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ORIGINAL ARTICLE

Clinical results of carbon-ion radiotherapy with separation surgery for primary spine/paraspinal sarcomas

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Abstract

Purpose To evaluate the clinical outcome of combination of carbon-ion radiotherapy with separation surgery (CIRT-SS) in patients with primary spinal/paraspinal sarcoma (PSPS) and epidural spinal cord compression (ESCC).

Methods CIRT-SS was performed in 11 consecutive patients. Patients treated in the primary and salvage settings were categorized into Group A ($n=8$) and Group B ($n=3$), respectively. Clinical results and imaging findings were collected, with a particular focus on ESCC grade, treatment-associated adverse events (AEs), and the locoregional control (LRC) rate and overall survival (OS).

Results The median follow-up period from the start of CIRT-SS was 25 months (7–57 months). ESCC was improved by SS in all cases. No patients exhibited radiation-induced myelopathy (RIM), but three developed Grade 3 vertebral compression fracture (VCF) during follow-up. Locoregional recurrences were observed in four patients [Group A: 1 (12.5%), Group B: 3 (100%)]. Over the entire follow-up period, three patients developed distant metastases and two patients died. The 2-year LRC rate and OS were 70% and 80%, respectively.

Conclusion CIRT-SS in the primary setting achieved acceptable LRC and OS without RIM in patients with PSPS and with ESCC. VCF was the most frequent AE associated with CIRT-SS.

Keywords Carbon-ion radiotherapy · Separation surgery · Primary spinal/paraspinal sarcoma · Epidural spinal cord compression · Vertebral compression fracture

Introduction

Treatment of primary spinal/paraspinal sarcoma (PSPS) is one of the most challenging issues in the field of orthopedic surgery. A previous report showed that conventional radiotherapy at a dose of 50–60 Gy was insufficient for long-term locoregional control (LRC) of certain PSPS such as chordoma [1]. Recently, several new radiation modalities, including carbon-ion radiotherapy (CIRT), have been developed. CIRT has greater biologic effectiveness than photon radiotherapy due to its higher linear energy transfer (LET) [2]. In addition, carbon-ion beams emit a low dose of radiation at the entrance point, reaching their maximum LET at the end of their range (Bragg peak), beyond which the LET drops distinctly. Given these advantages, the clinical results of CIRT in the treatment of PSPS are promising [3].

Most of the marginal recurrences after CIRT for PSPS develop adjacent to the spinal cord, and are often due to insufficient radiation doses to this area [3]. On the other hand, dose escalation between the tumor margin and the spinal cord might increase the risk of radiation-induced myelopathy (RIM), which has been reported after CIRT [3]. RIM is not a common adverse event, and there are insufficient data concerning the ability of the spinal cord to tolerate

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radiotherapy [4]; both of these factors are caveats in terms of using CIRT for the treatment of PSPS with epidural spinal cord compression (ESCC).

"Separation surgery" (SS) is an emerging concept in spinal oncology. The surgical intent of SS is that the extent of resection can be limited to epidural tumor, given the expectation that residual disease can be controlled by subsequent radiotherapy. Since SS is achievable by a less invasive procedure, it may preserve extensive blood loss and long operative time associated with gross total tumor resection [5]. Practically, SS consists of a limited posterolateral tumor resection with/without posterior segmental instrumentation. It achieves a small margin of several millimeters between the spinal cord and tumor, which can enable the safe administration of a sufficient curative radiation dose to the entire tumor volume, minimizing the risk of RIM.

Promising results of SS and subsequent photon radiotherapies such as single-fraction stereotactic radiosurgery (SRS) are now being reported, particularly in patients with metastatic spine tumors [6]. In contrast, there are limited clinical results of SS plus radiotherapy for PSPS [7]. In this study, we report middle-term LRC rates, overall survival (OS), and adverse events after CIRT with SS (CIRT-SS) for PSPS with ESCC.

