PET/MRI is useful for early detection of pelvic insufficiency fractures after radiotherapy for cervical cancer

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Abstract. Radiotherapy (RT) is used to manage cervical cancer, and pelvic insufficiency fracture (PIF) is known as a late complication of RT. The present study identified risk factors for PIF after radiotherapy for cervical cancer, and investigated its incidence rate. It also considered the usefulness of positron emission tomography/magnetic resonance imaging (PET/MRI) in PIF diagnosis. A total of 149 patients with cervical cancer who received definitive or adjuvant RT with/without concurrent chemotherapy between January 2013 and December 2018 were investigated in the present study and followed up for more than one month after RT at Kobe University Hospital. The median follow-up period was 32 months (range, 1-87 months), and the median age of all patients was 66 years (age range, 34-90 years). Computed tomography (CT), MRI, PET/CT or PET/MRI were used for image examination. Among the 149 patients, 31 (20.8%) developed PIF. The median age of these patients was 69 years (age range, 44-87 years). Univariate analysis using the log-rank test demonstrated that age (≥60 years) was significantly associated with PIF. The median maximum standardized uptake value of PIF sites on PET/CT was 4.32 (range, 3.04-4.81), and that on PET/MRI was 3.97 (range, 1.21-5.96) (P=0.162). Notably, the detection time of PIF by PET/MRI was significantly earlier compared with PET/CT (P<0.05). The incidence of PIF after RT for cervical cancer was 20.8%, and age was significantly associated with risk factors for such fractures. Taken together, these results suggest that PET/MRI, which offers the advantage of decreased radiation exposure to the patient, is useful for diagnosing PIF and can detect it earlier than PET/CT imaging.

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Introduction

Radiotherapy (RT) is used to manage cervical cancer, either postoperatively or as a primary treatment (1), and major improvements in definitive RT have improved survival rates over the past 15-20 years (2). Pelvic insufficiency fracture (PIF) is a late complication of the therapy (3). According to a meta-analysis by Sapienza *et al* (4), the overall incidence of PIF is between 10-18%, and the most common site for PIF is the sacrum. PIF can lead to intractable pain and limited mobility, which can seriously impact the quality of life of cervical cancer survivors (5). Risk factors associated with cervical cancer include age, postmenopausal period, low body weight and osteoporosis (5-14). Recently, intensity-modulated radiation therapy (IMRT) has been introduced to reduce acute and chronic gastrointestinal disorders (15). However, the most effective method in reducing PIF remains unclear.

Considering the increased number of cervical cancer survivors (16), it is important to clarify what factors increase the risk of PIF after RT for patients with cervical cancer, and detect PIF in the early phase before patients develop any symptoms. Most reports on PIF have used computed tomography (CT) and magnetic resonance imaging (MRI) as inspection methods (5-10,12-14,17-21). According to Lapina and Tiškevičius (22), the sensitivity and specificity in PIF diagnosis are 100 and 95.3% for MRI and 74.6 and 89.7% for CT, respectively. Recently, positron emission tomography (PET) is attracting great interest as an imaging test for the follow-up of cervical cancer recurrence (23). However, to the best of our knowledge, only a few reports have used PET (5,11,19,21), and PET/MRI is yet to be investigated (4). The present study aimed to identify risk factors for PIF and investigate its incidence rate. In addition, the usefulness of PET/MRI in PIF diagnosis was assessed.

