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Case report

Radiation-induced osteosarcoma in the pubic bone after proton radiotherapy for prostate cancer: a case report

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Abstract

Objective: Radiation-induced sarcoma (RIS), which develops after radiotherapy, occurs as a secondary sarcoma in the irradiated area after a long latency period following radiation exposure.
Patient: A 59-year-old man underwent hormone therapy for prostate cancer, followed by proton therapy (74 GyE) four years ago. Positron emission tomography/computed tomography performed 2.5 years later revealed ^{18}F-FDG accumulation in the left pubis. Three years after proton therapy, the patient developed gradually worsening left inguinal pain and visited our department. Imaging revealed bone destruction with a mixture of osteolysis and osteogenesis in the left pubis and the presence of an extraosseous tumor. Following biopsy, the patient was diagnosed with osteosarcoma.
Results: A systemic investigation revealed lung metastasis, and chemotherapy was initiated. The lung metastases shrank, and carbon ion radiotherapy (CIRT, 70.4 GyE) was performed on the left pubic lesion after colostomy. Six months after carbon ion radiotherapy, recurrence was observed in the irradiated field, and CIRT was performed again. However, the patient died 22 months after the initial diagnosis because of cancerous pleurisy and pericarditis.
Conclusions: Although RIS is rare, it should be actively identified using biopsy to confirm the diagnosis, keeping in mind that it is an important late complication of radiotherapy.

Key words: radiation-induced, osteosarcoma, prostate cancer, carbon ion radiotherapy

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Introduction

Radiation-induced sarcoma is a late complication that occurs as a secondary sarcoma in the radiation field after a long latency period after radiotherapy. Nevertheless, radiotherapy for localized prostate cancer is one of the main curative treatment methods. Proton therapy for prostate cancer has also shown good clinical results[1]. Using second malignancy risk models following radiation therapy for prostate cancer, Fontenot *et al.*[2] concluded that proton therapy could lead to a 26–39% risk reduction for secondary cancer relative to intensity-modulated X-ray therapy. Chung *et al.*[3] performed a retrospective cohort study of 558 patients treated with proton therapy and matched them with patients treated with photon radiation therapy. In each cohort, >30% of patients had prostate cancer. Overall, at a median follow-up of 6.7 years, the risk of secondary malignancy was lower among patients treated with proton therapy than among those treated with photon radiation therapy (5.2% vs. 7.5%; hazard ratio, 0.52; P=0.009). These retrospective studies appear to show that proton therapy for prostate cancer may reduce the risk of secondary malignancies relative to that following photon radiation treatment. We herein report a case of radiation-induced osteosarcoma that occurred in the pubis after proton therapy for prostate cancer.

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Case Presentation

Four years before his first visit to our department, a 59-year-old man with no past medical history received hormone therapy followed by proton therapy (74 GyE/37 fractions) and was followed up for prostate cancer (cT2aN0M0, Gleason score 3+4, initial prostate-specific antigen 9.6 ng/mL) (Figure 1). Two and half years after proton therapy, a positron emission tomography/computed tomography (PET/CT) scan obtained during workplace health screening showed abnormal ^{18}F-FDG accumulation in the left pubis. However, the patient was under observational monitoring because of the absence of symptoms. Three years after proton therapy, left inguinal pain appeared and gradually worsened; therefore, he consulted a local physician. A left tumor in the pubic bone was identified on plain radiography, and he was referred to our department. Blood tests revealed the following: leukocyte count, 6,700 cells/μL; C-reactive protein 0.33 mg/dL, alkaline phosphatase 1,184 U/L; and prostate-specific antigen, 0.67 ng/mL. A plain radiograph of the pelvis taken at the first visit showed cortical disruption in the superior and inferior rami of the left pubis and a mixture of bone translucency and sclerosis (Figure 2). At the first visit, plain CT revealed a mixture of osteolytic and sclerotic images in the superior and inferior rami of the left