Methods

Eleven consecutive patients with PSPS and ESCC who met all of the following eligibility criteria were included in this study: histologically proven primary sarcoma; tumors medically judged as unsuitable for curative resection by a multidisciplinary tumor board including spine surgeons, radiation oncologists, neuroradiologists, pathologists, and medical oncologists; grossly measurable tumors < 15 cm in their greatest dimension; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; no distant metastasis at the time of initial treatment referral; and no infection at the tumor site. This study was approved by the institutional review board at Kyushu university hospital (26–112).

The 11 patients were subsequently divided into two groups: Group A consisted of patients treated in the primary setting, and Group B comprised those treated in the salvage setting for locoregional recurrence (LRR). More specifically, two patients in Group B had undergone previous surgery (intralesional resection) and one patient received prior CIRT and had a marginal recurrence adjacent to the spinal cord. Clinical information was collected through a retrospective review of a prospectively maintained database. The evidence of disease progression (LRR and distance metastasis) was determined by various imaging modalities (plain radiography, computed tomography (CT), magnetic resonance imaging (MRI), and ^{18}FDG-positron emission tomography/CT (PET/CT), if applicable), from the time of start of CIRT-SS until last follow-up. According to a previous report [8], the status of ESCC was defined by MRI before the treatment, immediately after surgery, and during the follow-up period. In brief, ESCC was defined as according to the scoring system from 0 to 3: "0" as no spinal canal involvement, "1" as epidural impingement without spinal cord compression, "2" as spinal cord compression with cerebrospinal fluid (CSF) observed, and "3" as the most severe spinal cord compression with no CSF noted. In addition, the score of "1" is further subdivided into three categories. Grade 1a defines the epidural space involvement without compression of the dura, Grade 1b disease compresses the dura without abutment the spinal cord, and tumors of Grade 1c abuts with dura but does not compress or alter the course of the spinal cord. Treatment complications were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5. Locoregional control (LRC) was calculated from separation surgery to the date of local or regional recurrence/relapse. Overall survival time (OS) was calculated from separation surgery until death or last follow-up. LRC and OS were calculated using the Kaplan–Meier method. JMP version 13 software (SAS institute inc.) was used for statistical analysis.

The intent of SS was posterior epidural decompression, and gross total resection was not attempted in any patient. Surgery consisted of laminectomy at the levels of ESCC, as well as epidural tumor resection to achieve a normal thecal sac contour. In most cases, vertebral bodies and paraspinal masses were not resected [9]. Since surgical hardware can greatly reduce the amount of radiation reaching a tumor [10], we minimized spinal instrumentation as much as possible to lessen the adverse impact on subsequent CIRT. CIRT was performed at the SAGA heavy ion medical accelerator in Tosu, Japan, using the same approach as previously reported [11]. Briefly, a set of 2-mm-thick CT images was obtained under respiratory gating for treatment planning. The clinical target volume (CTV) usually included the potential area of tumor spread and was defined as a 3- to 5-mm margin around the gross tumor volume. Then, the planning target volume was established with an additional 3- to 5-mm margin around the CTV, but this depended on the distance from critical organs like the spinal cord, intestine, and skin. Three-dimensional treatment planning for CIRT was performed using the XiON software program (Elekta, Stockholm, Sweden; Mitsubishi Electric, Tokyo, Japan). The irradiated dose was expressed as the relative biological effectiveness (RBE)-weighted dose [Gy (RBE)], which was defined as the absorbed dose of carbon ions multiplied by the RBE. CIRT was performed once daily for 4 days a week, for a total of 16 fractions over a 4-week period.

Results

The median age at start of SS was 43 years (range 23–73 years) and the majority of patients were male ($n = 7$, 64%). The tumors were diagnosed histologically, with five cases of malignant peripheral nerve sheath tumor (MPNST); two cases of chondrosarcoma; and one case each of chordoma, osteosarcoma, undifferentiated pleomorphic sarcoma and malignant myoepithelioma. The location of the tumor was the cervical spine in four patients, the thoracic vertebrae in six patients, and the sacrum in one patient. Five patients received various chemotherapy regimens before and/or after CIRT. The median follow-up period from the start of SS was 28 months (range 7–57 months). In addition, the median follow-up period from the start of SS of survivors was 38 months (range 7–57 months). Patient and tumor characteristics are summarized in Table 1.