Materials and methods

Patient characteristics. The present study investigated 149 patients with cervical cancer who received definitive or adjuvant RT with/without concurrent chemotherapy between January 2013 and December 2018, and were followed up for more than one month after RT at Kobe University Hospital. Data collection ended in May 2020. The median follow-up

period was 32 months (range, 1-87 months), and the median age of all patients was 66 years (age range, 34-90 years). The histopathological type was squamous cell carcinoma (SCC) in 121 cases (81.2%), adenocarcinoma in 26 cases (17.4%), adenosquamous in one case (0.7%) and clear cell carcinoma in one case (0.7%). The median body mass index (BMI) was 21 (range, 14-40). A total of 27 cases (18.1%) were in The International Federation of Gynecology and Obstetrics (FIGO) stage (24) was I, 62 cases in stage II (41.6%), 40 cases in stage III (26.8%) and 20 cases in stage IV (13.4%). A total of 123 patients (82.6%) received RT as a definitive treatment, 26 (17.4%) received RT as postoperative adjuvant therapy, and 110 (73.8%) received concurrent chemoradiotherapy. Table I presents patient characteristics, according to the presence or absence of PIF. Notably, no significant differences were observed between both groups.

The inclusion criteria were as follows: Patients whose medical records and prognosis could be obtained from medical records, and patients who had a definite diagnosis of cervical cancer and were followed up for at least one month after the end of radiotherapy. The exclusion criteria were as follows: Patients who were offered to not participate in this study based on publicly available information, and patients participating in or planning to participate in clinical studies involving drug therapy interventions.

Treatment. For definitive RT, external beam RT (EBRT) was performed using the four-field box technique, and intracavitary brachytherapy (ICBT) was subsequently performed using a remote after-loading system, in combination with EBRT, using the central shield by anteroposterior/posteroanterior field technique at 10 MV photons. The upper limit of the standard irradiation field was the upper edge of the 5th lumbar vertebra, and the lower limit was at least 3 cm below the lower edge of the obturator foramen or the lower edge of the vaginal infiltration. The outer side of the anterior-posterior irradiation field was 1.5-2 cm outside the inner edge of the pelvis, and the anterior edge of the lateral irradiation field was ~0.5 cm in front of the anterior pubic symphysis. A total dose of EBRT (TrueBeam™; Varian Medical Systems) at 50.4 Gy (range, 40.0-50.4 Gy) and ICBT (Micro Selectron™; Nucletron BV) at 24 Gy (range, 18-30 Gy) was administered. For postoperative adjuvant RT, IMRT (TrueBeam™, Varian Medical Systems) was performed with a total dose of 50.4 Gy (range, 50.4-60.0 Gy). A total dose of 10.0 Gy (range, 3.6-16.2 Gy) lymph node boost (TrueBeam™; Varian Medical Systems) was given to 54 patients (36.2%) with positive lymph node metastasis. For concurrent chemoradiotherapy, cisplatin (Cisplatin Maruko™; Yakult Honsha Co., Ltd.) was administered once a week for 5-6 cycles at 40 mg/m².

Follow-up and diagnostic criteria of PIF. For cervical cancer, follow-up started 1 month after the end of radiation therapy, and in principle, it was continued for 5 years in the outpatient department. Follow-up was conducted every 1 to 3 months in the 1st and 2nd years, every 3 to 6 months in the 3rd year, and every 6 months in the 4 to 5th years. Patients underwent imaging tests twice a year for the first 2 years and then annually thereafter. CT, MRI, PET/CT or PET/MRI were used as follow-up imaging methods. At the discretion of the

two radiologists and two gynecologists, a recurrent check or follow-up was performed, and a CT, PET/CT or PET/MRI was selected. In addition, an MRI was selected depending on the symptoms, such as buttock or lower back pains. During the median follow-up period, 121 patients (81.2%) underwent imaging with PET, while 66 patients (44.3%) underwent imaging with PET/MRI. Patients who received multiple types of tests for the recurrence check or follow-up were excluded from the analysis.

The diagnostic criteria for PIF was as follows: CT for a fracture line or osteosclerosis without osteolytic changes, MRI for T1 hypointensity and T2 hyperintensity without a soft tissue mass, and PET for mild and diffuse fluorodeoxyglucose (FDG) accumulation. All images were diagnosed by two radiologists at Kobe University Hospital.

