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A retrospective study of post-radiation sarcoma from three institutions in Japan with a review of the literature

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ABSTRACT

This study investigated incidence, clinical characteristics, and outcomes of post-radiation sarcoma, a rare but severe complication following radiotherapy. Post-radiation sarcoma is a malignant tumor arising within irradiated areas after a latency period, histologically different from the primary tumor. We retrospectively analyzed cases from January 2000 to January 2025 at three institutions in Japan, employing widely accepted diagnostic criteria. Patient characteristics, treatment details, oncologic outcomes, and prognostic factors were evaluated. Our study included 14 patients with various primary cancers, including three breast cancers, three prostate cancers, and one each of other cancer types. Among the cases, six had osteosarcoma, six had undifferentiated pleomorphic sarcoma, one had chondrosarcoma, and one had malignant peripheral nerve sheath tumor, predominantly occurring in the trunk. The median latency period from last irradiation to diagnosis was 9.9 years (range, 3.0–19.5 years). The median total radiation dose administered before post-radiation sarcoma diagnosis was 52.5 Gy (range, 12–74 Gy). The median overall survival and probability of 5-year overall survival were 2.6 years and 46.8%, respectively. The only factor that tended to correlate with prognosis was whether complete resection was achieved (P = 0.09). A literature review confirmed an increasing number of post-radiation sarcoma cases following radiotherapy for prostate cancer in recent years. The incidence of post-radiation sarcoma is expected to rise alongside the number of patients undergoing radiotherapy. Early detection and appropriate treatment are essential to improve prognosis, highlighting the need for careful long-term monitoring of patients receiving radiotherapy for post-radiation sarcoma.

Keywords: post-radiation sarcoma, prostate cancer, radiotherapy, secondary malignancy

Abbreviation:
PRS: post-radiation sarcoma

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INTRODUCTION

Post-radiation sarcoma (PRS) is a rare but serious malignant tumor that develops within irradiated tissues several years after radiotherapy and is associated with a poor prognosis. The reported incidence of PRS ranges from 0.03% to 0.8%,[1] with the risk increasing over time. Since Beck and Marsch first described PRS,[2] several diagnostic criteria of PRS have been proposed.[3-5] The most widely accepted criteria require that the sarcoma arises within a previously irradiated area, develops after a latency period of at least several years, and is histologically distinct from the primary tumor.[3,4] Advancements in cancer treatment, including radiotherapy, have significantly improved patient survival, leading to an increased number of PRS cases.[6,7] Additionally, the indications for radiotherapy have expanded in recent years, particularly for prostate cancer. As prostate cancer incidence rises globally, radiotherapy has become an essential treatment modality, further contributing to the growing number of patients at risk of developing PRS.[8,9] Despite this trend, the incidence of PRS following radiotherapy for prostate cancer remains inadequately studied. In this study, we retrospectively analyzed PRS cases treated at three institutions in Japan to evaluate their clinical features, treatment outcomes, and prognostic factors. Furthermore, we conducted a systematic review of the literature to assess the frequency and trends of prostate cancer as a primary tumor of PRS. The aim of this study is to enhance the understanding of PRS and facilitate its early detection and appropriate treatment.

MATERIALS AND METHODS

Study population

In this retrospective observational study, we analyzed patients with PRS treated at Niigata Medical and Dental Hospital (Niigata, Japan), Niigata Cancer Center Hospital (Niigata, Japan), and Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital (Minami-Uonuma, Japan) from January 2000 to January 2025. Patients who met all the following criteria were diagnosed as PRS, based on a previous report[8]:

1. At least three years had passed between the last irradiation and the onset of sarcoma.
2. The sarcoma developed within the irradiated lesion.
3. The sarcoma was histologically distinct from the primary tumor.

This study was approved by Ethical Committee of Niigata University Medical and Dental Hospital in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants, and a total of 14 patients were enrolled. The primary endpoint of this study was overall survival. Secondary endpoints included patient characteristics, treatment approaches, and potential prognostic factors.

Survey of eligible patients

We analyzed the 14 enrolled patients by collecting data on individual characteristics, primary tumors, and PRS-related factors. Individual data included sex and age at PRS diagnosis. For primary tumors, we recorded histology, history of chemotherapy, and total irradiation dose. Regarding PRS, we collected data on histology, latency period from the last irradiation, tumor location, size (major axis), presence of initial metastasis, treatment modalities (surgery, chemotherapy, radiotherapy), follow-up duration (from diagnosis to last observation), subsequent metastasis, and clinical outcomes.

The age of patients with PRS was determined based on the date of PRS diagnosis. The latency period was defined as the interval between the last irradiation and PRS diagnosis. The

follow-up period was defined as the time from PRS diagnosis to either the patient's death or the last recorded observation.

To identify factors influencing overall survival in PRS patients, we conducted a univariate analysis by using the log-rank test. The 14 patients were divided into two groups of approximately equal numbers based on various factors, including age, tumor size, initial irradiation dose in total, latency period, and surgical outcomes, specifically whether R0 resection was achieved.