Radiologic high-grade ESCC (Grades 2 and 3) was observed preoperatively in nine patients (81.8%). A mean of 2.5 spinal levels (range 2–4) were decompressed. There was no postoperative neurologic deterioration. At the start of CIRT, all but one patient had ESCC Grade 0 (1) or 1 (a: 1, b: 2, c: 6). Regarding the CIRT setting, 4 patients were treated with 64 Gy (RBE) and 7 with 70.4 Gy (RBE), all in 16 fractions. There were no CTCAE Grade 4 and Grade 5 toxicities during follow-up after CIRT-SS. Grade 1 toxicities included one case each of dermatitis, pharyngeal mucositis, and pneumonitis in Group A. Grade 2 toxicities included one case of dermatitis in Group A and one case of vertebral compression fracture (VCF) in Group B. In Group A, there were three cases of Grade 3 VCF, which required spinal fixation with hardware due to intolerable pain. We observed no CIRT-SS-associated RIM after the final follow-up (see Table 2).

Table 3 shows a summary of patients' clinical information. Of the eight patients in Group A, only one showed LRR at last follow-up (LRC rate: 87.5%). Remarkably, all patients in Group B experienced LRR. Overall, the LRC rate of CIRT-SS was 63.6% (7/11 patients). Three cases of LRR occurred outside the radiation field, but there was one case of LRR within the radiation field in an osteosarcoma patient. Importantly, we observed no marginal recurrences between the spinal cord and tumor. Three patients developed distant metastasis during follow-up (27%). Two patients died over the entire follow-up period and all patients eventually died of the disease. The 2-year LRC rate and OS were 70% and 80%, respectively, and Kaplan–Meier curves for the LC rate and OS are shown in Fig. 1.

Table 2 Treatment-associated complications

CTCAE	All	Group A		Group B	
		No.	Toxicity	No.	Toxicity
Grade 1	3	3	Dermatitis, pharyngeal mucositis, pneumonitis	0	NA
Grade 2	2	1	Dermatitis	1	VCF
Grade 3	3	3	VCF	0	NA
Grade 4	0	0	NA	0	NA

CTCAE common terminology criteria for adverse events, *VCF* vertebral compression fracture, *NA* not applicable

Case presentations

Case 3

A 34-year-old female suffered from bilateral leg numbness and gait disturbance. An axial T2-weighted MRI demonstrated a paravertebral dumbbell-shaped mass extending into the spinal canal with severe spinal cord compression (ESCC Grade 3) (Fig. 2a). Histological examination showed a multinodular proliferation of epithelioid cells in nests or sheets, and oval to short spindle cells in a haphazard pattern with a chondromyxoid stroma, confirming the diagnosis of

Table 1 Patients' characteristics

Variable	Total	Group A (Primary)	Group B (Salvage)
Age (median)	43.5 (23–73)	48 (34–73)	43 (23–70)
Sex (male/female)	7/4	5/3	2/1
Median follow-up (mo)	28 (7–57)	26.5 (7–45)	38 (22–57)
Location			
Cervical	5	5	0
Thoracic	5	2	3
Lumbar	0	0	0
Sacral	1	1	0
Chemotherapy	5	4	1

mo months

Table 3 Summary of clinical information by patients

Case no.	Sex	Age	Tumor location	Histology	CIRT dose [Gy (RBE)]/fractions	ESCC preop	ESCC postop	Locoregional control	Distant metastasis	Overall survival (months)	Complication (CTCAE grade)	Status
Group A												
1	M	40	C2–4	MPNST	64/16	3	1a	Yes	Yes (lung, bone, brain)	10	Dermatitis (1), pharyngeal mucositis (1)	DOD
2	M	48	T1	MPNST	70.4/16	3	1c	No	Yes (lung, bone)	18	VCF(3), dermatitis (2)	DOD
3	F	34	T3–4	Malignant myoepithelioma	70.4/16	3	1b	Yes	No	43	Pneumonitis (1)	NED
4	F	73	C1–2	UPS	70.4/16	1a	0	Yes	No	30	VCF (3)	NED
5	M	40	C3-4	Chordoma	64/16	3	1c	Yes	No	25		NED
6	M	46	C3–5	MPNST	70.4/16	3	1c	Yes	No	45		NED
7	F	41	S1–2	MPNST	70.4/16	3	1c	Yes	No	7		NED
8	M	49	T11–12	MPNST	70.4/16	2	1b	Yes	No	41	VCF (3)	NED
Group B												
1	M	43	T3–4	CS	64/16	1b	1c	No	No	57		AWD
2	M	23	T5–7	OS	64/16	3	2	No	Yes (bone)	24	VCF (2)	AWD
3	F	70	T3–6	CS	70.4/16	3	1c	No	No	22		AWD