Statistical analysis. Statistical analysis was performed using R version 4.0.0 (https://cran.r-project.org/bin/windows/base/). For each factor in the fracture (n=31) and non-fracture groups (n=118), χ^2 or Fisher's exact tests were used to assess the differences in frequency. The Mann-Whitney U test was used to compare differences between continuous variables. Each exposure or each predictor was assessed using the log-rank test as univariate analysis. P<0.05 was considered to indicate a statistically significant difference. This observational study complied with the STROBE guidelines (25).

Results

Incidence. Among the 149 patients investigated in the present study, 31 (20.8%) developed PIF, and the median time for developing the condition was 17 months (range, 2-47 months). The median age of the fracture group was 69 years, of which 28 patients (90.3%) were postmenopausal. The median age of the non-fracture group was 66 years, of which 94 patients (79.7%) were postmenopausal. Notable, no significant differences in age and postmenopausal status were observed between the two groups. The median BMI was 20.9 in the fracture group and 21.0 in the non-fracture group, and the median number of deliveries was two in both the fracture and non-fracture groups, respectively. With regards to medical history, two patients (6.5%) had diabetes, while three (9.7%) had osteoporosis in the fracture group, whereas 15 patients (12.7%) had diabetes, four (3.4%) had rheumatic arthritis and 14 (11.9%) had osteoporosis in the non-fracture group. There were no significant differences in medical history between the two groups. No patients received hormone replacement therapy (HRT) in the fracture group, while 10 patients received HRT in the non-fracture group. The histopathological types were 27 cases (87.1%) of SCC, three (9.7%) of adenocarcinoma and one (3.2%) of adenosquamous in the fracture group, compared with 94 cases (79.7%) of SCC, 23 (19.5%) of adenocarcinoma and one (0.8%) of clear cell carcinoma in the non-fracture group. There were no significant differences in histopathological types between the two groups. A total of two cases (6.5%) were in FIGO stage I, 14 (45.2%) in stage II, 13 (41.9%) in stage III and two (6.5%) in stage IV in the fracture group. Conversely, 25 cases (21.2%) were in FIGO stage I, 48 (40.7%) in stage II, 27 (22.9%) in stage III and 18 (15.3%)

Table I. Patient characteristics.

Characteristic	Fracture (+) (n=31)	Fracture (-) (n=118)	P-value
Median age (range), years	69 (44-87)	66 (34-90)	0.0727
Median age of menopause (range), years	50 (40-57)	50 (40-60)	0.3720
Menopausal status			0.2938
Postmenopause	28 (90.3%)	94 (79.7%)	
Premenopause	2 (6.5%)	20 (16.9%)	
Unknown	1 (3.2%)	4 (3.4%)	
Body mass index, kg/m^2	20.9 (16.8-34.8)	21.0 (13.7-40.3)	0.5858
Parity	2 (0-5)	2 (0-6)	0.4134
Medical history			
Diabetes mellitus	2 (6.5%)	15 (12.7%)	0.5265
Rheumatoid arthritis	0 (0.0%)	4 (3.4%)	0.5804
Osteoporosis	3 (9.7%)	14 (11.9%)	1
Hormone replacement therapy	0 (0.0%)	10 (8.5%)	0.1224
Histopathological type			0.1571
Squamous cell carcinoma	27 (87.1%)	94 (79.7%)	
Adenocarcinoma	3 (9.7%)	23 (19.5%)	
Adenosquamous	1 (3.2%)	0 (0.0%)	
Clear cell carcinoma	0 (0.0%)	1 (0.8%)	
FIGO stage			0.0552
I	2 (6.5%)	25 (21.2%)	
II	14 (45.2%)	48 (40.7%)	
III	13 (41.9%)	27 (22.9%)	
IV	2 (6.5%)	18 (15.3%)	
Treatment			0.2129
Adjuvant CCRT	0 (0.0%)	12 (10.2%)	
Adjuvant RT	2 (6.5%)	12 (10.2%)	
Definitive CCRT	22 (71.0%)	76 (64.4%)	
Definitive RT	7 (22.6%)	18 (15.3%)	
ICBT			0.2009
Yes	28 (90.3%)	94 (79.7%)	
No	3 (9.7%)	24 (20.3%)	
Lymph node boost			1
Yes	11 (35.5%)	43 (36.4%)	
No	20 (64.5%)	75 (63.6%)	
IMRT			0.1069
Yes	2 (6.5%)	23 (19.5%)	
No	29 (93.5%)	95 (80.5%)	
PET/CT			0.1561
Yes	13 (41.9%)	68 (57.6%)	
No	18 (58.1%)	50 (42.4%)	
PET/MRI			0.6859
Yes	15 (48.4%)	51 (43.2%)	
No	16 (51.6%)	67 (56.8%)	