A systematic review of the literature on PRS

Search strategy and criteria. A systematic review of the literature was conducted on February 15, 2025, and March 1, 2025, using PubMed and Google Scholar. To identify case series including five or more PRS cases, we performed a literature search on PubMed (Title/Abstract) and Google Scholar (Title) using the following terms: "post-radiation" OR "radiation-induced" OR "post-irradiation" OR "irradiation-induced" AND "sarcoma." After the search above, to determine the eligibility of PRS case series, the following inclusion criteria were applied: (1) Reports including at least five PRS cases, (2) Series that did not restrict the location or histological type of either the primary tumor or PRS, and (3) Studies providing a sufficient description of the histological type of the primary tumor.

Screening of articles. For the systematic review of PRS case series, separate searches were conducted by two reviewers (T.M. and N.O.) using PubMed and Google Scholar. As a result, 876 and 430 titles were retrieved, respectively. The retrieved titles were subsequently uploaded to EndNote (Veritas Health Information), where 192 duplicate entries were identified and excluded. Two reviewers independently screened titles and abstracts, excluding 1,018 articles that didn't meet the criteria. In cases of disagreement, the senior author (A.O.) was consulted, and the final decision was reached by consensus. A total of 96 articles underwent full-text review, of which 30 met the inclusion criteria (Figure 1).[1,4,10-37]

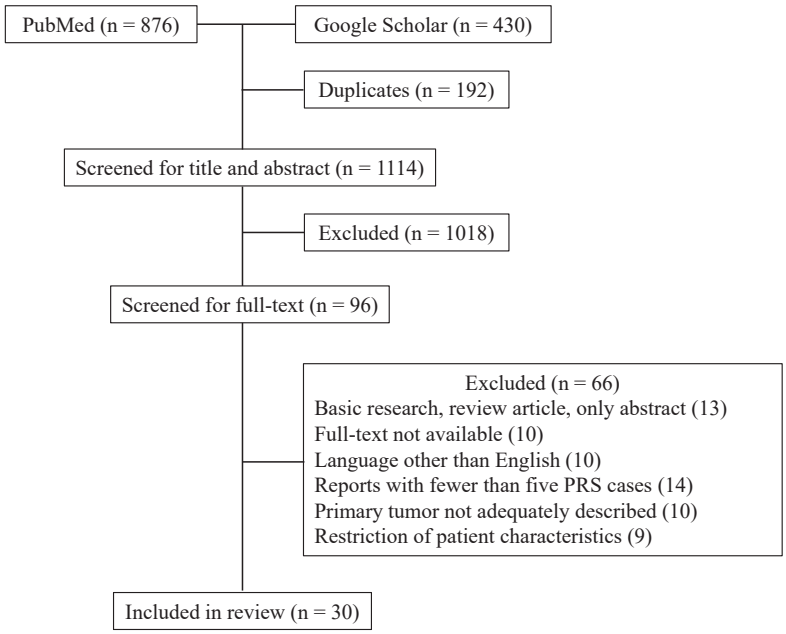

Fig. 1 Flowchart of the literature selection process for case series including five or more cases
PRS: post-radiation sarcoma

Additional search for articles with PRS cases secondary to radiotherapy for prostate cancer. We conducted an additional search to identify more PRS cases secondary to radiotherapy for prostate cancer from reports that excluded in Figure 1. Using EndNote, we searched for articles containing the term "prostate" in the title or abstract among the 1,114 articles screened by title and abstract in Figure 1. This search yielded 38 articles, which underwent full-text review. Of these, 18 articles did not report PRS cases secondary to radiotherapy for prostate cancer, one was unavailable in full text, and one had already been included in Figure 1 as a report with five or more cases. Consequently, 18 additional articles[38-55] were analyzed alongside Figure 1.

Characteristics of included articles. Although breast cancer is reported to be the most common primary tumor in PRS,[32,34,36] prostate cancer (n = 3) was equally prevalent with breast cancer among the 14 cases in our study. Therefore, we investigated the most common histologic types of primary tumors in previous case series and assessed the frequency of prostate cancer as the primary tumor. In 30 included articles, we analyzed the two most common primary tumors and the number of cases in which prostate cancer was identified as the primary tumor.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 10 software (GraphPad Software, CA, USA). The Kaplan-Meier method was used to estimate the overall survival of patients with PRS. Overall survival and survival period was measured from the date of PRS diagnosis to either the date of death or the last recorded follow-up. Differences in survival periods were analyzed using the log-rank test. $P < 0.05$ was considered statistically significant, while $P < 0.10$ was interpreted as indicating a trend toward significance.

RESULTS

Table 1 presents the details of the 14 patients (seven males and seven females), while Table 2 summarizes their overall characteristics. The treatment details for the patients with PRS are presented in Table S1. The median age at PRS diagnosis was 63 years (range, 16–79 years). The primary tumors included three cases of breast cancer and prostate cancer and one case each of cervical cancer, retinoblastoma, acute promyelocytic leukemia, non-Hodgkin's lymphoma, acute lymphoblastic leukemia, neuroblastoma, hard palate carcinoma, and esophageal cancer. Additionally, 10 patients received chemotherapy for their primary tumors. The median total radiation dose was 52.5 Gy (range, 12–74 Gy).

