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Case Report

A case of pelvic *EWSR1-PATZ1* fusion sarcoma treated with carbon ion radiotherapy ☆

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ABSTRACT

EWSR1-PATZ1 fusion sarcoma is a type of round-cell sarcoma with *EWSR1-non-EST* fusion that was newly categorized in the 2020 World Health Organization classification of soft tissue and bone tumors. In general, local disease is managed via surgical resection; however, at present, there is no standard therapy for locally advanced or metastatic disease. Here, we report our experience with a middle-aged male patient with pelvic *EWSR1-PATZ1* fusion sarcoma who was treated with carbon ion radiotherapy and maintained stable disease for 13 months. The patient's clinical course suggests that carbon ion radiotherapy may be effective in patients with locally advanced *EWSR1-PATZ1* fusion sarcoma.

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Introduction

EWSR1-PATZ1 fusion sarcoma is a type of round-cell sarcoma with *EWSR1-non-EST* fusion that was newly categorized in the 2020 World Health Organization classification of soft tissue and bone tumors [1]. A few case reports and retrospective analyses of a small number of patients have described the clinical, pathological, and genomic features of *EWSR1-PATZ1* fusion sarcoma; however, knowledge of this rare sarcoma is limited. In general, local disease is managed via surgical resection. However, currently, there is no standard therapy for locally advanced or metastatic disease. To the best of our knowledge, no previous case report has precisely evaluated the efficiency of standard radiation therapy or carbon ion radiotherapy (CIRT) in *EWSR1-PATZ1* fusion sarcoma. Herein, we present a rare case of locally advanced pelvic *EWSR1-PATZ1* fusion sarcoma that was treated with CIRT and remained stable for 13 months.

Case report

A middle-aged male patient with a pelvic mass was referred to our hospital for diagnosis and treatment. The patient had no relevant medical or family history. The patient complained of left buttock pain and consulted a nearby clinic 3 weeks prior to visiting our hospital. A pelvic mass was identified using magnetic resonance imaging (MRI), and the patient was transferred to a nearby hospital. Endoscopic ultrasound-fine needle aspiration from the rectum was performed, and the histological diagnosis was spindle cell tumor (unclassified). The patient was transferred to our hospital for further diagnosis and treatment.

On the first visit to our hospital, the patient complained of moderate left buttock pain, which increased in the seated position. Laboratory test results were almost normal. The axial view of the T2-weighted MRI revealed a lobulated, mild, high-intensity mass with a maximum diameter of 75 mm that compressed the rectum, prostate, seminal vesicle, urethra, and bladder to the right (Fig. 1A). The axial view of fat-suppressed T1-weighted images on gadolinium contrast-enhanced MRI revealed that the mass was well enhanced (Fig. 1B). 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG)-positron emission tomography/computed tomography (PET/CT) revealed that the tumor had a high intensity (maximum standardized uptake value, 5.0), but no metastatic lesions were detected.

Subsequently, a CT tomography-guided biopsy was performed. Histologically, the biopsied specimens revealed monomorphic spindle cell proliferation in the fibrous stroma interspersed with hyalinized-walled vessels. Immunohistochemically, the tumor cells were focally positive for SOX10, GFAP, desmin, MyoD1, PAX7, and pan-TRK, and negative for cytokeratin AE1/AE3, S100 protein, SMA, myogenin, and SSX. A provisional diagnosis of spindle cell neoplasm (not readily classifiable) was established (Figs. 2A and B).

Surgeons at our hospital decided that the tumor could be marginally resected by total pelvic exenteration; however, the patient refused invasive surgery. Systemic chemotherapy was initiated to reduce the tumor volume. It consisted of doxorubicin hydrochloride 30 mg/m^2 intravenous (IV) infusion (day 1-2) and ifosfamide 2 g/m^2 IV infusion (day 1-5). Following the initiation of chemotherapy, the results of a commercial DNA panel analysis (FundationOne^R: Fundation Medicine, Inc. USA) revealed that the tumor harbored *EWSR1-PATZ1* (*EWSR1* exon 8-*PATZ1* exon 1). The tumor was diagnosed as *EWSR1-PATZ1* fusion sarcoma. The efficacy of chemotherapy after 1 cycle was stable, but the tumor size increased slightly.