FIGO, International Federation of Gynecology and Obstetrics; CCRT, computer-controlled radiation therapy; RT, radiotherapy; ICBT, intracavitary brachytherapy; IMRT, intensity-modulated radiation therapy; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging.

in stage IV in the non-fracture group. These results suggest that the FIGO stage was slightly higher in the fracture group compared with the non-fracture group (P=0.0552). In the facture group, no patients received adjuvant concurrent

Table II. Characteristics of PIF.

Patient	Age, years	Time, months	Site	Symptom	Diagnostic medium	PET/CT (SUV_{max})	PET/MRI (SUV_{max})
1	72	32	Sacrum	Asymptomatic	CT	NA	NA
2	66	28	Sacrum	Buttocks pain	CT	NA	NA
3	80	12	Lumber spinal vertebrae	Buttocks pain	PET/CT	3.68	NA
4	82	38	Sacrum	Buttocks pain	CT	NA	NA
5	81	33	Sacrumpubis	Buttocks pain	CT	NA	NA
6	76	25	Sacrum	Asymptomatic	PET/CT	4.52	NA
7	87	12	Sacrum	Buttocks pain	MRI	NA	NA
8	61	15	Sacrum	Buttocks pain	PET/CT	4.81	NA
9	66	34	Sacrumpubis	Asymptomatic	PET/CT	4.30	NA
10	46	36	Sacrumpubis	Buttocks pain	PET/MRI	NA	5.96
11	67	4	Sacrum	Asymptomatic	PET/CT	4.11	NA
12	67	47	Sacrumpubis	Asymptomatic	PET/CT	4.81	NA
13	51	22	Sacrum	Asymptomatic	CT	NA	NA
14	58	14	Sacrum	Buttocks pain	CT	NA	NA
15	69	7	Sacrum	Buttocks pain	PET/MRI	NA	4.06
16	79	9	Sacrumlumber spinal vertebrae	Asymptomatic	PET/MRI	NA	4.02
17	82	2	Lumber spinal vertebrae	Buttocks pain	CT	NA	NA
18	60	32	Sacrum	Buttocks pain	PET/MRI	NA	1.21
19	66	29	Sacrum	Asymptomatic	PET/MRI	NA	3.92
20	69	13	Sacrum	Asymptomatic	PET/MRI	NA	5.23
21	70	29	Sacrumpubis	Asymptomatic	CT	NA	NA
22	75	15	Sacrum	Asymptomatic	PET/MRI	NA	2.50
23	52	18	Sacrum	Asymptomatic	PET/CT	3.04	NA
24	74	7	Lumber spinal vertebrae	Asymptomatic	PET/CT	4.27	NA
25	73	23	Sacrumpubis	Buttocks pain	PET/CT	4.33	NA
26	44	17	Sacrum	Asymptomatic	PET/MRI	NA	3.39
27	80	8	Sacrumpubis	Asymptomatic	CT	NA	NA
28	62	21	Sacrumpubis	Buttocks pain	PET/MRI	NA	4.07
29	76	6	Sacrumpubis	Buttocks pain	PET/CT	4.34	NA
30	67	8	Sacrumthoracic spinal vertebrae	Asymptomatic	CT	NA	NA
31	56	8	Sacrum	Asymptomatic	PET/MRI	NA	3.88