Table 1 Details of all patients

		Primary tumor			Post-radiation sarcoma									
Pt	Age/Sex	Histology	CTx	Total dose (Gy)	Histology	Latency period (year)	Location, Size (major axis, mm)	Initial metastasis	Surgery	Other treatment	Follow-up period (year)	LR	Subsequent metastasis	Outcome
1	53/F	Cervical cancer	+	74	UPS	9.4	Pelvis, 120	–	–	CTx RTx‡	2.5	N/A	Lung	DOD
2	16/F	Retinoblastoma	–	50	OS	15.6	Face, 50	Intracranial Lung	–	CTx	1.2	N/A	Lung	DOD
3	43/F	Breast cancer	+	60	UPS	3.3	Neck, 55	–	R0	CTx	1.4	+	–	DOD
4	75/M	APL	+	55	OS	7.9	Chest, 55	–	–	CTx	0.5	N/A	–	DOOD
5	23/M	NHL	+	40	UPS	8.1	Neck, 85	–	R1	CTx RTx	1.4	–	Lung	DOD
6	64/F	Breast cancer	+	50	OS	11.6	Chest, 35	–	R0	–	11.0	–	–	CDF
7	16/M	Neuroblastoma	+	12†	OS	10.4	Humerus, 70	–	R0	CTx	15.4	–	–	CDF
8	27/F	ALL	+	13†	CS	19.5	Femur, 35	–	R0	–	4.5	–	–	CDF
9	61/M	Hard palate cancer	+	60	OS	14.8	Jaw, 80	–	R0	CTx	3.0	–	Intracranial Lung Kidney	AWD
10	78/M	Prostate cancer	–	70	OS	14.0	Pelvis, 110	Lung	–	RTx	0.2	N/A	Lung	DOD
11	78/M	Prostate cancer	–	50	UPS	15.1	Lumber, 135	–	R2	–	1.0	–	–	AWD
12	79/F	Esophageal cancer	+	60	UPS	3.0	Back, 55	–	R0	–	6.0	–	–	DOOD
13	63/F	Breast cancer	+	50	UPS	7.5	Axilla, 85	–	R0	CTx	1.2	–	Lung Skin	DOD
14	71/M	Prostate cancer	–	65	MPNST	4.0	Sacrum, 80	–	–	RTx*	15.5	N/A	–	AWD

Pt, patients; M, male; F, female; APL, Acute promyelocytic leukemia; NHL, non-Hodgkin's lymphoma; ALL, Acute lymphoblastic leukemia; CTx, chemotherapy; RTx, radiotherapy; UPS, undifferentiated pleomorphic sarcoma; OS, osteosarcoma; CS, chondrosarcoma; MPNST, malignant peripheral nerve sheath tumor; LR, local recurrence; N/A, not applicable; CDF, continuous disease free; AWD, alive with disease; DOD, died on disease; DOOD, died on other disease.
†, total-body irradiation; ‡, proton therapy; *, carbon-ion radiotherapy.

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Table 2 Characteristics of patients

Factor	Number or median (range)	Factor	Number or median (range)
Age	63 (16–79)	Tumor size (major axis)	75 (35–135)
Sex	Male, 7; Female, 7	Initial metastasis	Yes, 2; No, 12
Histology (primary tumor)	Breast cancer: 3 Prostate cancer: 3 Others: 1 each	Surgery outcome	R0 resection: 7 R1 resection: 1 R2 resection: 1 None: 5
Previous chemotherapy	Yes, 10; No, 4	Other treatment to PRS	CTx alone: 6 RTx alone: 2 CTx + RTx: 2 None: 4
Initial dose, total (Gy)	52.5 (12–74)	Follow-up period (year)	2.0 (0.2–15.5)
Histology (PRS)	OS, 6; UPS, 6 CS, 1; MPNST, 1	Local recurrence	Yes, 1; No, 8; N/A, 5
Latency period (year)	9.9 (3.0–19.5)	Subsequent metastasis	Yes, 6; No, 8
Location (PRS)	Limb, 2; Trunk, 12	Outcome	CDF, 3; AWD, 3 DOD, 6; DOOD, 2

PRS, post-radiation sarcoma; CTx, chemotherapy; RTx, radiotherapy; UPS, undifferentiated pleomorphic sarcoma; OS, osteosarcoma; CS, chondrosarcoma; MPNST, malignant peripheral nerve sheath tumor; N/A, not applicable; CDF, continuous disease free; AWD, alive with disease; DOD, died of disease; DOOD, died of other diseases

Among the 10 PRS cases, histological subtypes included osteosarcoma (n = 6), undifferentiated pleomorphic sarcoma (n = 6), chondrosarcoma (n = 1), and malignant peripheral nerve sheath tumor (n = 1). The median latency period was 9.9 years (range, 3.0–19.5 years). PRS occurred in the trunk in 12 patients and in the limbs in two patients. The median tumor size (major axis) was 75 mm (range, 35–135 mm). Initial metastasis was observed in two patients.

Regarding treatment, nine patients underwent surgery, with seven achieving R0 resection, one undergoing R1 resection, and one undergoing R2 resection. Additional treatments included chemotherapy in eight patients, radiotherapy in four patients—including carbon ion radiotherapy in one patient, and a combination of chemotherapy and radiotherapy in two patients. The median follow-up period was 2.0 years (range, 0.2–15.5 years). Local recurrence occurred in one patient following surgery, while subsequent metastasis after PRS diagnosis was observed in six patients.