Therefore, CIRT was performed for *EWSR1-PATZ1* fusion sarcoma. A laparoscopic transverse colostomy was performed before the initiation of CIRT to prevent rectal complications. A prescription dose of 70.4 Gy (relative biological effectiveness [RBE]) in 16 fractions was selected as the standard dose for soft tissue sarcoma treatment in Japan. Contrast-enhanced CT and MRI imaging were used as references, and the tumor was outlined on the CT images as the gross tumor volume (GTV). The clinical target volume (CTV) was defined as the GTV plus a 10 mm margin, excluding organs at risk (OAR), such as the rectum. To evaluate the combined dose distribution of each beam, the planning target volume (PTV) was defined as the CTV plus a safety margin of 3 mm. Treatments were performed 4 times a week in the supine and prone positions, with 1 field per day. Because a spacer could not be inserted between the tumor and the OARs, a shrinking-field technique was used, in which 10 fractions were irradiated in a large field, and the next 6 fractions were irradiated in a small field to reduce the dose for OARs. The distribution of the treatment doses is shown in Figure 3. The GTV and CTV volumes were 142 cc and 303 cc, respectively, and were well covered by the treatment dose. The D2cc of the rectum was 51.8 Gy (RBE) and the D5cc of the bladder was 63.1 Gy (RBE), which were within the dose constraints of 58 Gy (RBE) and 65 Gy (RBE), respectively. Moreover, CIRT resulted in stable disease for the *EWSR1-PATZ1* fusion sarcoma (Figs. 4A and B), lasting for 13 months after treatment completion. Additionally, no late adverse effects on OARs, including the bones and nerves, have been observed to date.

Discussion

EWSR1-PATZ1 fusion sarcoma can occur in deep soft tissues; it has a predilection for the chest wall and abdomen, but other sites, such as the extremities, head, and neck, have also been reported [2–4]. The age range of patients with *EWSR1-PATZ1* fusion sarcoma is broad, with a median of 50 years [4]. Furthermore, the sex distribution is unclear.

The pathological features of *EWSR1-PATZ1* fusion sarcoma are diverse. Sarcoma cells of the *EWSR1-PATZ1* fusion sarcoma are a combination of round, spindled, and epithelioid cell types, which are often accompanied by fibrous stroma [1,3,4]. Immunohistochemically, the coexpression of myogenic markers (desmin, myogenin, MyoD1, and PAX7) and neurogenic markers (S100-protein, GFAP, and SOX10) is observed at various levels [1–4]; however, a histological diagnosis is difficult because of its rarity. In many cases of *EWSR1-PATZ1* fusion sarcoma, next-generation sequencing analysis is essential for diagnosis [3,4]. Currently, there

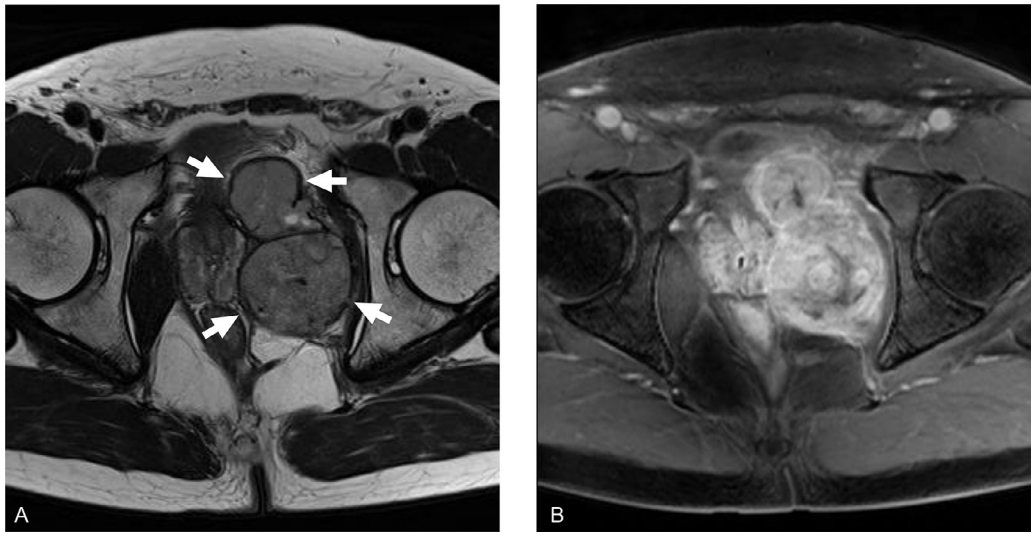

Fig. 1 – Axial view of T2-weighted magnetic resonance imaging (MRI) (A) revealed a lobulated mild high-intensity mass (white arrows). Axial view of fat-suppressed T1-weighted gadolinium contrast-enhanced MRI (B) revealed that the mass was well enhanced.