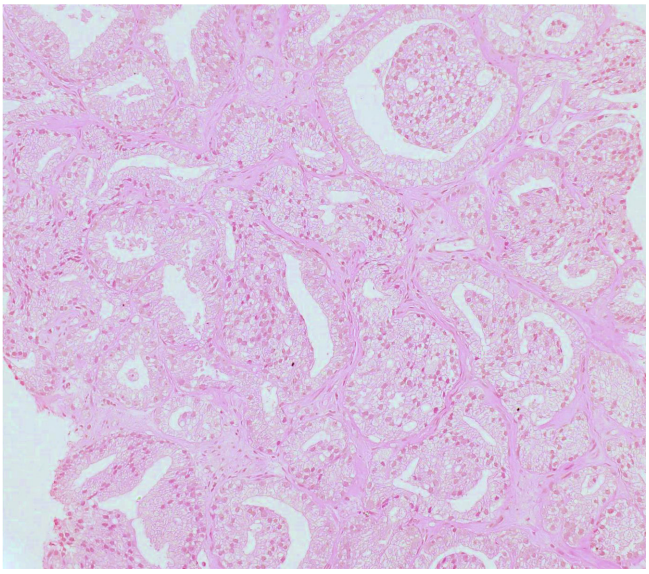

Figure 1 Histopathological findings of needle biopsy specimen of the prostate (hematoxylin and eosin stain).
×200 magnification. Adenocarcinoma of the prostate, Gleason grade 3+4 = score of 7.

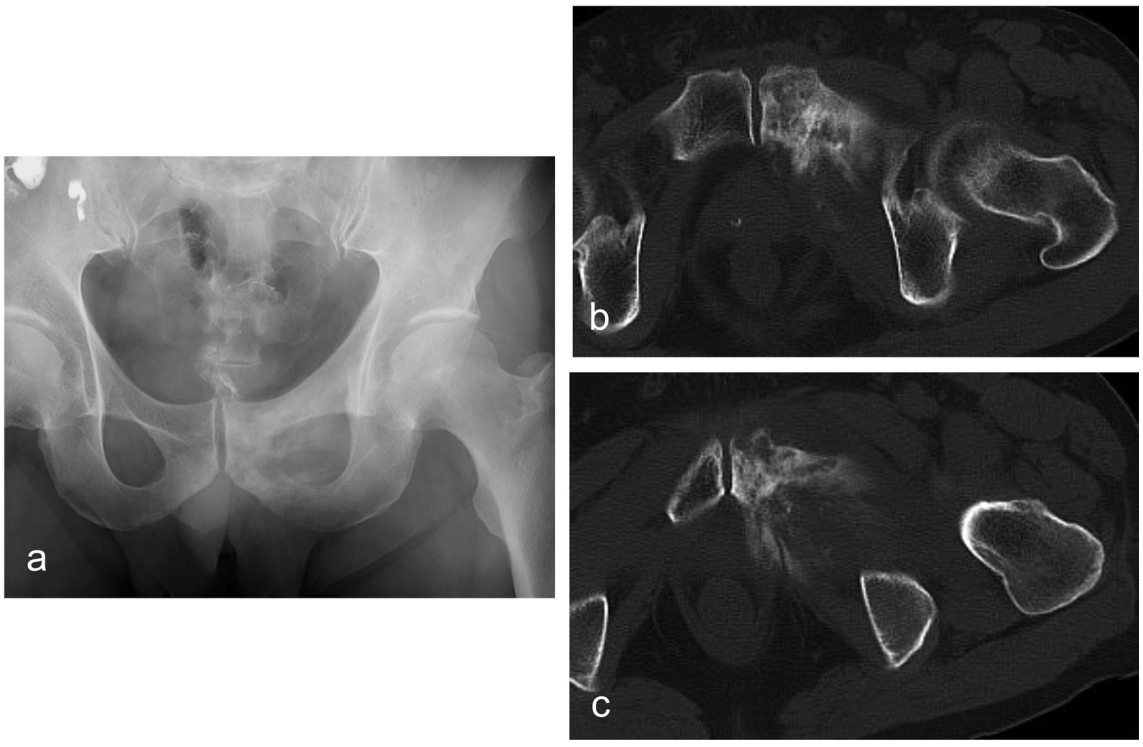

Figure 2 Plain X-ray and plain CT of the pelvis at the first visit.
(a) Radiograph showing cortical disruption in the superior and inferior rami of the left pubis. (b, c) Plain CT showing a mixture of osteolytic and sclerotic changes in the superior and inferior rami of the left pubis and ossification in the extraosseous soft tissue.

