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Post-carbon-ion radiotherapy vertebral pathological fractures in upper cervical primary malignant spinal tumors treated by occipito-cervical fusion

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Abstract

Purpose To describe the characteristic features of post-carbon-ion radiotherapy (CIRT) vertebral pathological fractures (VPFs) in upper cervical primary malignant spinal tumors (PMSTs) treated by occipito-cervical (OC) fusion.

Methods OC fusion was performed for three consecutive patients with post-CIRT VPFs. The clinical results and imaging findings, including bone single-photon emission computed tomography (SPECT)/CT were prospectively collected.

Results No surgery-related wound complication and surgical site infection were noted. One patient experienced re-fracture and displacement of dens with the loosening of occipital screws and was treated by posterior revision surgery. At the final follow-up, all patients were alive without evidence of disease, and the solid OC fusion was confirmed. Bone SPECT/CT clearly revealed the effect of CIRT on bone turnover in the irradiated field.

Conclusion The OC fusion with autologous bone grafts was a reliable option for the treatment of post-CIRT VPCs in the patients with upper cervical PMSTs. In addition, evaluation of the bone turnover at the irradiated field by bone SPECT/CT would help surgeons select an effective plan of care, such as fusion level and postoperative care.

Keywords Carbon-ion radiotherapy · Occipito-cervical fusion · Vertebral pathological fracture · Upper cervical primary malignant spinal tumor

Introduction

Primary malignant spinal tumors (PMSTs) arising at the upper cervical spine is a rare and most challenging disease in the field of spine surgery [1]. It is well known that complete and en bloc resection of tumor improves the clinical outcomes in patients with PMSTs [2]. However, due to the complex surrounding structures at the upper cervical spine, a curative en bloc resection of the tumor is often impossible. Furthermore, even when it can be executed, there remains a huge risk of surgical complication with unsatisfactory prognosis [3].

Recently, novel methods of radiosurgery with a curative intent have been developed for primary spinal tumors [4]. One such method is carbon-ion radiotherapy (CIRT). CIRT is characterized by its high biologic effectiveness in comparison to proton and photon radiotherapy, with confirmed excellent local control (LC) rate in the treatment of PMSTs [5, 6]. However, we previously reported the high rate of post-CIRT vertebral pathological fractures (VPFs) [7]. VPFs in the upper cervical spine may result in severe pain and devastating neurological deficit. In most of such cases, an occipito-cervical (OC) fusion is mandatory; however, the clinical results of OC fusion after CIRT have not been shown to date. In this case series, we reported three cases with post-CIRT VPFs in the upper cervical PMSTs treated by OC fusion, particularly with a focus on the effects of CIRT on bone turnover in the irradiated field.

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Materials and methods

Patients

Three consecutive patients with PMSTs who met all of the following eligibility criteria were prospectively reviewed: histologically proven primary sarcoma; tumors judged to be medically inoperable by a multidisciplinary tumor board comprising spine surgeons, radiation oncologists, pathologists, and oncologists; no distant metastasis at the initial referral for treatment. The study period was between April 2013 and August 2017. Patients who provided informed consent were given the option to opt out of the study, and the study was approved by the institutional review board at the Kyushu University Hospital (26-112). The median follow-up period was 22 months (range 14–25 months).

Treatment

Carbon-ion radiotherapy was performed at SAGA heavy ion medical accelerator in Tosu, using the same approach as reported previously [7]. Briefly, a set of 2-mm-thick computed tomography (CT) images was obtained under respiratory gating for treatment planning. The clinical target volume (CTV) usually included the potential area of tumor spread and established as a 3- to 5-mm margin around the gross tumor volume (GTV). Then, the planning target volume was set up with an additional 3- to 5-mm margin to the CTV, but 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. To evaluate the risk factors for post-CIRT VPFs, each treated vertebral segment was scored according to the spinal instability neoplastic score (SINS) criteria [7].