CIRT carbon-ion radiotherapy, *ESCC* epidural spinal cord compression, *mo* month, *CTCAE* common terminology criteria for adverse events, *VCF* vertebral compression fracture, *MPNST* malignant peripheral nerve sheath tumor, *UPS* undifferentiated pleomorphic sarcoma, *CS* chondrosarcoma, *OS* osteosarcoma, *DOD* died of disease, *NED* no evidence of disease, *AWD* alive with disease

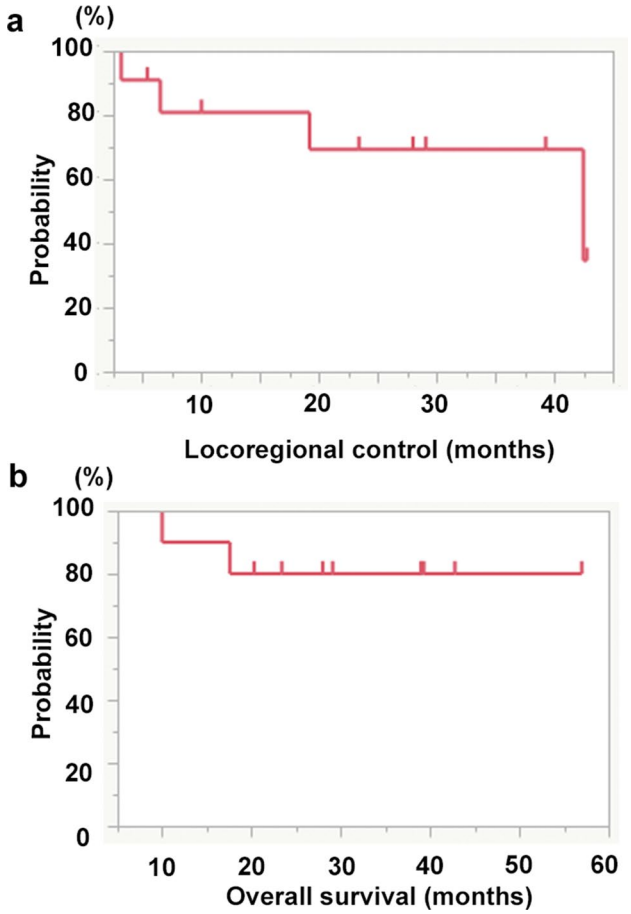

Fig. 1 Kaplan–Meier curve for locoregional control (**a**) and overall survival (**b**) in patients treated by CIRT-SS

malignant myoepithelioma. Preoperative PET/CT indicated that the tumor had high metabolic activity (SUV_{max} = 5.11) (Fig. 2d). The patient underwent T3–4 laminectomy and the epidural component of the tumor was resected. Her postoperative ESCC Grade improved to 1b (Fig. 2b). She then underwent CIRT (70.4 Gy (RBE)/16 Fr) and the 90% isodose line (arrow, red line in Fig. 2e) was set near the spinal cord. The maximum dose and D2cc to spinal cord was 42.29 Gy (RBE) and 20.6 Gy (RBE), respectively. At final follow-up, axial T2-weighted MRI confirmed shrinkage of the tumor mass with ESCC Grade 0 (Fig. 2c). On postoperative PET/CT, the tracer uptake of the tumor was faint (SUV_{max} = less than 2), indicating almost no metabolic activity (Fig. 2f). She was alive with no evidence of disease at 43 months after SS.