The clinical outcomes of the 14 patients were as follows: three patients remained continuous disease free (CDF), three patient was alive with disease (AWD), six patients died of disease (DOD), and two patients died of other disease (DOOD) due to pneumonia and other cancer.

Figure 2A presents the Kaplan-Meier survival curve for all 14 patients, with a median overall survival of 2.6 years (95% CI, 1.2–NA years). The 5-year overall survival probability was 46.8%

(95% CI, 19.6–70.2%). Figures 2B–2F illustrate Kaplan–Meier survival curves based on various factors, including age, tumor size, initial radiation dose, latency period, and surgical outcome. Among these factors, R0 resection exhibited a trend toward an association with improved survival (P = 0.09). Latency period (P = 0.18), age (P = 0.86), tumor size (P = 0.78), and initial radiation dose (P = 0.94) were not identified as significant contributors to survival in this study.

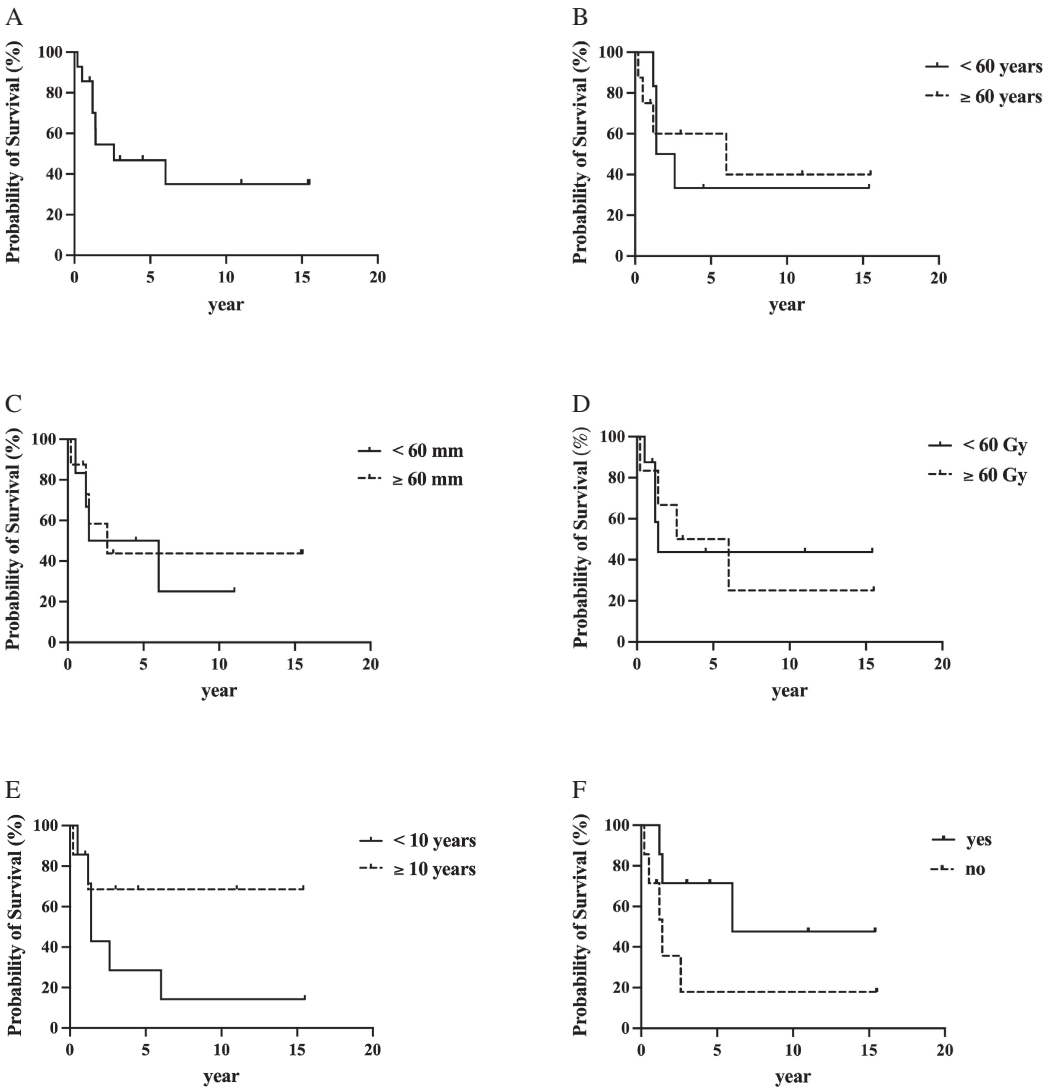

Fig. 2 Kaplan-Meier survival curves according to various factors
Fig. 2A: Overall survival of all 14 patients.
Fig. 2B: Overall survival according to age. Log-rank test, P = 0.86.
Fig. 2C: Overall survival according to tumor size. Log-rank test, P = 0.78.
Fig. 2D: Overall survival according to initial dose. Log-rank test, P = 0.94.
Fig. 2E: Overall survival according to latency period. Log-rank test, P = 0.18.
Fig. 2F: Overall survival according to surgical outcome. Log-rank test, P = 0.09.