Regarding the surgery, OC fusion was performed as follows: under general anesthesia and with adequate exposure of the occipital bone and cervical vertebrae. Four occipital screws were implanted in the occipital plate, and lateral mass screws and/or pedicle screws were placed as distal anchors. Suitable bended rods were installed, and iliac autogenous bone graft was performed with meticulous decortication.

Clinical follow-up

After CIRT, the patients were assessed at 1-month post-treatment and at every 3 months thereafter. X-rays, magnetic resonance imaging (MRI), CT, and ^{18}F-deoxyglucose positron emission tomography CT (FDG-PET–CT) were used to evaluate radiological follow-up. VPFs were defined as the development of de novo fractures or the deterioration of pre-existent VPFs with clinical symptoms. To evaluate the effect of CIRT on bone turnover in the irradiated field, a bone single-photon emission CT (SPECT)/CT was taken at 2–4 weeks after OC fusion.

Case presentation

Case 1

A 40-year-old man presented with left neck pain to our hospital. He was neurologically normal and had no remarkable medical history. On MRI, paravertebral and spinal canal extension of the tumor with high-grade extradural compression of the spinal cord was noted (Fig. 1a, b). In the cervical CT images, extensive bone destructions of C3 and C4 were observed (Fig. 1c). Overall, the SINS score was evaluated as 12 points. The CT image-guided biopsy was performed, and the tumor was diagnosed as chordoma. Because of the extension of the tumors, curative surgical resection was not feasible. Thus, after the decompression surgery, he was treated by CIRT (64.0 Gy(RBE)/16 Fr). After 4 months of CIRT, the patient still felt neck pain and experienced deterioration of the collapse of C3 (Fig. 1d; arrow). Thus, we performed OC fusion (O–C6: iliac cortical bone and cancellous bone at O–C2, cancellous bone at C2–C6), with no delay of postoperative wound healing and surgical site infection (SSI). His neck pain disappeared immediately after the surgery. At 6 months after surgery, the solid OC fusion was confirmed (Fig. 1e), and he was continuously disease-free at 22 months of CIRT.

Case 2

A 73-year-old woman experienced severe neck pain and was referred to our hospital. MRI revealed a neoplastic lesion on the left side of C1 (Fig. 2a). In addition, the osteolytic destruction of the left portion of the C1 was observed on CT imaging (Fig. 2b). We defined the SINS score as 10 points for this patient. An open biopsy was performed, and a diagnosis of spindle cell sarcoma with high-grade malignancy was made. There was no distant metastasis, and the CIRT (70.4 Gy(RBE)/16 Fr) was planned for curative intent. After the completion of CIRT, adriamycin was administered as an