Case 8

A 49-year-old man experienced right-sided chest pain and was referred to our hospital. An axial T2-weighted MRI revealed a paravertebral neoplastic lesion with an intraspinal lesion at the T11/12 level, and ESCC was regarded as Grade 2 (Fig. 3a). In addition, osteolytic destruction of the posterior portion of T11 was observed on CT imaging (Fig. 3d). A CT-guided needle biopsy was performed and a diagnosis of MPNST was made. The patient underwent T11–12 laminectomy and the epidural component of the tumor was removed. The immediate postoperative MRI revealed the improvement in ESCC (Grade 1b) (Fig. 3b). Subsequently, he underwent CIRT [70.4 Gy (RBE)/16 Fr] and 90% of the dose was delivered adjacent to the spinal cord (arrow, red line in Fig. 3c). The maximum dose and D2cc to spinal cord were 32.8 Gy (RBE) and 8.9 Gy (RBE), respectively. Eight months after completion of CIRT-SS, he felt severe back pain and follow-up sagittal CT imaging demonstrated a VCF at T11 (Fig. 3e, arrows). Posterior spinal fusion was performed with instrumentation and his symptoms were relieved (Fig. 3f). He was continuously disease free for 41 months after SS.

Discussion

The sufficient radiation dose for treating PSPS has been investigated in various radiotherapy settings. For example, a previous report showed that the 2-year LC rate and OS were 65% and 79%, respectively, in patients with unresectable PSPS treated with a median radiation dose of 66 Gy in standard fractionation with intensity-modulated radiotherapy (IMRT) [12]. On the other hand, De Laney et al. demonstrated a favorable clinical outcome in 50 patients with PSPS who received combined photon and proton radiotherapy [13]. In that study, preoperative and/or postoperative radiotherapy was delivered up to a total of 77.4 Gy (RBE) after radical surgery for gross total resection. The 3-year and 5-year LC rates were 84% and 78%, respectively. In another study, unresectable sacral chordomas were treated with CIRT at a median total dose of 67.2 Gy(RBE), and the 5-year LC rate was 77.2% [14]. In addition, unresectable PSPS in the mobile spine was treated with a median total dose of 64 Gy(RBE), with a 5-year LC rate of 79% [3]. Based on these findings, the total sufficient dose for achieving LC in PSPS is estimated to be 60 Gy (RBE) or more.

There are a few reports concerning spinal cord dose constraints [4]. In one report, the dose to the central spinal cord was limited to 54 Gy (RBE) in 30 fractions [13]. In another report, the maximum spinal cord dose was limited to 13 Gy in a single fraction or 20 Gy in 3 fractions [15]. These thresholds for preventing RIM are apparently smaller than those for achieving LC of PSPS. Thus, an adequate radiation dose cannot be delivered to tumors adjacent to the spinal cord in PSPS patients with ESCC. One study found that all five marginal recurrences in patients with PSPS who were treated with CIRT occurred between the spinal cord and the tumor [3]. Actually, we considered that the reason for