PIF, pelvic insufficiency fracture; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; SUV_{max}, maximum standardized uptake value; NA, not available.

chemoradiotherapy (CCRT), two (6.5%) received adjuvant RT, 22 (71.0%) received definitive CCRT and seven (22.6%) received definitive RT. Conversely, in the non-fracture group, 12 patients (10.2%) received adjuvant CCRT, 12 (10.2%) received adjuvant RT, 76 (64.4%) received definitive CCRT and 18 (15.3%) received definitive RT. A total of 28 patients (90.3%) received ICBT, 11 (35.5%) received a lymph node boost and two (6.5%) received IMRT in the fracture group, whereas 94 patients (79.7%) received ICBT, 43 (36.4%) received a lymph node boost and 23 (19.5%) received IMRT in the non-fracture group. Notably, no significant differences in the type of treatment were observed between the two groups. A total of 13 patients (41.9%) had PET/CT as the imaging test, while 15 (48.4%) had PET/MRI in the fracture group. Conversely, 68 patients (57.6%) had PET/CT as the imaging test, while 51 (43.2%) had PET/MRI in the non-fracture group. There were no significant differences in image examination between the two groups (Table I).

Sites. Table II presents the result of 31 patients who were diagnosed with PIF, 17 of which (54.8%) were asymptomatic. A total of 28 patients has their fracture site in the sacrum, nine in the pubis and four in the lumber spinal vertebrae. A total of 11 patients (35.5%) had multiple fractures (Table II), while 17 (54.8%) were asymptomatic. Furthermore, 10 patients (32.3%) were diagnosed with PIF on CT, one (3.2%) on MRI, 10 (32.3%) on PET/CT and 10 (32.3%) on PET/MRI. In addition, 12/17 patients (70.6%) with asymptomatic PIF were diagnosed by PET-CT or PET-MRI.

Analysis of risk factors. The associations between PIF, patient characteristics and treatment related factors were

Table III. Univariate analysis of risk factors for PIF.

Variable	95% CI	P-value
Age, years (≥60)	47-NA	<0.05
BMI, kg/m² (<21)	NA-NA	0.505
Postmenopausal status	NA-NA	0.199
Parity (≥3)	33-NA	0.289
SCC	NA-NA	0.622
FIGO stage (≥III)	33-NA	0.0732
ICBT	36-NA	0.438
Lymph node boost	36-NA	0.188
IMRT	NA-NA	0.125
Definitive radiotherapy	NA-NA	0.0816

PIF, pelvic insufficiency fracture; CI, confidence interval; BMI, body mass index; SCC, squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics; ICBT, intracavitary brachytherapy; IMRT, intensity-modulated radiation therapy; NA, not available.
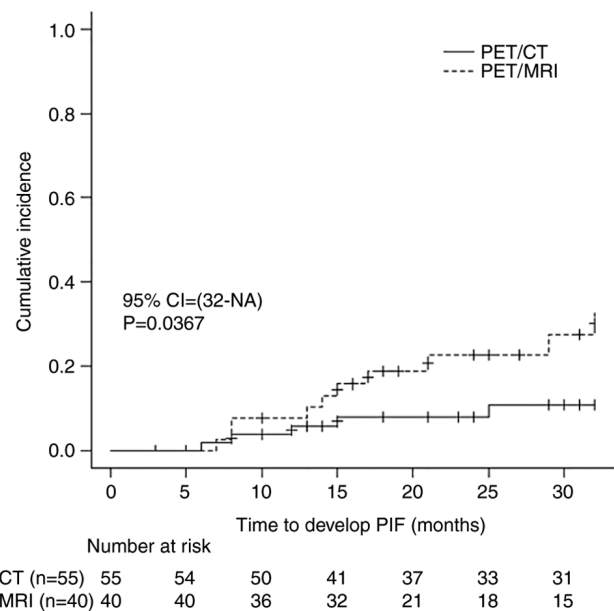