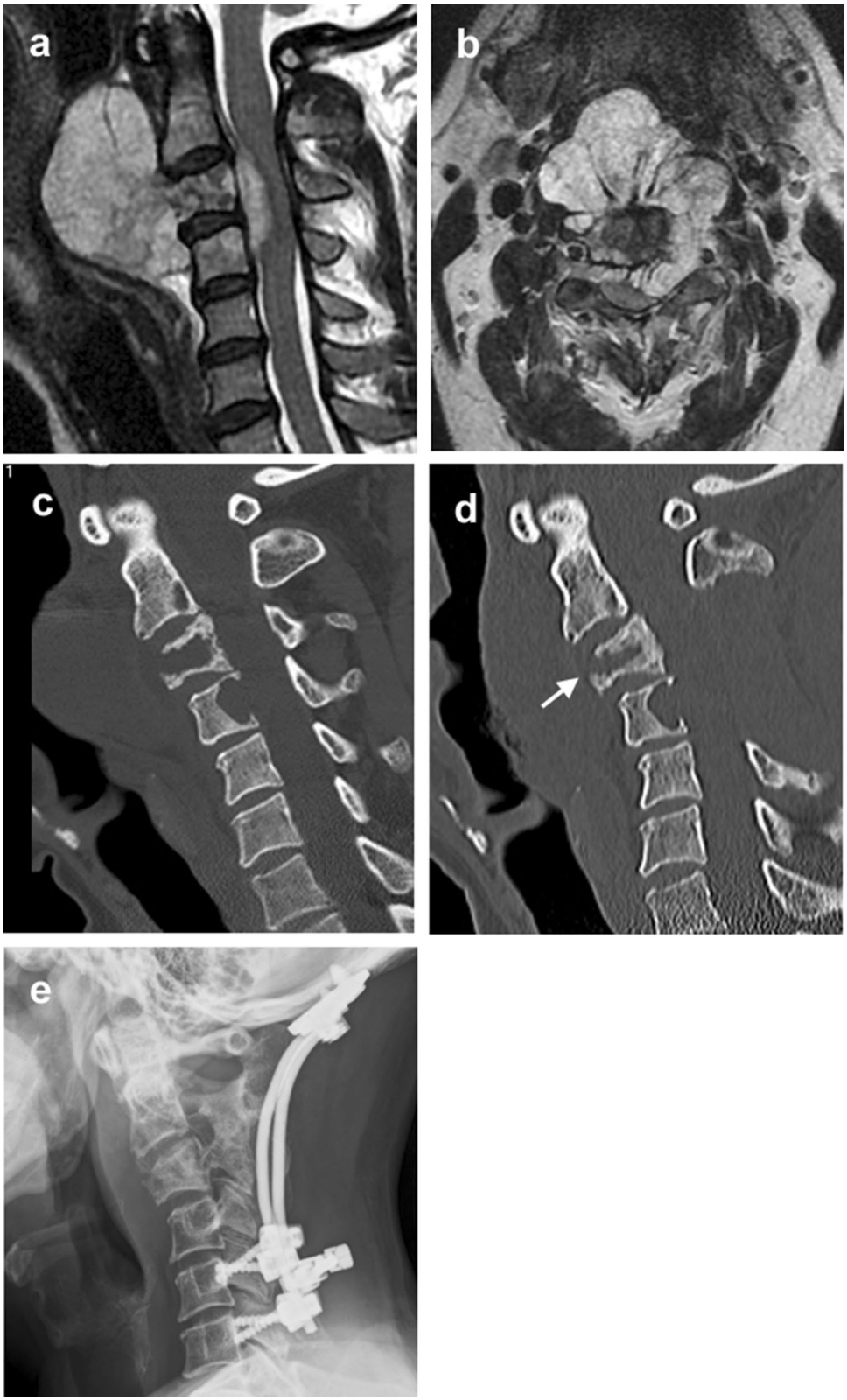

Fig. 1 A 40-year-old man with the involved C3 and C4. Sagittal (**a**) and axial (**b**) T2-weighted MRI showing a paravertebral and spinal canal extension of the tumor with high-grade extradural compression of the spinal cord; **c** sagittal CT image demonstrating extensive bone destruction of C3 and C4; **d** deterioration of the collapse of C3 (arrow) observed at 4 months after CIRT; **e** solid OC fusion (O–C6) confirmed at 6 months after surgery

adjuvant setting. Her neck pain persisted, and an aggravation of destruction and fracture of C1 was demonstrated (Fig. 2c). Thus, we performed OC fusion (O–C4: iliac cortical bone and cancellous bone at O–C2, cancellous bone at C2–C4) with the diagnosis of post-CIRT fracture. After surgery, her symptoms were relieved. She was free from postoperative