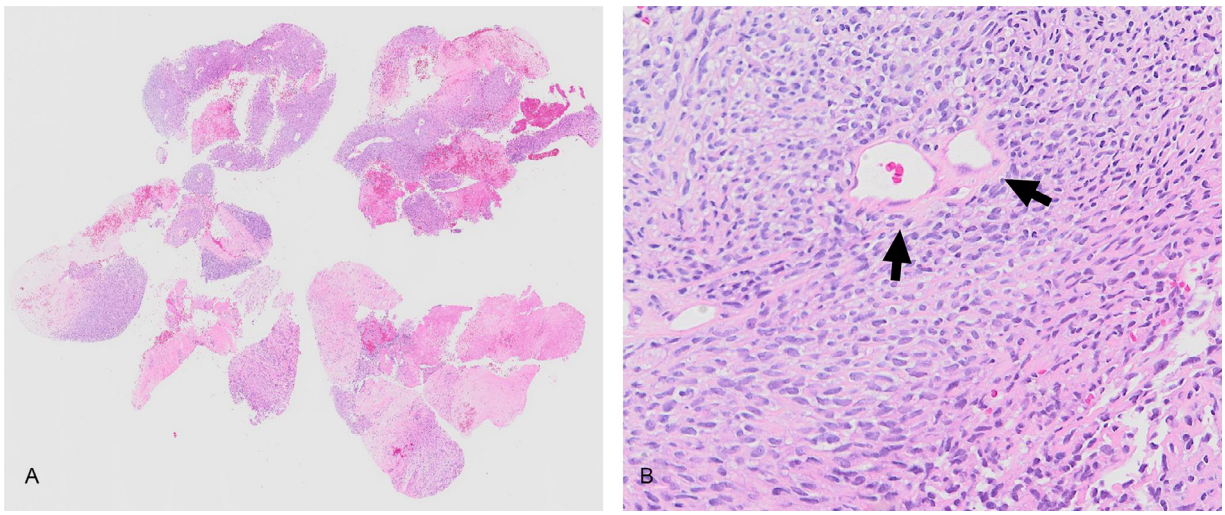

Fig. 2 – Microscopic findings of hematoxylin and eosin-stained sections (low power view (A) and high-power view (B)). The tumor exhibited diffuse proliferation of monomorphic spindle cells interspersed with hyalinized-walled vessels (black arrow).

is no standard therapy for metastatic *EWSR1-PATZ1* fusion sarcoma. Generally, typical Ewing sarcoma responds well to chemotherapy in the early stages of the disease. However, our patient's *EWSR1-PATZ1* fusion sarcoma did not respond to the first round of chemotherapy. Currently, there are only a few case reports that have investigated the effects of different cytotoxic drugs on *EWSR1-PATZ1* fusion sarcoma [2,5]. Thus, more case reports are needed to properly evaluate the effectiveness of chemotherapy for this type of sarcoma.

In contrast, in patients with local *EWSR1-PATZ1* fusion sarcoma, no evidence of disease was reported 19 months after resection [2]. Dehner reported that 13 of 15 patients with *EWSR1-PATZ1* fusion sarcomas who underwent complete surgical resection survived without evidence of disease [4]. Local therapy may play an important role in the treatment of locally advanced *EWSR1-PATZ1* fusion sarcoma.

Our patient had locally advanced pelvic *EWSR1-PATZ1* fusion sarcoma, which grew slightly after 1 course of chemotherapy. The *EWSR1-PATZ1* fusion sarcoma may have been resected via total pelvic exenteration. However, the patient refused invasive surgery and preferred CIRT. The treatment effect was evaluated as stable disease 13 months after CIRT completion. In some reports of *EWSR1-PATZ1* fusion sarcoma, radiation therapy was used for various purposes. Michal reported nine cases of *EWSR1-PATZ1* fusion sarcomas [3]. Two of them received radiation therapy. One of them underwent surgery and received adjuvant radiation therapy for abdomi-