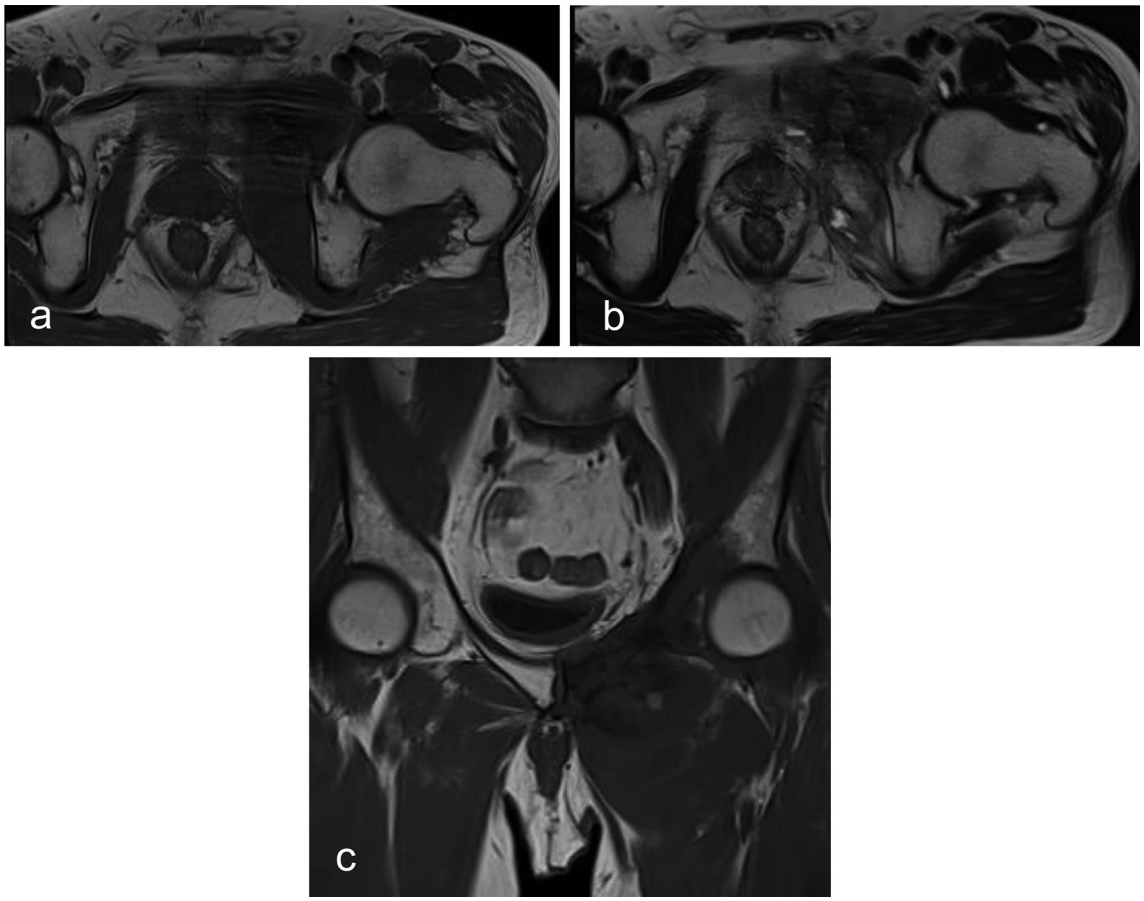

Figure 3 MRI of the pelvis at first visit.
MRI showing an isointense signal on an axial T1-weighted image (a) and inhomogeneous hyperintense signal on an axial T2-weighted image, with extension in the obturator and pectineus muscles (b). A coronal plane image indicates extension to the acetabulum (c).

pubis and ossification in the extraosseous soft tissue (Figure 2). Magnetic resonance imaging performed at the first visit revealed an isointense T1-weighted image and an irregular hyperintense T2-weighted image of the pubic bone, with extension in the obturator and pectineus muscles. Moreover, the coronal plane image suggested continuity of the acetabulum (Figure 3). Based on these findings, we clinically considered bone metastasis of prostate cancer and osteosarcoma and performed an incision biopsy. The pathological findings of the biopsy tissue showed proliferation of atypical spindle-shaped cells forming an osteoid, and a diagnosis of osteosarcoma was made (Figure 4). The pubis was present within the area treated with proton therapy for prostate cancer, and a PET/CT scan taken 2.5 years after proton therapy showed ^{18}F-FDG accumulation in the inferior ramus of the left pubis (Figure 5). The patient was diagnosed with radiation-induced osteosarcoma because the tumor was suggested to have developed in the proton irradiation field 2.5 years after proton therapy and was histopathologically identified as osteosarcoma.