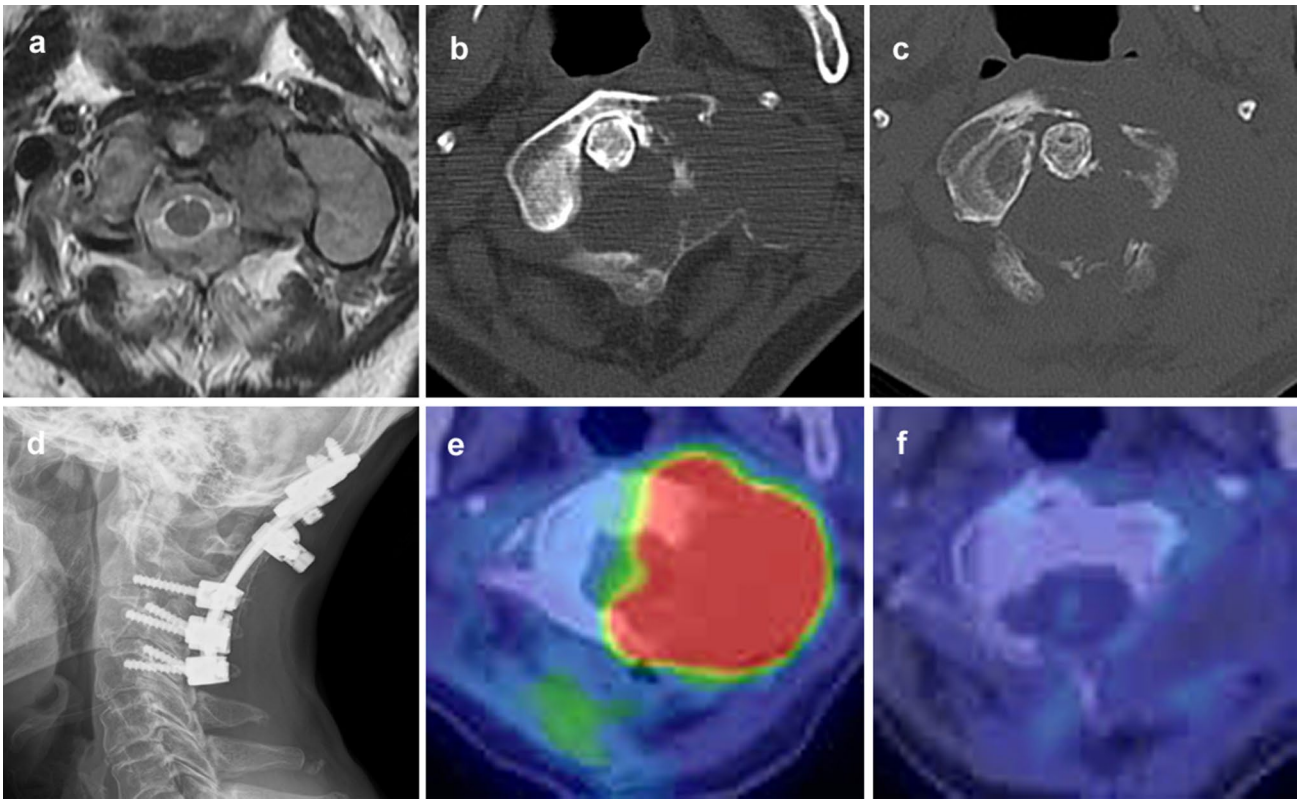

Fig. 2 A 73-year-old woman with spindle cell sarcoma of high-grade malignancy. **a** Axial T2-weighted MRI showing a neoplastic lesion on the left side of C1; **b** osteolytic destruction of the left part of the C1 observed on CT imaging; **c** after completion of CIRT, an aggravation of destruction and fracture of C1 seen on CT imaging; **d** solid OC fusion observed 6 months after surgery (**e**, **f**). Pre- (**e**) and post-operative (**f**) FDG-PET–CT scan, indicating tumor shrinkage along with the reduction in metabolic tumor activity (SUV_{max} pre = 24.8, post = 1.94)

wound complication and SSI. The solid OC fusion was observed 6 months after surgery (Fig. 2d). Pre- and post-operative FDG-PET–CT scan confirmed tumor shrinkage along with the reduction of the metabolic tumor activity (SUV_{max} pre = 24.8, post = 1.94) (Fig. 2e, f, respectively). She was continuously disease-free at 14 months of CIRT.

