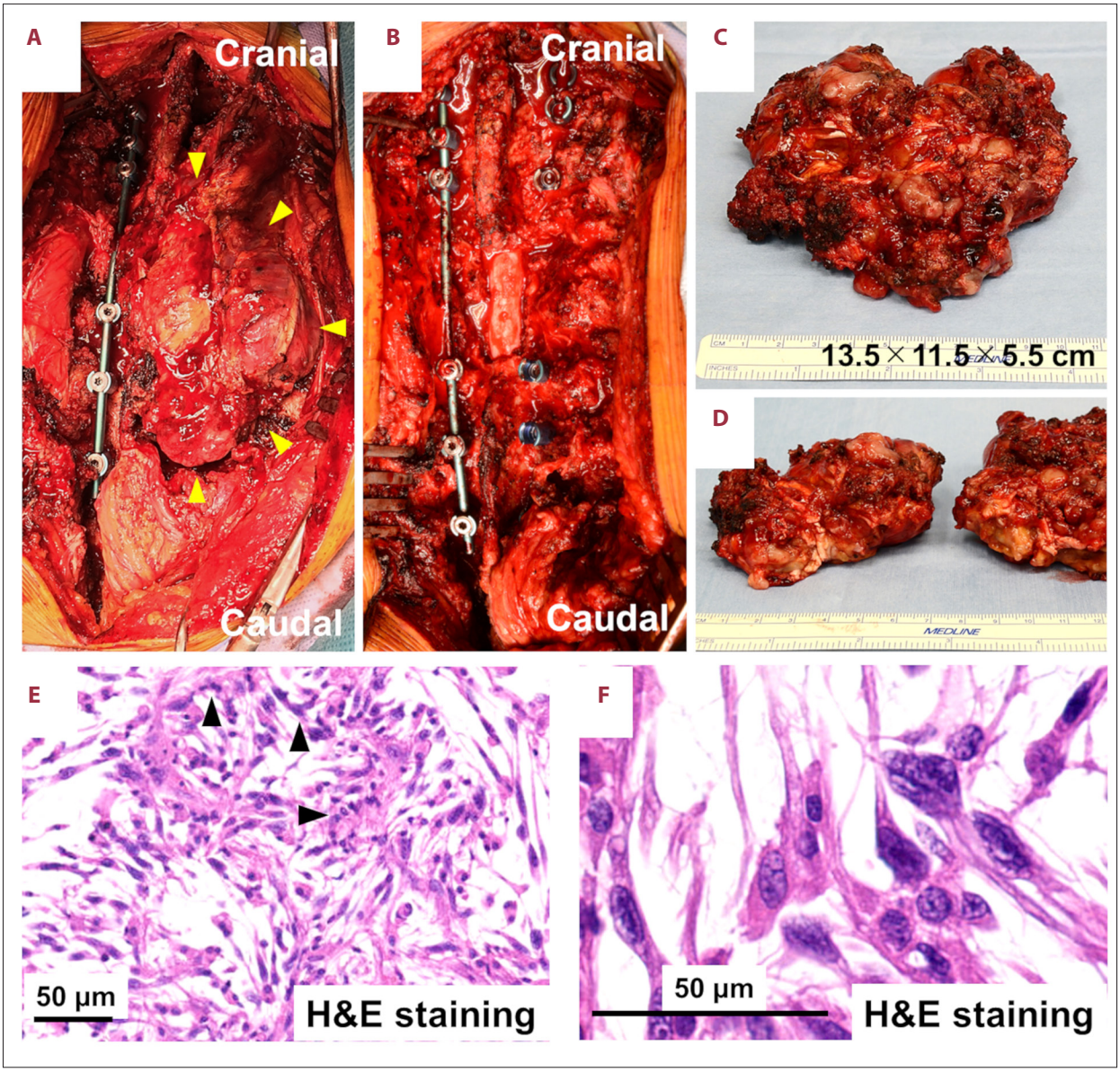

Figure 4. Intraoperative photographs and microscopic and macroscopic photographs of the high-grade myxofibrosarcoma. (**A, B**) Intraoperative photographs before (**A**) and after (**B**) removal of the tumor. Yellow triangles indicate the tumor. (**C, D**) Macroscopic photographs of the removed tumor measuring 13.5×11.5×5.5 cm (**C**). The cut surface shows a white multiple mass lesion with rich myxoid and intratumor hemorrhage (**D**). (**E, F**) Hematoxylin and eosin (H&E) staining microphotographs showing storiform pattern of spindle-shaped tumor cells with mucus (**E**) and pleomorphic cellular infiltrates with pleomorphic cell nuclei (**F**). The bars indicate 50 μm. Black triangles indicate storiform pattern of tumor cells.

histiocytoma at the spine with postoperative radiotherapy was 14 months [8]. Of these 7 patients, 4 (57.1%) patients developed local recurrence within 17 months [8]. Even 4 (80.0%) of 5 patients with total *en-bloc* surgery for resectable tumor developed local recurrence within 39 months [8]. Local recurrence around the spinal cord can result in neurological dysfunction, leading to severe deterioration of patients' quality of life and activities of daily living. Since one of the goals of the treatment is to maintain patients' quality of life (QOL) until the terminal phase, local control is indispensable for treatment in patients with a sarcoma close to the spinal cord even if the tumor is unresectable. A case report of debulking and vertebroplasty without postoperative radiotherapy for malignant fibrous histiocytoma demonstrated insufficiency of neurological improvement and short survival after surgery (6 weeks) [9].