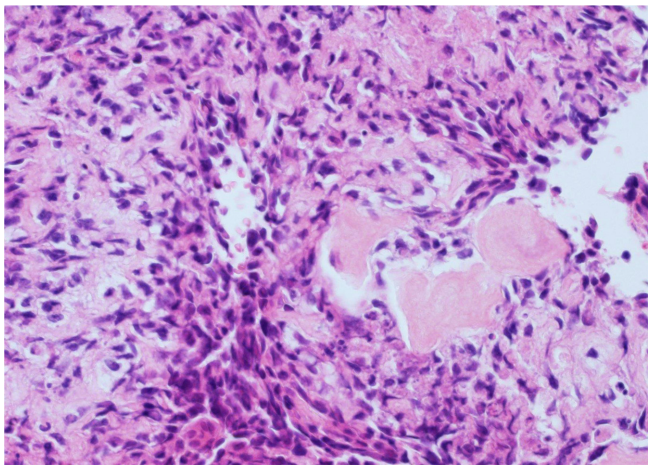

Figure 4 Histopathological findings of open biopsy specimen (hematoxylin and eosin stain).
×400 magnification. Pathological findings of the open biopsy tissue demonstrating proliferation of atypical spindle cells forming an osteoid, leading to a diagnosis of osteosarcoma. Immunohistochemical examination showed that the tissue was positive for vimentin and negative for AE1/AE3.

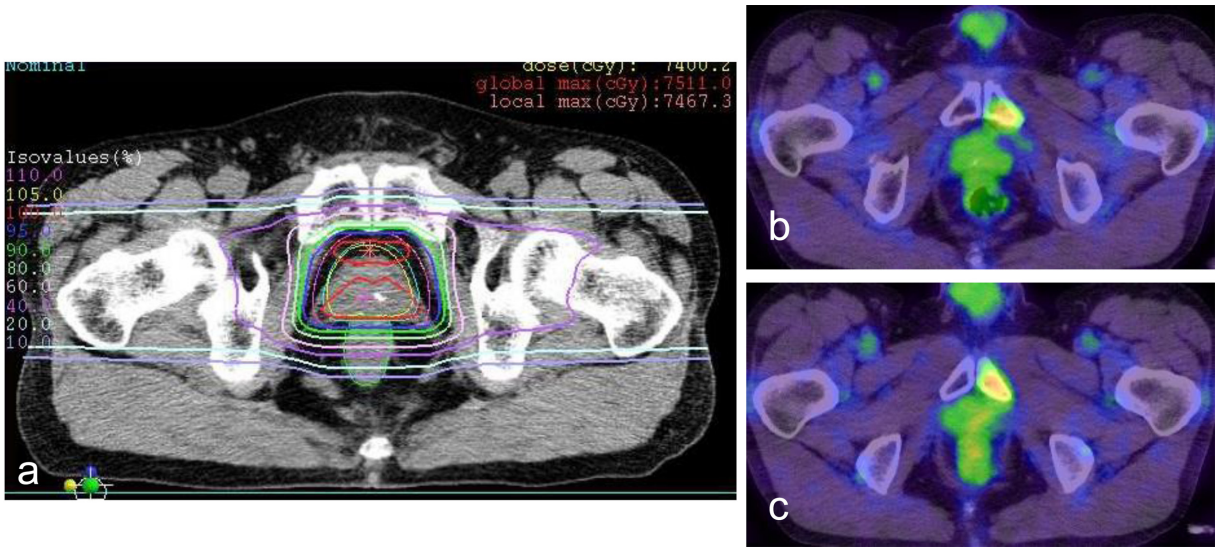

Figure 5 (a) Dose distribution of proton therapy (PT) for prostate cancer (isodose values: red 100%, blue 95%, green 90%, pink 60%, purple 40%, light blue 10%); the pubis is within the area administered PT. (b-c) A PET/CT scan taken 2.5 years after PT shows accumulation of ^{18}F-FDG in the inferior ramus of the left pubis.