Case 3

A 61-year-old man was referred to our hospital with neck pain and numbness in the back. He had a history of cervical spinal tuberculosis. In physical examination, no particular neurological disorders were detected. The cervical radiograph revealed spontaneous spinal fusion at C2–C5 with kyphotic deformity and lytic destruction of the C2 and C3 (Fig. 3a). On the cervical MRI, the tumor extension from C2 to C4 was noted (Fig. 3b, c). Overall, the SINS score of this case was specified as 11 points. The tumor was diagnosed as chordoma by incisional biopsy. The patient was treated by CIRT (64.0 Gy(RBE)/16 Fr). After 1 month of CIRT, he suffered from severe neck pain and a dens fracture, as confirmed on CT (Fig. 3d; arrow). He was treated by OC fusion (OC–T1: iliac cortical bone and cancellous bone at O–C2, cancellous bone at C5–T1) (Fig. 3e). Postoperatively, his symptoms were resolved. At 4 months after surgery, he again reported strong neck pain without any history of trauma, and the CT image showed re-fracture and displacement of dens with the loosening of occipital screws (Fig. 3f). A posterior revision surgery was performed, and his neck pain subsided. The solid OC fusion was achieved at 10 months after revision surgery. During the primary and revision surgeries, there were no neurological deficits, respiratory issues, wound problems, and SSI. He was continuously disease-free at 25 months of CIRT.

Effects of CIRT on bone turnover

Bone SPECT/CT was obtained for each case to evaluate the effect of CIRT on bone turnover at the irradiated field and grafted bone. In Case 1, the active bone formation was confirmed in the autograft and surrounding bone (Fig. 4d; arrow). Remarkably, the collapsed vertebra (C3) revealed a weak but positive tracer uptake (Fig. 4d; arrowhead). In Case 2, bone graft was placed on the peripheral region of the