Figure 1 illustrates the literature selection process for our systematic review, while Table 3 provides an overview of the included articles. As shown in Table 3, a total of 30 articles published between 1965 and 2022, reporting on 1784 patients, were analyzed. The two most common primary tumors in each case series are listed, along with the number of prostate cancer cases. A total of 82 prostate cancer cases were identified across the 30 studies. Table 4 presents the articles including "prostate" in their titles or abstracts. A total of 18 articles between 1993 and 2022, reporting on 22 patients, were listed. Figure 3 presents the number of reported PRS cases secondary to irradiation for prostate cancer by age, based on cases obtained from Table 3 and Table 4. Notably, 29 cases were reported before 2010, whereas 75 cases were reported from 2010 onward (Figure 3).

Table 3 Primary tumors in case series comprising more than five cases of post-radiation sarcoma

Source	Total	Primary tumor	
		Predominantly (n)	Prostate CA
Steiner,[10] 1965	12	Giant cell tumor (5), others one each	0
Arlen,[4] 1971	28	Giant cell tumor (8), Breast CA (4)	0
Kim,[11] 1978	20	Retinoblastoma (4), HL (3)	0
Tountas,[12] 1979	10	Breast CA (3), Cervical CA (2)	1
Smith,[13] 1982	43	HL (10), Breast CA (8)	0
Kim,[14] 1983	10	HL (6), others one each	0
Davidson,[15] 1986	20	Breast CA (6), Cervical CA (2), HL (2)	0
Laskin,[16] 1988	53	Breast CA (12), HL (10)	1
Lorigan,[17] 1989	19	Breast CA (5), HL (4)	1
Wiklund,[18] 1991	33	Breast CA (3), Endometrial CA (3), Cervical CA (3)	0
Mark,[1] 1994	37	Breast CA (7), Cervical CA (6)	0
Pitcher,[19] 1994	38	Breast CA (13), HL (5)	0
Bloechle,[20] 1995	11	Breast CA (4), Cervical CA (3)	0
Murray,[21] 1999	20	Cervical CA (6), Breast CA (3)	0
Inoue,[22] 2000	130	Giant cell tumor (19), Breast CA (18)	0
Lagrange,[23] 2000	80	Breast CA (33), NHL (9)	0
Sheppard,[24] 2001	63	Breast CA (17), Lymphoma (10)	1
Fang,[25] 2004	14	Uterine CA (7), Breast CA (4)	0
Cha,[26] 2004	111	Breast CA (32), Lymphoma (17)	15
Thijssens,[27] 2005	27	Breast CA (14), HL (4)	0
Holt,[28] 2006	48	Breast CA (10), HL (9)	0
Bjerkehagen,[29] 2008	90	Breast CA (16), Uterine CA (13)	0
De Smet,[30] 2008	46	Breast CA (23), Cervical CA (5)	1
Mavrogenis,[31] 2012	52	Breast CA (16), NHL (7)	1
Kim,[32] 2016	33	Breast CA (9), Cervical CA (8)	0
Zhang,[33] 2017	419	Breast CA (212), Head and neck CA (40)	14

Joo,[34] 2018	43	Breast CA (9), Cervical CA (6)	2
Tsuda,[35] 2020	25	Ewing's sarcoma (5), Breast CA (4)	1
Snow,[36] 2021	242	Breast CA (126), Prostate cancer (44)	44
Laurino,[37] 2022	7	Breast CA (5), others one each	0

CA: cancer
HL: Hodgkin's lymphoma
NHL: non-Hodgkin's lymphoma

Table 4 PRS cases secondary to irradiation for prostate cancer retrieved through an additional search with "prostate" in the title or abstract

Source	PRS cases secondary to irradiation for prostate cancer		
	Age	Location	Histology
O'Donnell,[38] 1993	73	Groin	Osteosarcoma
Nghiem,[39] 1995	48	Prostate	High-grade sarcoma
	54	Prostate	High-grade sarcoma
Terris,[40] 1998	43	Prostate	High-grade sarcoma
	93	Prostate	High-grade sarcoma
	81	Pubis	Osteosarcoma
McKenzie,[41] 1999	74	Pubis, ischium	Osteosarcoma
	75	Ilium, ischium	Osteosarcoma
Prevost,[42] 2004	74	Groin	High-grade sarcoma
Papalas,[43] 2011	62	Pubis	Osteosarcoma
Gumber,[44] 2013	78	Ilium	Osteosarcoma
Horiguchi,[45] 2014	69	Prostate	Leiomyosarcoma
Gupta,[46] 2015	71	Prostate	Angiosarcoma
Lai,[47] 2016	75	Pelvis	High-grade sarcoma
Prameela,[48] 2017	77	Scrotum	Leiomyosarcoma
Plouznikoff,[49] 2019	67	Perineum	UPS
Wakabayashi,[50] 2019	77	Perineum	High-grade sarcoma
Hiraoka,[51] 2020	74	Prostate	UPS
Propst,[52] 2021	72	Rectum	Spindle cell sarcoma
Rodriguez-Perez,[53] 2021	85	Penile base	UPS
Nakashima,[54] 2022	59	Pubis	Osteosarcoma
Thota,[55] 2022	78	Prostate	High-grade sarcoma