In the present case, total *en-bloc* resection was difficult owing to the multifocal tumor lesions. Radiotherapy including IMRT

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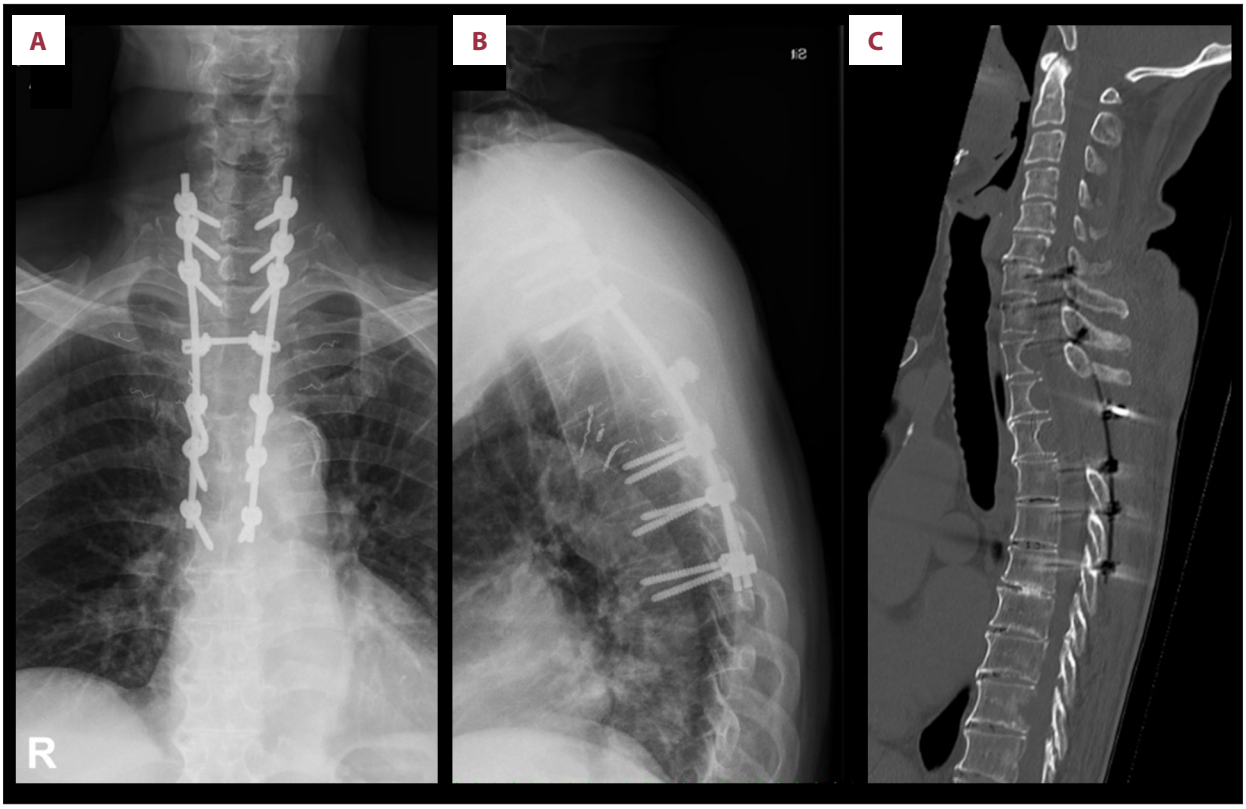

Figure 5. Postoperative images of the thoracic spine with posterior fusion between C7 and T7 and circumferential decompression at T2-4. (**A**) A posteroanterior radiograph. (**B**) A lateral radiograph. (**C**) A sagittal computed tomography (CT) image showing sufficient decompression at T2-4.

was not applicable at surgery because of the tumor adjacent to the spinal cord. Particle therapy [16,17] and chemotherapy were also not applicable due to the patient's age and performance status. However, the patient required a semi-urgent surgery to salvage neurological dysfunction. Hence, we selected separation surgery with postoperative IMRT. Accumulating evidence has recently demonstrated the efficacy this combination therapy for spinal metastases and chordoma [10,11,18]. However, little evidence regarding the combination therapy in patients with myxofibrosarcoma exists. Our experience of no lifetime appearance of local recurrence should be valuable for clinicians when treating such a patient, although the follow-up period was 16 months, which was similar to the median survival time of malignant fibrous histiocytoma involving the spine [8]. In terms of local control, palliative simple posterior decompression might be insufficient to maintain patients' QOL. Spine surgeons would better consider not only posterior decompression but circumferential decompression including the anterior aspect of spinal cord even in case of emergency despite high risks for neurological deterioration and bleeding. Separation surgery with postoperative IMRT can be an effective treatment option in patients with impending neurological damage by spinal tumors even in cases with unresectable rare tumor due to the size, location, or adhesion.