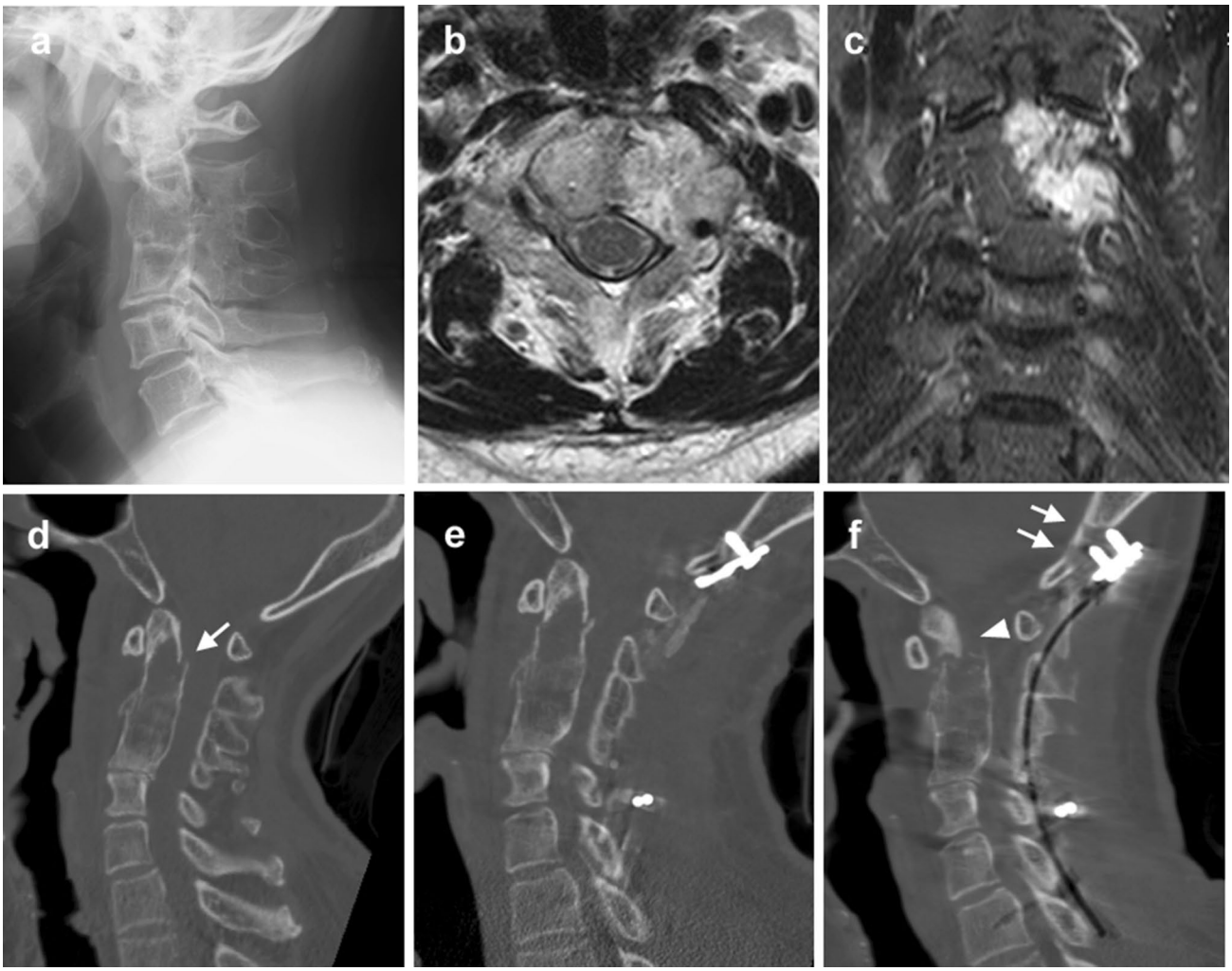

Fig. 3 A 61-year-old man with chordoma. **a** Plain radiographs showing spontaneous spinal fusion at C2–C5 with kyphotic deformity along the osteolytic destruction of the C2 and C3; on axial (**b**) and coronal (**c**) T2-weighted MRI, the tumor extension from C2 to C4 was observed; **d** 1 month after CIRT, a dens fracture was confirmed by CT imaging (arrow). **e** Postoperative (OC–T1 fusion) CT image (**f**) 4 months after surgery, the fracture and displacement of dens (arrowhead) with the loosening of occipital screws (arrows)

irradiated field (Fig. 4b), and the bone turnover was active both in the host and graft bone (Fig. 4e). Meanwhile, the bone metabolic activity in the dens fracture of Case 3 was abrogated (Fig. 4f; arrow), suggesting occurrence of osteoradionecrosis after CIRT. In contrast, slight but certain tracer uptake was observed in the autograft and host bone.

Discussion

For patients with PMSTs, complete resection of the tumors may lead to curative and favorable clinical outcomes [2]. However, en bloc resection of the upper cervical spine may result in severe complications [8], and Wei et al. reported five local recurrences out of ten patients with PMSTs at the upper cervical spine treated by spondylectomy, suggesting that the rate of LC after radical surgery was not satisfactory for this type of tumors [3]. Thus, the curative radiotherapy for patients with upper cervical PMSTs is strongly desired. In this sense, CIRT is one of the promising treatment options for the upper cervical PMSTs. For example, the LC and overall survival of CIRT for the treatment of upper cervical/skull base chondrosarcoma is up to 96.1% and 88% at 5 years, respectively [9], suggesting the effectivity of CIRT for patients with upper cervical PMSTs.