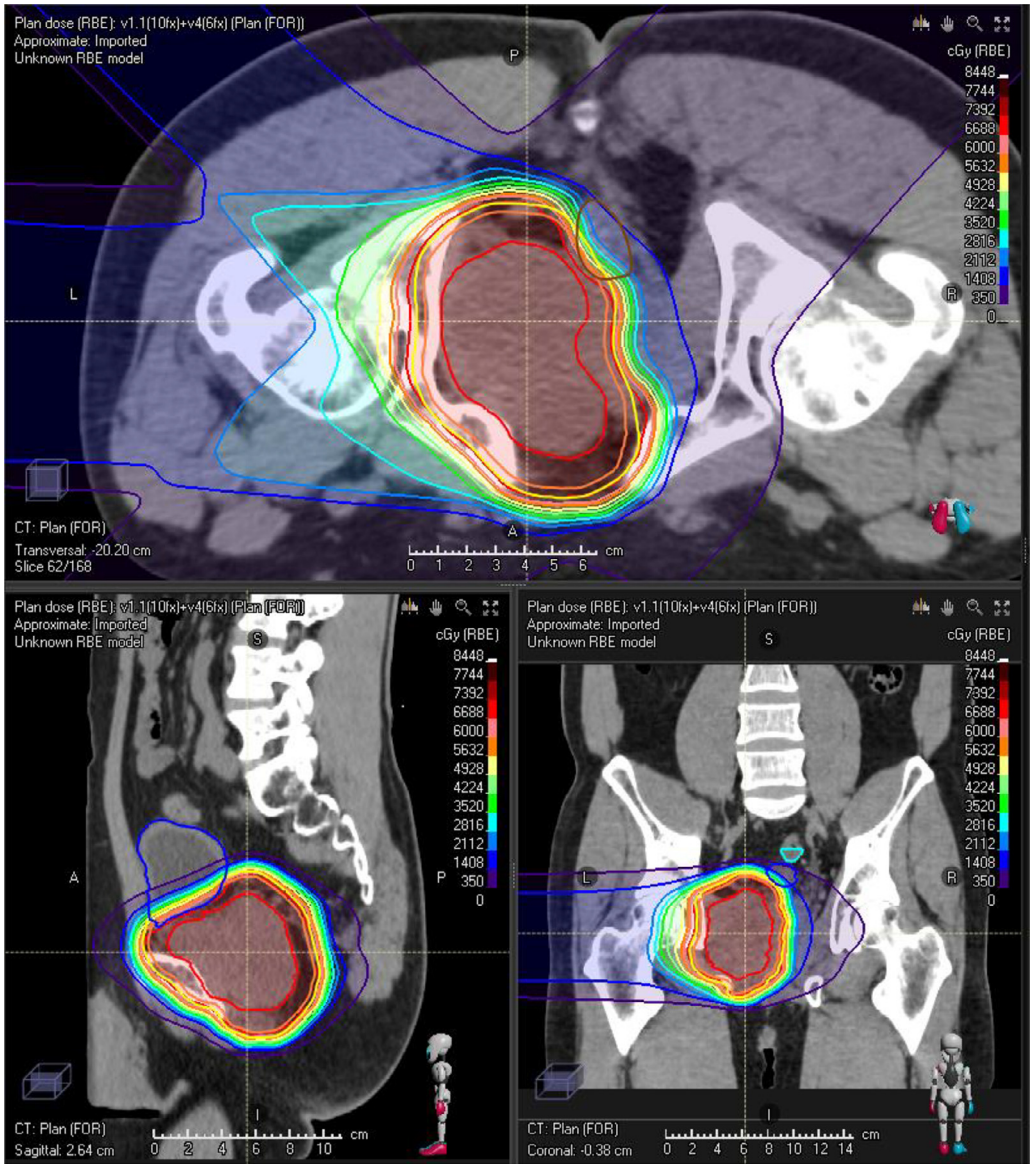

Fig. 3 – Dose distribution of treatment planning with 70.4 Gy (relative biological effectiveness) in 16 fractions.

nal primary *EWSR1-PATZ1* fusion sarcomas, but multiple pulmonary metastases were detected 3 and 4 years after the diagnosis of the primary lesion. The second case was advanced, and the patient received chemotherapy (cyclophosphamide) with concurrent radiation therapy. Initially, the patient experienced stable disease, but 4 months later, the progression of the sarcoma occurred. Deher reported 17 cases of *EWSR1-PATZ1* fusion sarcomas [4]. Five of the cases with localized disease received radiation therapy (4 cases in the neoadjuvant setting and 1 case in the adjuvant setting). One case that received neoadjuvant radiation therapy developed lung metastases 2 months after the diagnosis; however, the other 4 cases remained alive without evidence of disease at the time of reporting.

As mentioned above, radiation therapy for this sarcoma was mostly reported to be used as part of multimodal treatment, and evaluating the effect of radiation therapy itself is currently challenging.