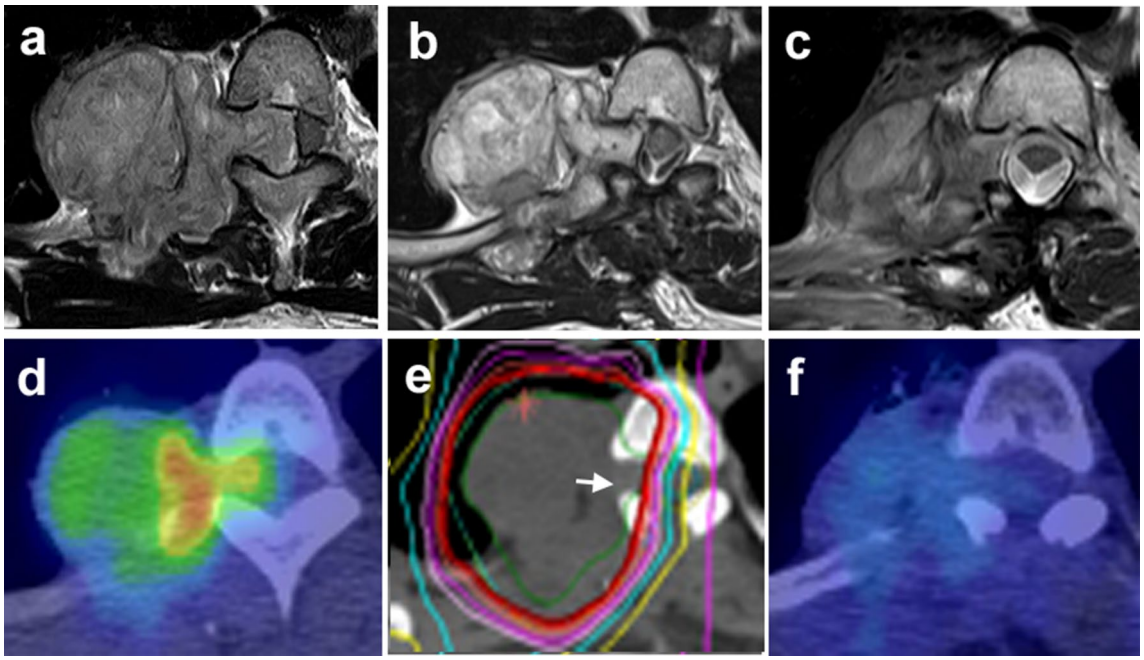

Fig. 2 Case 3. A 34-year-old female with malignant myoepithelioma involving T3 and T4. **a**–**c** Axial T2-weighted MRI of the tumor. ESCC before surgery, after surgery, and at final follow-up was Grade 3, Grade 1b, and Grade 0, respectively. **d**, **f** Preoperative PET/CT (**d**) indicates high tumor metabolic activity (SUV_{max} = 5.11), whereas postoperative PET/CT demonstrates almost no metabolic activity (SUV_{max} = less than 2). **e** Planning of CIRT. The 90% isodose line (red line indicated by arrow) was set near the spinal cord

the first LRR before CIRT-SS in case # 2 in Group B might be attributed to the insufficient dose for the margin of the spinal cord. This may also confirm that insufficient margins might have caused the LRR, which is a difficult problem in the treatment of PSPS with ESCC. Of note, SS provides a small margin of 2–3 mm between the spinal cord and the tumor, thereby enabling a full radiation dose to be delivered to the residual tumor and reducing the need for complex approaches and gross total resection [9]. Importantly, we observed an acceptable LC without RIM, suggesting that CIRT-SS is a safe and effective approach in patients with PSPS and ESCC.

In this study, we experienced four patients with LRR, two of whom underwent salvage surgery for LRR of chondrosarcoma. The primary surgery was intra-regional resection. In this method, iatrogenic tumor spillage into the surgical field was unavoidable, and the seeded tumor cells presumably caused the LRR. Therefore, carefully planning combined SS and CIRT at first presentation provides the best chance to achieve durable LRC of PSPS with ESCC [16].

In terms of treatment planning, the timing of surgery is an important factor. For example, in our patient with MPNST (case #2), we observed regrowth with ESCC after initial separation surgery because of the long standby time prior to CIRT (approximately 3 weeks). Thus, if rapid tumor growth is anticipated after surgical decompression, the wait time between SS and CIRT should be as short as possible, or the addition of neo-adjuvant chemotherapy before CIRT should be considered.

The most frequent complication in the present series was post-CIRT-SS VCF. Importantly, in cases of spinal sarcoma treated with proton radiotherapy, there is a higher rate of LRR in patients with metallic implants, possibly due to insufficient delivery of the radiation dose [17]. Thus, we did not apply spinal fixation during separation surgery, leading to post-CIRT-SS VCF. The spinal instability neoplastic score (SINS), developed by the Spine Oncology Study Group, is a reliable scoring system to detect spinal instability [18]. Six radiographic and clinical components are evaluated and added together and the total score is divided into three categories of stability: stable (0–6 points), potentially unstable (7–12 points), and unstable (13–18 points). The clinical relevance of the SINS in terms of predicting post-radiation VCF is confirmed by several tumor histology, including PSPS [11]. Remarkably, the 1-year cumulative incidence rate of any VCF after CIRT for PSPS was 80% for patients with a SINS score of 8 or higher. Thus, we consider that the patients of PSPS with a SINS of 8 points or higher should ideally be discussed by a multidisciplinary cancer board and prophylactically stabilized after completion of CIRT-SS [11].