The evaluation of toxicity after new treatment modality is critical. One of the important adverse events with radiosurgery, such as CIRT, is the post-radiation VPFs [7]. We previously evaluated the 30 cases of PMST treated with CIRT. In that study, we observed that the rate of post-CIRT VPFs that might be attributed to osteonecrosis was as high as 19%, with the overall SINS score of ≥ 8 being associated with

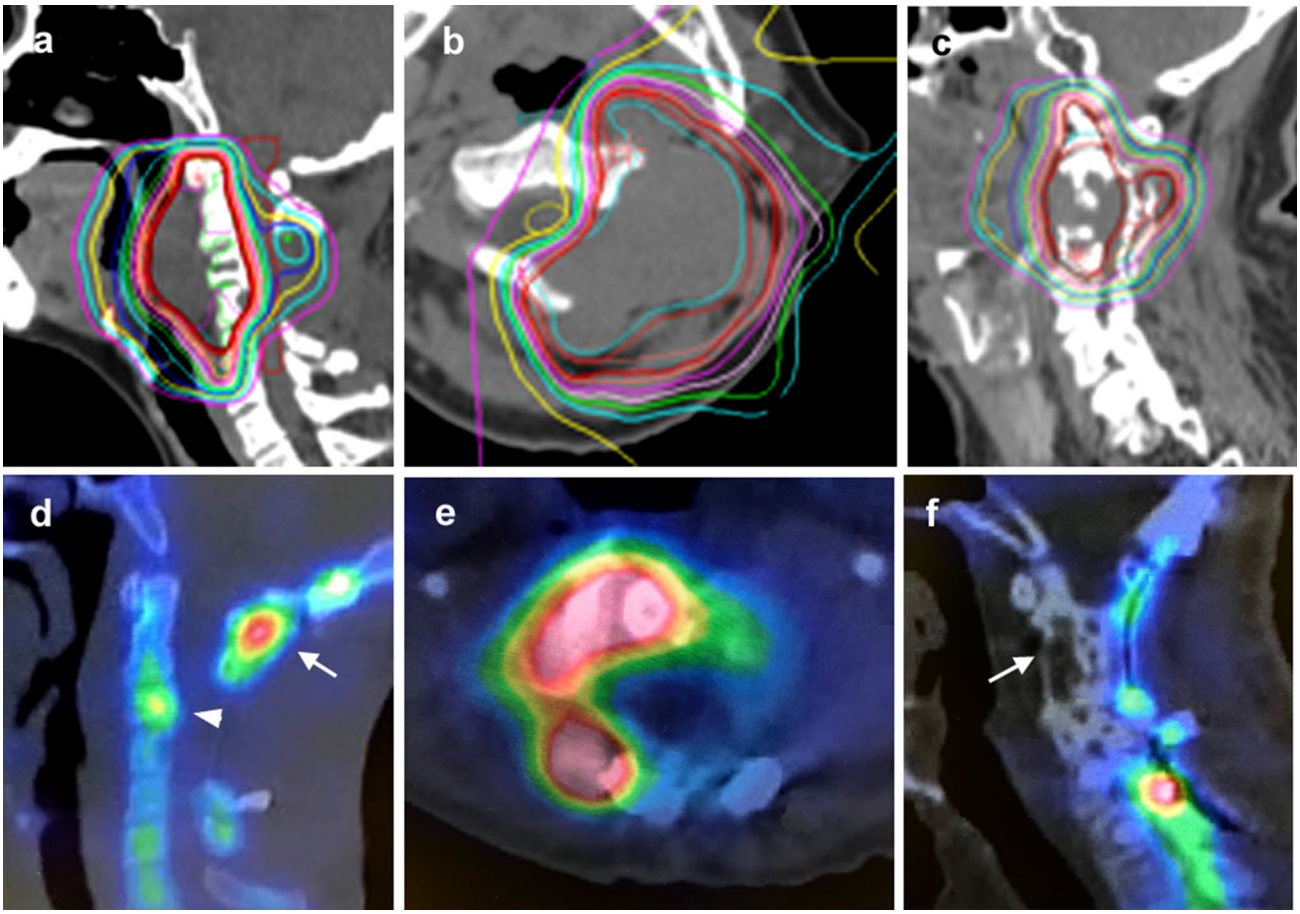

Fig. 4 The dose distribution (**a**–**c**) and bone SPECT/CT (**d**–**f**) for each case to evaluate the effect of CIRT on bone turnover. The red line indicates 90% isodose of the prescribed dose. **a**, **d** In Case 1, the active bone formation was confirmed in the autograft and surrounding bone (**d** arrow). Remarkably, the collapsed vertebra (C3) showed weak, but positive tracer uptake (**d** arrowheads). In Case 2, bone graft was placed on the peripheral region of irradiated field (**b**), and the active bone turnover was confirmed both in the host and graft bones (**e**). **c**, **f** Bone metabolic activity in the dens fracture of Case 3 was not seen (**f** arrow)

the risk of post-CIRT VPFs [7]. Consistent with this finding, the SINS score of presented cases were 12, 10, and 11, respectively. Since osteolytic PMSTs at the upper cervical region with mechanical pain were almost always assigned with an SINS score of ≥ 8 points (location = 3; pain = 3; bone lesion = 2), the spinal stabilization including OC fusion should be considered after completion of CIRT for the upper cervical PMSTs.

Radiotherapy may induce osteoradionecrosis and delay of bone regeneration, ultimately leading to the failure of bone fusion [10]. Thus, the development of unsuccessful arthrodesis would be a major concern as an important adverse event after CIRT. Remarkably, in all presented cases, the bone SPECT/CT revealed a positive tracer uptake in the autograft and peripheral host bone. As a result, we observed solid OC fusion in all patients at 6, 6, and 10 months, respectively. A recent systematic review of OC fusion showed that, in most cases (90%), fusion occurred at approximately 4 months after surgery [11]. In addition, as shown in Case 3, CIRT may cause osteoradionecrosis, particularly in the middle of the irradiated field, which would result in the failure of bone fusion. Therefore, it is reasonable to consider that OC fusion in cases with CIRT would take slightly longer time as compared to that in patients without radiotherapy, and the strict observance of cervical orthosis is recommended until the confirmation of solid fusion by radiographs or CT scan.