As for Ewing's sarcoma family, CIRT was used for unresectable [6] or locally recurrent tumors [7] as a component of the multimodal treatment approach. However, its effectiveness was limited, particularly in controlling distant metastases. As for *EWSR1-PATZ1* fusion sarcoma, to the best of our knowledge, no previous case report has thoroughly evaluated the effectiveness of CIRT. The clinical course of this patient suggests that CIRT may be effective for patients with locally advanced *EWSR1-PATZ1* fusion sarcoma.

This case report had several limitations. First, we acknowledge that a 13-month observation period is not sufficient to evaluate the efficiency of CIRT. However, some studies have reported a relatively good prognosis for local *EWSR1-PATZ1* fusion sarcomas [3,4]. Secondly, it is possible that in the present case, the patient's sarcoma was an indolent subtype of *EWSR1-PATZ1* fusion sarcoma. Michal roughly divided *EWSR1-PATZ1* fusion sarcoma into 3 morphological subgroups: low-grade spindle/round cell tumors, predominantly round cell sarco-

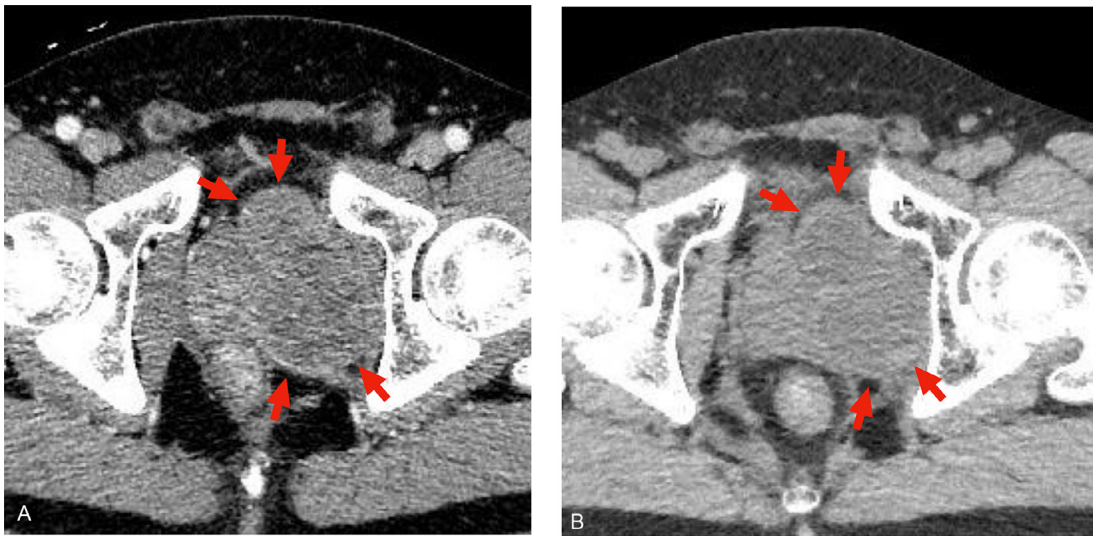

Fig. 4 – Computed tomography images (A) before the carbon ion radiotherapy and (B) 13 months after completion of the treatment show no remarkable change in the tumor size (red arrows).

mas, and high-grade spindle/round cell sarcomas [3]. The microscopic imaging results of the present patient suggested a low-grade spindle/round cell tumor. Bridge suggested that *CDKN2A/CDKN2B* loss is frequent in *EWRS1-PATZ1*-related tumors, which may have prognostic significance [2]. In addition, in our patient, *EWSR1-PATZ1* fusion sarcoma did not show any *CDKN2A/CDKN2B* mutations or copy number losses.

In summary, we report a case of locally advanced *EWSR1-PATZ1* fusion sarcoma that was treated with CIRT and maintained stable disease for 13 months. The patient's clinical course suggested that CIRT may be effective in patients with locally advanced *EWSR1-PATZ1* fusion sarcoma. Further accumulation of similar *EWSR1-PATZ1* fusion sarcoma cases is necessary to elucidate the efficacy of CIRT for locally advanced *EWSR1-PATZ1* fusion sarcoma.

Patient consent

I declare the following description "Written informed consent was obtained from the patient for the publication of patient data and associated images."

Data availability

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethical approval

The sample of the patient's soft tissue mass was collected after written informed consent was obtained according to the protocol approved by Osaka International Cancer Institute (Osaka, Japan).

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