Figure 1. Comparison of the incidence of PIF in PET/CT and PET/MRI during the median follow-up period. The detection time of PIF by PET/MRI was significantly earlier than that by PET/CT. PIF, pelvic insufficiency fracture; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; CI, confidence interval; NA, not available.

assessed (Table III). Univariate analysis using the log-rank test demonstrated that age (≥60 years) was significantly associated with PIF (P<0.05). However, BMI <21, postmenopausal status, parity ≥3, SCC, FIGO stage ≥III, ICBT, a lymph node boost, IMRT and definitive RT were not significant risk factors for developing PIF.

Characteristics of PET/CT and PET/MRI in PIF diagnosis. The association between PIF diagnosis and the method of fracture detection, using either PET/CT or PET/MRI, was assessed. The median maximum standardized uptake value (SUV_{max}) of PIF sites on PET/CT was 4.32 (range, 3.04-4.81) and that on PET/MRI was 3.97 (range, 1.21-5.96), which was not statistically significant (P=0.162; Table II). Kaplan-Meier analysis was performed to compare patients who underwent image follow-up with PET/CT or PET/MRI during the median follow-up period, except for those who underwent both PET/CT and PET/MRI. The results demonstrated that the detection time of PIF by PET/MRI (n=40) was significantly earlier than that of PET/CT (n=55) (P=0.0367; Fig. 1).

A diffuse linear FDG uptake. A diffuse linear FDG uptake was observed in parallel with the sacroiliac joint as a characteristic pattern of sacral fracture (Fig. 2). In addition, the features of FDG uptake were similar between PET/CT and PET/MRI in the present study (Fig. 2). The earliest MR sign, medullary edema, was seen and characterized as T1 hypointensity and T2 hyperintensity (Fig. 3).

Discussion

The results of the present study demonstrated that PET/MRI was useful for early diagnosis of recurrent cervical cancer, and for early detection of PIF compared with PET/CT. Currently, a few studies have investigated the incidence and risk factors of PIF via PET/CT as the imaging method; however, the effects of PET/MRI have not yet been investigated (5,26-28). To the

best of our knowledge, the present study was the first to report the incidence rate and risk factors of PIF via PET/MRI as the imaging method.

Radiation therapy of the pelvis can cause demineralization and decrease elastic resistance of the bone matrix (28). According to a recent meta-analysis, the overall incident rate of PIF was 14% (95% confidence interval, 10-18%, based on 21 studies) (4). The incidence rate of PIF in the present study was 20.8%, which was slightly higher than the meta-analysis. Age has also been reported as a risk factor in several studies (5-11), as well as the present study. However, the results of the present study failed to exhibit significant differences in other risk factors between the groups. This may have been due to the small sample size used in the present study. Previous studies have identified risk factors for PIF, including postmenopausal status (6-8,10,12), low body weight (5,9-11) and osteoporosis (13,14). In the present study, no significant differences were observed between the groups for some parameters such as menopausal status or BMI.