Meanwhile, in the setting of CIRT, carbon-ion beams emit a low dose of radiation at the entrance point, achieving their maximum linear energy transfer (LET) at the end of their range (Bragg peak), beyond which the LET drops distinctly [6]. Given these advantages, a part of vertebral body that was not affected by tumor cells might still maintain the osteoblastic activity as shown in Fig. 4d, e. Therefore, in such cases, the osteogenesis of anterior part of spinal column would be anticipated even after CIRT, finally resulted in the anterior spinal fusion.

In this case series, the anterior columns of the spine were destroyed by the tumor mass, and CIRT is believed to have

caused shrinkage of tumor mass and bony necrosis in the remaining vertebral body. Thus, the loss of the anterior strut of the spine was inevitable [12]. This biomechanical flaw can cause implant loosening, as in Case 3. Thus, we now routinely apply the two techniques to strengthen the implant fixation [1]; augment the occipital plate by the ultra-high molecular weight polyethylene (PE) cables. Practically, we perforate additional holes in occipital bone, put two PE cables through the holes, and secure an occipital plate by tightening the PE cables [2] place the anchors (pedicle screws or lateral mass screws) at least three vertebrae below the tumor.

Skin toxicity is another important adverse event of CIRT [13]. Regarding soft tissue-related complications, we observed no delay in wound healing, wound dehiscence and the subsequent SSI. Together, we considered that the OC fusion after post-CIRT VPFs was feasible and durable; however, the delay in bone fusion requires consideration.

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Compliance with ethical standards

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

Ethical approval The study was approved by the institutional review board at the Kyushu University Hospital (26-112).

Informed consent Informed consent was obtained from all individual participants included in the study.

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