The limitations of this study were its retrospective design, the small number of patients with limited variety in tumor histology, and the relatively short follow-up period. Further

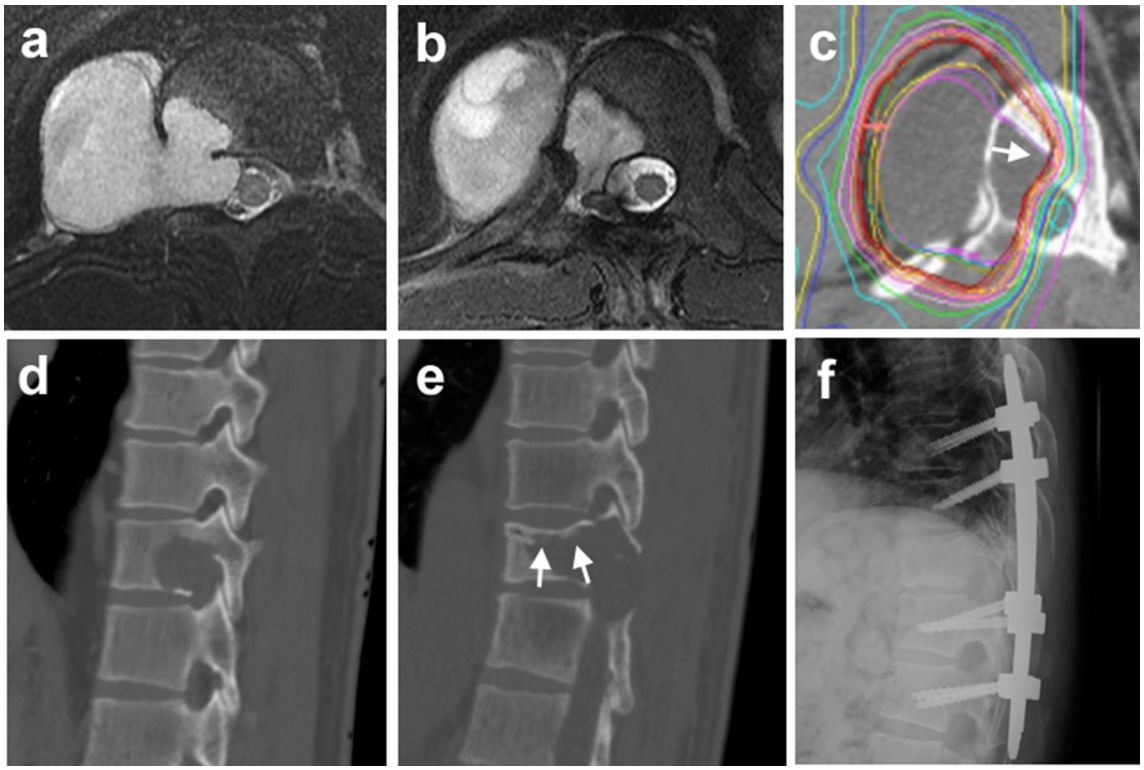

Fig. 3 Case 8. A 49-year-old man with MPNST at T11 and T12. **a**, **b** Axial T2-weighted MRI reveals a paravertebral neoplastic lesion with an intraspinal lesion. Preoperative (**a**) and postoperative (**b**) ESCC was regarded as Grade 2 and Grade 1b, respectively. **c** Planning of CIRT. The 90% isodose line (red line indicated by arrow) was set adjacent to the spinal cord. **d**, **e** Osteolytic destruction of the posterior portion of T11 is observed on CT imaging (**d**). Eight months after completion of CIRT-SS, the patient felt severe back pain; follow-up sagittal CT imaging demonstrates a VCF at T11 (arrows in **e**). **f** Posterior spinal fusion with instrumentation was performed

investigations are needed to address these limitations. In summary, by introducing CIRT-SS, acceptable LRC was achieved without RIM in patients with PSPS and ESCC in the primary setting and post-CIRT-SS VCFs were the most frequent treatment-associated adverse event.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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