This study was a retrospective study and thus relies on medical records for information. However, data on the presence or absence of osteoporosis was insufficient and thus was not evaluated. Prospective studies are required to incorporate this data by screening patients prior to chemoradiotherapy. It has been reported that rheumatoid arthritis (RA) (12) and HRT (14) are risk factors for PIF. However, the present study was unable to assess the associations between PIF and RA or HRT as only a few patients had RA or had received HRT. Oh *et al* reported that a high radiation dose is a risk factor of PIF (11). At Kobe University Hospital, both EBRT and IMRT are performed during the treatment period in some cases and at the discretion of the radiation oncologist; therefore, it was not possible to calculate the total pelvic irradiation dose by simply adding the irradiation doses together in the present
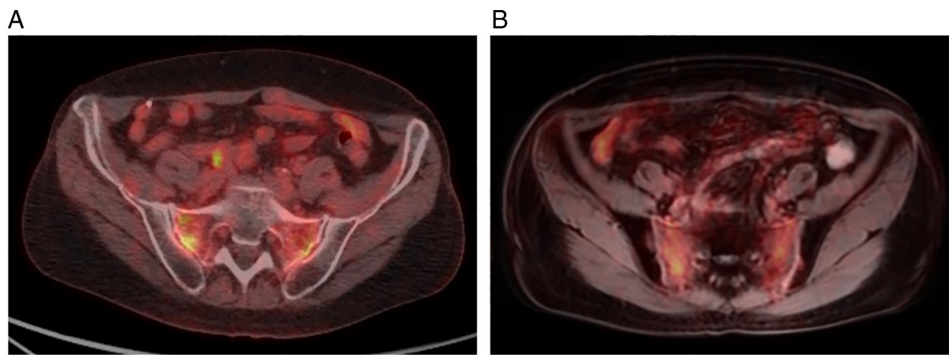
Figure 2. A diffuse linear FDG uptake parallel with the sacrum. The features of FDG uptake were similar between PET/CT and PET/MRI. (A) Patient 11 diagnosed by PET/CT (SUV$_{max}$ 4.11). (B) Patient 19 diagnosed by PET/MRI (SUV$_{max}$ 3.92). FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; SUV$_{max}$, maximum standardized uptake value.
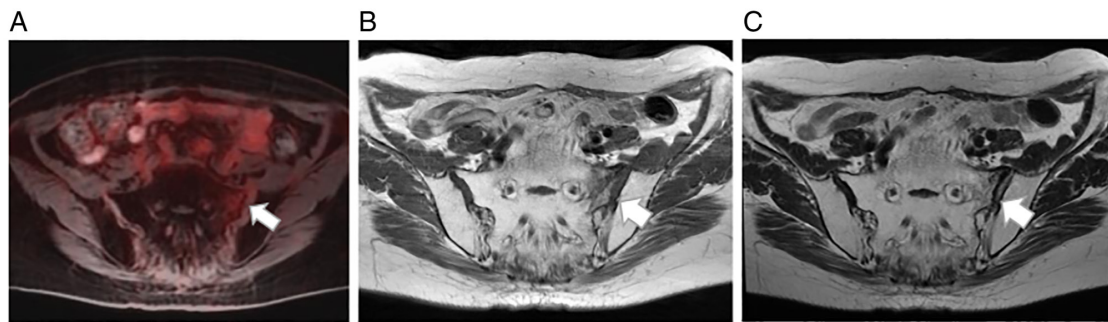

Figure 3. Earliest MR sign. The earliest MR sign, medullary edema, which is characterized as T1 hypointensity and T2 hyperintensity. (A) Patient 22 diagnosed by PET/MRI (SUV$_{max}$ 2.5) (B) T1-weighted image: Hypointensity and (C) T2-weighted image: Hyperintensity on the left side of the sacrum. PET, positron emission tomography; MRI, magnetic resonance imaging; SUV$_{max}$, maximum standardized uptake value.

study. Concurrent chemoradiotherapy is considered a risk factor of PIF; however, no previous studies have identified chemotherapy as a risk factor (7,12,17), and neither did the present study. Ogino *et al* (29) reported that a history of three or more deliveries is a risk factor of PIF, but we did not find a significant difference in the present study. The sacrum is the predominant site of PIF and is reported to account for 73.6% of incidences (4). In the present study, fractures in the sacrum occurred in 27/31 patients (87.0%).