PRS: post-radiation sarcoma
UPS: undifferentiated pleomorphic sarcoma

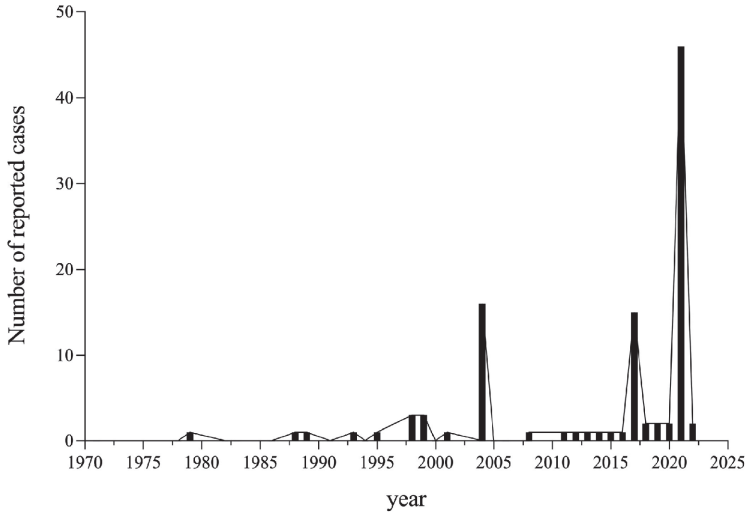

Fig. 3 The number of reported PRS cases following prostate cancer by age per the literature review
PRS: post-radiation sarcoma

DISCUSSION

We examined 14 cases of PRS from three institutions in Japan and analyzed their characteristics. The median age of the PRS patients was 63 years (range, 16–79 years), which was generally consistent with previously reported values (median age, 52–59 years).[56] According to previous reports, breast cancer is the most common histological type of primary tumor.[32,34,36] In this study, while breast cancer was the most frequently observed primary tumor, prostate cancer was equally common, which is a notable finding. In patients with PRS, osteosarcoma is reported as the most common bone sarcoma, whereas undifferentiated pleomorphic sarcoma (UPS) is the most frequent soft tissue sarcoma[32,34]; these findings were consistent with our observations. The trunk is the most common site of PRS occurrence,[34,57,58] which was also noted in our series. In a study on radiation-induced sarcoma, conducted by Bjerkehagen et al, tumors arising in central sites were reported to be associated with a low likelihood of achieving R0 resection as well as a poor prognosis.[58] In this study, 12 of the 14 cases of PRS originated in the trunk, while the remaining 2 arose in the limbs. Among the 12 trunk-related cases, 4 occurred in the head and neck region, with R0 resection achieved in 2 cases (50%); 4 in the thoracic or dorsal region, with R0 resection achieved in 3 cases (75%); and 4 in the lumbar spine, sacrum, or pelvis, with no case achieving R0 resection (0%). In contrast, both limb-related cases achieved R0 resection (100%). These findings suggest that achieving R0 resection is particularly challenging when the tumor arises in the trunk and involves deep anatomical sites. The median latency period reported in the literature is 8–14 years.[56] In our study, the median latency period was 9.9 years, consistent with previous findings. In this series of 14 cases, the cumulative 5-year overall survival rate was 46.8%, consistent with previous reports, ranging 32–58%.[5,34,58] In general, the prognosis for patients with PRS is reported to be worse than that for patients with conventional sarcoma. Bjerkehagen et al reported a 5-year survival rate of 51% for conventional sarcoma compared with 32% for post-irradiation sarcoma.[58] Their multivariate analysis further identified incomplete surgical remission as the factor most strongly associated with prognosis in patients with post-irradiation sarcoma (hazard ratio, 4.48; 95% CI, 3.08–6.52).[58] Similarly in our study,

complete resection showed a trend toward an association with prognosis ($P = 0.09$), although the difference was not statistically significant. Regarding the latency period, Joo et al reported 5-year overall survival rates of 60.6% and 36.5% for soft-tissue PRS cases with latency periods of less than 15 years and more than 15 years, respectively ($P = 0.669$, univariate).[34] Kim et al reported median survival periods of 115 months and 23 months for PRS cases involving the bone and soft tissue, respectively, with latency periods of 12 years or less and more than 12 years ($P = 0.233$, univariate).[32] In this study, the median survival period was 1.4 years for patients with a latency period of less than 10 years, whereas it was not reached for those with a latency period of more than 10 years ($P = 0.18$), demonstrating no substantial difference from the previous reports. This finding may be attributed to the small sample size of this study, suggesting the need for further investigation into the correlation between latency period and prognosis.

In this study, 3 of the 14 patients had breast cancer as the primary tumor, consistent with previous reports.[32,34,36] Angiosarcoma developing after breast cancer surgery, particularly in association with lymphedema, is known as Stewart–Treves syndrome. However, none of the three breast cancer patients in this study exhibited lymphedema.[59-63] Further, regarding the histological types of PRS observed in these patients, two were diagnosed as undifferentiated pleomorphic sarcoma and one as osteosarcoma. Given the high incidence of breast cancer and its relatively favorable prognosis compared to that of other cancers, the number of PRS cases following breast cancer is expected to increase over time. Therefore, in patients presenting with new lesions after resection for breast cancer, the possibility of PRS should be considered when a tumor arises within the irradiated area.