Because nodular lung metastasis was detected at the first visit, chemotherapy with ifosfamide (IFO) and doxorubicin (DXR) was administered. Because a reduction in lung metastasis was observed, carbon ion radiotherapy (70.4 GyE) was administered after colostomy. The boundary of the primary lesion became clear, and osteosclerotic changes of the extraosseous tumor were observed, which was deemed to reflect a partial response (Figure 6). Cryotherapy was administered for the metastatic lung lesion, followed by chemotherapy with IFO, carboplatin, and etoposide. The patient was followed up on an outpatient basis. However, 6 months after carbon ion radiotherapy, recurrence occurred in the irradiation field posterior to the acetabulum and proximal to the iliac bone. Therefore, we performed re-irradiation with carbon-ion radiotherapy and chemotherapy (IFO/DXR, gemcitabine, and docetaxel). However, 4 months after the completion of carbon-ion radiotherapy, invasion of the primary lesion into the surrounding organs was observed. Subsequently, cancerous pleurisy and cancerous pericarditis occurred, and the patient died 1 year and 10 months after the initial diagnosis. Consent for publication was obtained from the patient's family.

Discussion

The diagnostic criteria for radiation-induced sarcoma (RIS) are that it has a latency period of at least 3 years before the onset of the sarcoma, that it occurred in the previous radiation field, and that the tissues of the primary cancer that required radiotherapy are different from sarcoma tissues[4, 5]. In our case, the latency period was slightly short (2.5 years). There has been controversy in the literature regarding latency periods. In general, many long-term studies have reported a latency period of 10 years or more, but recent reports suggest that a diagnosis may be made if the latency period is 6 months[6].

Zhang *et al.*[7] investigated 419 patients with radiation-induced sarcoma and demonstrated that sex (female), type of first malignancy (breast cancer), age at diagnosis of the first malignancy (>47 years old), and chemotherapy for the first malignancy were all associated with a shorter interval to RIS in the univariable analysis. However, they identified that in the multivariable analysis, older age and chemotherapy for the first malignancy were independently associated with a shorter interval to RIS. They hypothesized that older age might be attributable to age-related underlying impairments of DNA repair and immune dysregulation, and that chemotherapy might enhance the effect of bone and soft tissue damage due to radiation or interfere with DNA repair. In the present case, the patient was 59 years old, which is older than 47 years; however, the patient had a history of anti-androgen agent and LH-RH agonist treatment, but no history of anticancer drug treatment for his first malignancy.

The development of RIS is influenced by radiation dose, radiation field, and patient factors[8]. It is generally accepted that radiation-induced carcinomas arise in tissues exposed to lower doses, whereas radiation-induced sarcomas arise in heavily radiated tissues within or at the edge of the radiation field[9]. In proton therapy, high-dose areas are likely to occur near the radiation field because of the smaller number of beam ports. In the present case, the tumor developed in the pubic bone exposed to 40% (29 Gy) of the total radiation