Conclusions

When total *en-bloc* resection is challenging, separation surgery with postoperative IMRT can be a useful option in patients with impending neurological damage by unresectable soft-tissue tumors including myxofibrosarcoma due to the size, location, or adhesion.

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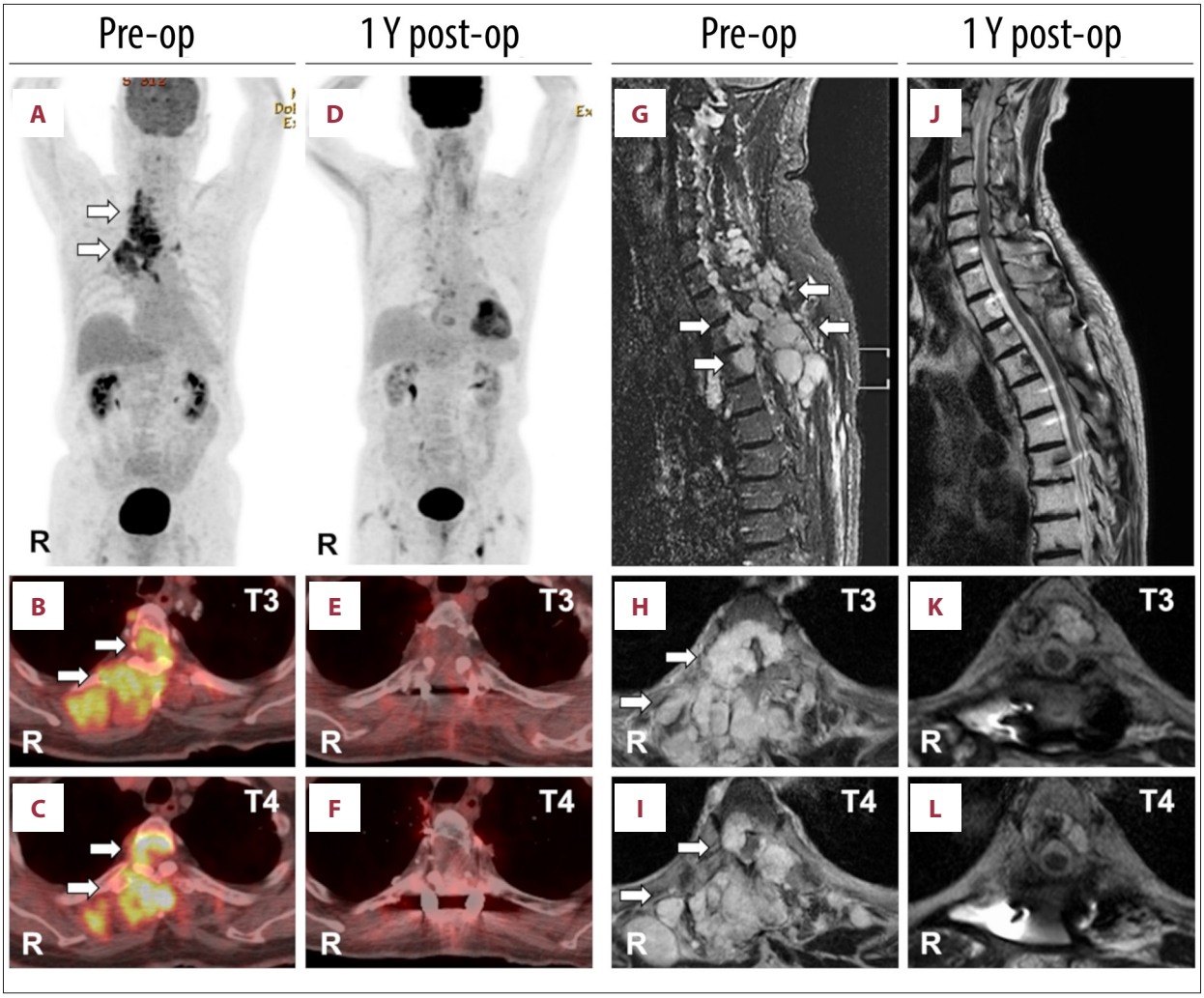

Figure 6. Comparison of preoperative and one-year postoperative images showing no local recurrence of the tumor. (**A-C**) Preoperative positron emission tomography (PET) images of coronal (**A**) and axial at T3 (**B**) and T4 (**C**) sections. (**D-F**). One-year postoperative PET images of coronal (**D**) and axial at T3 (**E**) and T4 (**F**) sections. (**G-I**) Preoperative T2-weighted magnetic resonance images (MRI) of sagittal (**G**) and axial at T3 (**H**) and T4 (**I**) sections. One-year postoperative T2-weighted MRI of sagittal (**J**) and axial at T3 (**K**) and T4 (**L**) sections. White arrows indicate the tumor.

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