Interestingly, three of the 14 patients presented with prostate cancer as the primary tumor, making it the most common primary tumors alongside breast cancer in this study. To determine whether the number of reported cases of prostate cancer as the primary tumor has increased in recent years, we conducted a systematic review of PRS following the flowchart presented in Figure 1. As shown in Table 3, case series including five or more PRS cases published before 2010 identified prostate cancer as the primary tumor in 20 out of 963 cases. In contrast, reports published in 2010 or later identified prostate cancer in 62 out of 821 cases. Although a direct comparison is not feasible due to the time gap between the publication year and the period of data collection, the proportion of prostate cancer among all reported PRS cases increased by approximately 3.6 times around 2010. When an additional search was conducted for articles on PRS cases, including those with fewer than five cases, as indicated in Table 4, nine PRS cases secondary to irradiation for prostate cancer were found before 2010, and 13 were found in 2010 or later. Many cases remain unreported, and some were not captured in our survey; however, these findings suggest a recent increase in PRS cases following radiotherapy for prostate cancer.

In fact, the global incidence of prostate cancer has been increasing in recent years. Shelton et al reported that over the 25 years from 1993 to 2018 in the United Kingdom, prostate cancer exhibited the most significant increase in incidence among men.[64] Siegel et al reported that prostate cancer had the highest increase in cancer incidence among men over the 25 years from 1993 to 2018 in the United States.[65] Zhu et al reported that the incidence of prostate cancer multiplied by approximately sixteen times between 1980 and 2010 in Japan.[66] In addition, radiotherapy has become a crucial treatment option for prostate cancer, leading to a growing number of patients undergoing radiotherapy.[9,67] In the United States, the proportion of patients with prostate cancer undergoing hormone therapy has significantly declined since the 1990s, while the proportion receiving surgery or radiation therapy has increased.[68] In a survey conducted in Japan, hormone therapy was the most used initial treatment for prostate cancer until 2010. However, among patients diagnosed between 2016 and 2018, the proportion undergoing surgery or radiation therapy increased, while the use of hormone therapy significantly declined.[69] The recent

increase in patients with prostate cancer, along with a growing number of patients undergoing radiotherapy, have contributed to a rise in PRS following irradiation to prostate cancer.

According to our research, PRS arising in the bone is frequently diagnosed as osteosarcoma, a striking clinical feature of PRS following prostate cancer. Since both osteosarcoma and prostate cancer metastases present with osteogenic lesions, distinguishing between them is essential. As imaging alone cannot reliably differentiate the two, a biopsy is needed to distinguish them. Therefore, in patients with a history of irradiation for prostate cancer who develop a bony lesion, the possibility of both prostate cancer bone metastasis and PRS should be considered, and a biopsy should be performed when necessary. Furthermore, in this study, we investigated the clinical outcomes of PRS cases following prostate cancer, by analyzing the cases listed in Tables 3 and 4, for whom follow-up periods and oncological outcomes were available. These cases (n = 18) are summarized in Table S2. A previous report analyzing 98 cases of patients with PRS found that complete resection was achieved in 45 cases (46%).[58] In comparison, among the 18 cases listed in Table S2, complete resection was achieved in 8 cases (44%), a finding comparable to the previous study.[58] However, on examining the details, it was found that complete resection was achieved in only 5 of the 8 cases (63%), where PRS developed in the prostate, penis, or scrotum. In contrast, complete resection was achieved in only 2 of the 9 cases (22%) where PRS developed in the groin, perineum, or pelvis. As previously noted, this suggests that complete resection is more challenging when PRS arises in deep or central regions of the body. In terms of prognosis, the median overall survival of the 18 patients was 8 months, which was poorer than the previously reported median survival of 29–36 months for patients with PRS.[31,32,37] One contributing factor for this may be related to the tendency of prostate cancer occurring in older men. The median age of the 18 patients was 74 years, which is higher than the previously reported median age of patients with PRS, ranging from 52 to 59 years.[56]

This study has several limitations. First, the number of PRS patients included was 14, and the small sample size may have influenced the results of the univariate analysis. Second, the data available for the 14 PRS cases in this study were limited. We assumed that the radiation dose to the primary tumor site and that to the PRS site were not necessarily the same. Therefore, we investigated the potential impact of radiation dose to the PRS site by retrospectively reviewing past treatment records. However, since most of the patients included in this study had received radiotherapy a long time ago, dose distribution records (such as isodose curves) were not available. As a result, we were unable to evaluate the total radiation dose delivered to the PRS site. Third, recent advancements in radiotherapy and chemotherapy may continue to impact the prognosis of PRS patients in the future. In this study, complete resection was identified as a factor correlating with prognosis; however, even in cases where complete resection is not achievable, as seen in the patient number 14, long-term survival has been observed with novel treatments such as carbon ion radiotherapy. Therefore, it is important to continue accumulating cases and conducting further investigations.

In conclusion, in this study, we retrospectively analyzed 14 cases of patients with PRS. Among the prognostic factors in patients with PRS, the feasibility of complete surgical resection demonstrated a trend toward significance. Thus, it is important to closely monitor patients for early detection of PRS. In our series, the most common histological type of primary tumor was breast cancer, consistent with that observed in previous reports. However, a systematic review revealed a marked increase in the number of reported PRS cases following prostate cancer in recent years. Thus, when osteogenic lesions are identified within the irradiated field in patients with prostate cancer, clinicians should not only consider metastatic prostate cancer but also the possibility of PRS.