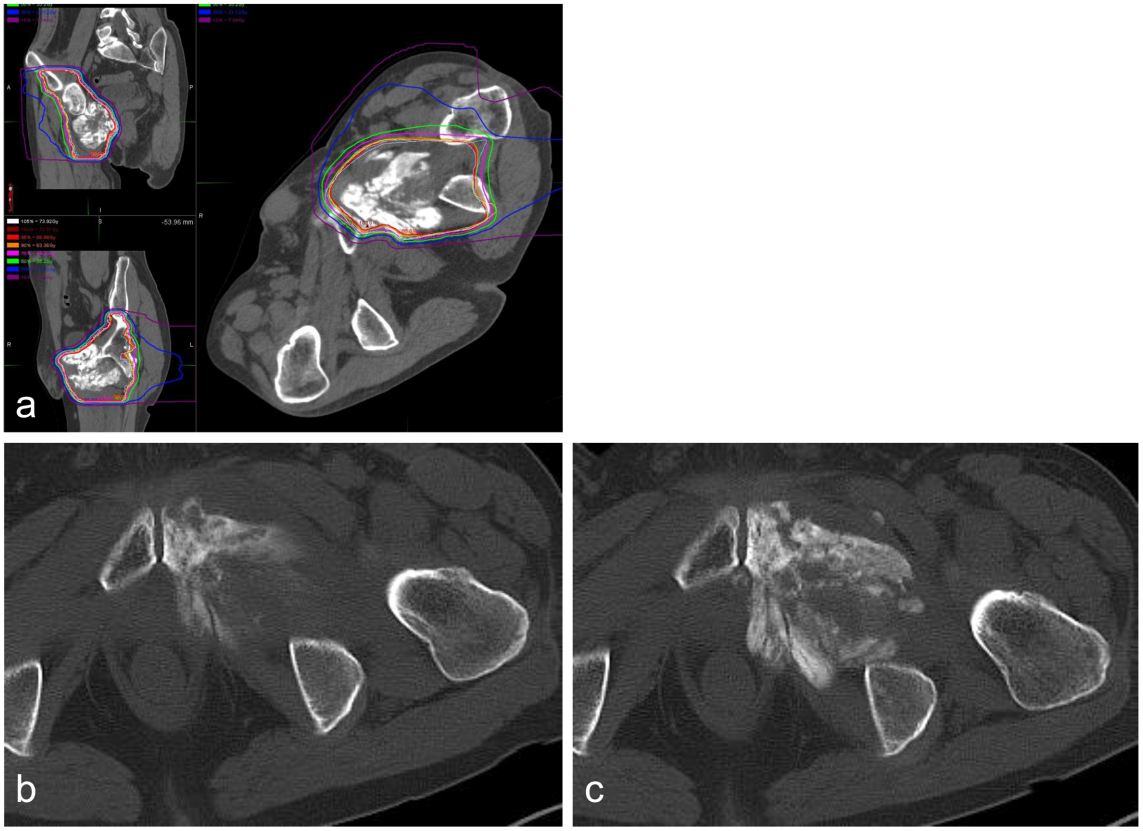

Figure 6 (a) Dose distribution of carbon ion therapy (CIRT) for radiation-induced osteosarcoma (red line indicates 90% isodose of the prescribed dose). (b) Computed tomography (CT) image obtained before CIRT. (c) CT image obtained after CIRT, showing that the boundary of the primary lesion has become clear and osteosclerotic changes of the extraosseous tumor.

dose. John *et al.*[10] reported that the mean latency period was significantly shorter in radiation-induced breast angiosarcoma (6 years) than in radiation-induced soft tissue sarcoma (10 years), suggesting that chronic lymphedema, a risk factor associated with the development of angiosarcoma, may shorten the latency period. The reason for the short latency period of 2.5 years in our case is unknown, but it may be related to irradiation dose and condition of the bone and soft tissue in the irradiation area, such as edematous status.

The frequency of occurrence of RIS after radiotherapy is extremely rare, occurring in 0.03–0.9% of cases within 15 years after radiation therapy[11, 12]. Breast and cervical cancers are the most common primary cancers in RIS[11, 13, 14], while prostate cancer is rare. A large cohort study of proton therapy for prostate cancer revealed late complications of the gastrointestinal tract and genitourinary system at 62–70 months' follow-up, with no occurrence of RIS[1, 15–17].

To the best of our knowledge, there are no reports of radiation-induced osteosarcoma after proton therapy for prostate cancer, and this is the first case study to report this finding.

Most reports of osteosarcoma after radiation therapy for prostate cancer were case reports, and nine cases have been reported (Table 1)[8, 14, 18–22]. The average patient age was 71 years, and the average latency period was 10.6 years; distant metastasis was observed in 33% of cases. Among the patients in whom the outcome was described, 42.9% had died at an average of 10.7 months, and the prognosis was extremely poor. In our case, the effects of chemotherapy and carbon ion radiotherapy were temporarily determined; hence, the survival time was slightly longer.