DECLARATION OF CONFLICTING INTERESTS

All authors declare no conflicts of interest.

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SUPPLEMENTARY INFORMATION

Table S1 Treatment details for post-radiation sarcoma

Pt	Treatment for post-radiation sarcoma					
	Surgery	Chemotherapy			Radiotherapy	
		Drug	Dose	Times	Irradiated site	Total dose
1	–	Doxorubicin	24 mg/m^2	8	Pelvis	84 GyE[†]
		Ifosfamide	1.6 g/m^2	20		
		Gemcitabine	1000 mg/m^2	34		
		Paclitaxel	175 mg/m^2	17		
		Carboplatin	580 mg	3		
		Etoposide	100 mg/m^2	9		
		Irinotecan	100 mg/m^2	8		
2	–	Methotrexate	NA	NA	–	–
		Cisplatin	NA	NA		
		Vincristine	NA	NA		
		Ifosfamide	NA	NA		
		Etoposide	NA	NA		
		Carboplatin	NA	NA		
		Topotecan	0.75 mg/m^2	15		
		Irinotecan	12 mg/m^2	10		
		Temozolomide	100 mg/m^2	5		
3	R0	Doxorubicin	50 mg/m^2	2	–	–
		Eribulin	1.4 mg/m^2	4		
		Gemcitabine	1000 mg/m^2	8		
		Paclitaxel	175 mg/m^2	4		
4	–	Carboplatin	300 mg	4	–	–
		Etoposide	50 mg	8		
5	R1	Carboplatin	450 mg	4		
		Etoposide	100 mg/m^2	12		
		Ifosfamide	4.9 g	5		
		Cisplatin	9 mg	1		
6	R0	–	–	–	–	–

7	R0	Doxorubicin	25 mg/m^2	4	–	–
			30 mg/m^2	4		
		Cisplatin	200 mg/m^2	5		
		Vincristine	2 mg	1		
		Methotrexate	3 g/m^2	1		
			6 g/m^2	6		
			7 g/m^2	1		
			8 g/m^2	1		
		Vindesin	4.5 mg	1		
		Ifosfamide	1 g/m^2	8		
			3 g/m^2	4		
		Carboplatin	100 mg/m^2	8		
8	R0	–	–	–	–	–
9	R0	Doxorubicin	24 mg/m^2	2	–	–
		Ifosfamide	1.6 g/m^2	5		
		Gemcitabine	1000 mg/m^2	29		
		Paclitaxel	175 mg/m^2	15		
		Carboplatin	815 mg	4		
		5-Fluorouracil	800 mg/m^2	16		
		Pembrolizumab	200 mg	4		
10	–	–	–	–	Pelvis	30 Gy
11	R2	–	–	–	–	–
12	R0	–	–	–	–	–
13	R0	Doxorubicin	24 mg/m^2	2	–	–
			22.5 mg/m^2	2		
		Ifosfamide	1.6 g/m^2	5		
			1.5 g/m^2	5		
14	–	–	–	–	Sacrum	70.4 Gy*

Pt: patients
NA: not available
† proton therapy
* carbon-ion radiotherapy

Table S2 Clinical outcome of PRS cases secondary to irradiation for prostate cancer

Source	PRS cases secondary to irradiation for prostate cancer					
	Age	Location	Histology	Surgery	FUP (month)	OC
O'Donnell,[38] 1993	73	Groin	Osteosarcoma	R0	2	CDF
Terris,[40] 1998	54	Prostate	High-grade sarcoma	R0	12	DOD
	43	Prostate	High-grade sarcoma	R0	12	DOOD
	93	Prostate	High-grade sarcoma	–	3	DOOD
McKenzie,[41] 1999	81	Pubis	Osteosarcoma	–	4	DOD
	74	Pubis, ischium	Osteosarcoma	–	1	DOD
	75	Ilium, ischium	Osteosarcoma	–	10	DOD
Prevost,[42] 2004	74	Groin	High-grade sarcoma	–	6	DOD
Mavrogenis,[31] 2012	74	Thigh	Fibrosarcoma	R0	14	DOD
Gumber,[44] 2013	78	Ilium	Osteosarcoma	R0	8	DOD
Horiguchi,[45] 2014	69	Prostate	Leiomyosarcoma	R0	8	DOD
Gupta,[46] 2015	71	Prostate	Angiosarcoma	R0	6	AWD
Lai,[47] 2016	75	Pelvis	High-grade sarcoma	–	4	AWD
Prameela,[48] 2017	77	Scrotum	Leiomyosarcoma	–	2	DOD
Wakabayashi,[50] 2019	77	Perineum	High-grade sarcoma	–	4	DOD
Hiraoka,[51] 2020	74	Prostate	UPS	R0	2	DOD
Rodriguez-Perez,[53] 2021	85	Penile base	UPS	–	10	DOD
Nakashima,[54] 2022	59	Pubis	Osteosarcoma	–	22	DOD

PRS, post-radiation sarcoma; UPS, undifferentiated pleomorphic sarcoma; N/A, not available; FUP, follow-up period; OC, outcome; CDF, continuous disease free; AWD, alive with disease; DOD, died of disease; DOOD, died of other diseases.