Regarding the diagnosis of radiation-induced osteosarcoma, osteosclerosis and an ossified/calcified extraosseous tumor were observed in the pubis, and it was clinically difficult to distinguish between bone metastasis from prostate cancer and osteosarcoma. If a malignant tumor is suspected in a previously irradiated area, then the possibility of radiation-induced sarcoma should be considered, and biopsy should be performed proactively to confirm its presence. However, we think that it is not necessary to actively perform a biopsy when a patient with prostate cancer has multiple bone metastases because there are usually multiple bone metastases from prostate cancer and they rarely form extraosseous tumors.

Table 1 Reported cases of radiation-induced osteosarcoma after radiation therapy for prostate cancer

Author (year)	Age	Radiotherapy, dose delivered (Gy)	Latency period (years)	Location	Metastasis	Follow-up periods (months)	Outcome
O'Donnell TF (1993)[21]	73	69	10	External iliac artery	No	2	AWD
McKenzie M (1999)[22]	72	55	7	Pubis and ischium	Lung / Liver	12	DOD
	75	55	16	Acetabulum and ischium	Lung / Liver	12	DOD
Nukui F (2004)[19]	74	65.2	10	Pubis and sacrum	No	8	AWD
Papalas JA (2011)[18]	62	NA	10	Pubic symphysis	Lung / Liver	2	AWD
Gumber D (2013)[20]	78	70	11	Ilium	No	8	DOD
Joo MW (2018)[14]	75	NA	NA	Pelvis	No	NA	NA
	60	NA	NA	Pelvis	No	NA	NA
Omata S (2021)[8]	70	70	10	Pubis	No	12	CDF
Nakashima H (2021)	59	Proton, 74GyE	2.5	Pubis	Lung	22	DOD

Gy: Gray; GyE: Gray Equivalent; NA: not available; AWD: alive with disease; DOD: dead of disease; CDF: continuous disease free.

Regarding the treatment of radiation-induced osteosarcoma, prognosis can be expected if tumor resection with a wide margin is possible[13, 14]. However, the tumor margin is often unclear because of the history of irradiation, and tumors often develop in the trunk, such as in the pelvic region. Therefore, it is often anatomically complicated and difficult to perform wide resection[16]. There is no evidence of susceptibility or efficacy to chemotherapy, and chemotherapy is palliative. It is also not thought to influence prognosis[23]. Osteosarcoma is radiation resistant. Moreover, because osteosarcoma occurs at a site that has been previously irradiated, many complications occur due to re-irradiation, and radiotherapy is therefore difficult[11]. In our case, lung metastasis was observed at the first visit, and resection with wide margins was expected to be difficult due to adhesion after proton therapy and inadequate wound healing after irradiation was feared. Since there was a solitary lung metastasis and it was reduced in size by chemotherapy, we determined that the metastasis could be resected or treated with cryotherapy. As such, carbon ion radiotherapy was selected to treat the primary lesion. There are a few reports on the use of carbon ion radiotherapy for osteosarcoma of the trunk. Ciernik *et al.*[24] reported the results of proton therapy for unresectable or inadequately resected trunk osteosarcoma in 55 patients. Among them, 12 had local recurrence, and four patients experienced early recurrence at 2 months after proton beam irradiation. In addition, 10 of the 12 cases relapsed in the irradiation field, and two cases recurred outside the irradiation field. Matsunobu *et al.*[25] reported that 78 patients with unresectable osteosarcoma of the trunk were treated with carbon ion radiotherapy, and 21 patients relapsed within a median of 15 months (4–96 months) after diagnosis. Among these cases, three were radiation-induced osteosarcoma (one of which occurred 7 years after radiation therapy for prostate cancer), but the details of prognosis are not clear. Yang *et al.*[26] reported the results of carbon ion radiotherapy for locally recurrent sarcoma of the head and neck and RIS in 19 cases. Seven of the 19 cases were RIS, two of which were osteosarcomas, and the tumors were found to be growing at 5.6 and 8.5 months after carbon ion radiotherapy. In our case, the tumor recurred in the irradiation field 6 months after carbon ion radiotherapy. Although re-irradiation was performed, the tumor was found to be growing 4 months after re-irradiation. In cases of RIS, even carbon ion radiotherapy may have only short-term effects.

In conclusion, although radiation-induced osteosarcoma is rare, it should be actively identified using biopsy to confirm the diagnosis, keeping in mind that it is an important late complication of radiotherapy.

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

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