According to some reports, 43-77% of PIF cases are symptomatic, and patients experience pain that affects their quality of life (5,30,31). Maintaining the quality of life for cancer survivors has become an important issue in recent years. It is even more important in patients with cervical cancer as it has a relatively young age of onset and has a long survival time when completely cured (32). According to the results of the present study, 45.2% of patients with PIF were symptomatic. Treatment is generally conservative, with analgesic administration and rehabilitation (33). Early diagnosis and treatment may improve pain, immobilization and thus mortality (33).

Imaging tests are rarely performed to solely diagnose PIF, and PIF is often found when checking the recurrence of cervical cancer. In previous reports, PET/CT was demonstrated to be more sensitive in detecting recurrence or metastasis compared with CT or MRI (34,35) PET/MRI has been reported to exhibit comparable or better performance than PET/CT in detecting the recurrence of gynecologic cancer (36). Furthermore, PET/MRI has the advantage of lesion detection within the

brain, breast, liver, kidneys, bone and pelvic lesion compared with PET/CT (37). In addition, PET/MRI offers the advantage of decreased radiation exposure compared with PET/CT (38). It is important for patients with cervical cancer to not only assess the detection of their recurrent disease but also to avoid the radiation-induced malignancies that can occur during a long follow-up period. Currently, several studies have reported on the usefulness of CT and MRI data in PIF diagnosis (20,22,39), and according to Lapina and Tiškevičius (22), the sensitivity and specificity in PIF diagnosis are 100 and 95.3% for MRI and 74.6 and 89.7% for CT, respectively. Although the characteristics of PET/CT in PIF diagnosis have been previously reported (5,27,28), their value remains unclear. In the present study, 54.8% of patients with PIF were asymptomatic, 70.6% of which were diagnosed by PET-CT or PET-MRI. Conversely, a previous report has indicated that only 39% of patients with asymptomatic PIF were diagnosed by CT or MRI (20).

It has been reported that low-grade FDG uptake is often observed at the fracture site (5). A diffuse linear FDG uptake is observed in parallel with the sacroiliac joint as a characteristic pattern of sacral fracture (Fig. 2). It is important to distinguish between benign and malignant fractures. The SUV$_{max}$ value and the FDG uptake pattern differ between malignant and benign fractures (40,41). These reports are based on PET/CT and cannot be generally applied to PET/MRI; however, the results of the present study demonstrated no significant differences in the degree of SUV$_{max}$ between PET/CT and PET/MRI. In addition, the features of FDG uptake were

similar between PET/CT and PET/MRI in the present study (Fig. 2). Furthermore, the results demonstrated that PET/MRI may detect PIF earlier than PET/CT (Fig. 1). This suggests that the detection time of PIF is earlier in MRI compared with CT (22). According to Grangier *et al* (42), the earliest MR sign, medullary edema, which is characterized as T1 hypointensity and T2 hyperintensity, is seen as early as 18 days after the onset of symptoms and persist as long as 516 days (Fig. 3). These findings suggest that PET/MRI imaging may detect PIF at an earlier stage before patients have developed symptoms compared with PET/CT, CT or MRI alone.

The present study is not without limitations. Given that this study was retrospective, there may be data that has not yet been revealed. Furthermore, the present study failed to conduct a questionnaire to determine whether patients had any symptoms, and only depended on medical records. Thus, patients may have had symptoms, even in cases that were considered asymptomatic. Furthermore, image follow-up was performed mainly for the purpose of checking the recurrence of cervical cancer and not for PIF examination. Given that the specific timing of image follow-up was left to the attending physician, there may have been some variation in the imaging timing for each patient. In addition, the attending physician decided which imaging medium to follow up with, and since it was not randomized, there may have been selection bias. Patients who had many images taken due to recurrence may have had PIF found earlier. There is also the possibility that SUV_{max} may have had different values depending on the elapsed time after fracture. Furthermore, PIF may have been found secondarily during the recurrence check for cervical cancer, and it was not clear when it occurred. In addition, measured SUVs on PET/CT and PET/MRI could be significantly different even in the same patient due to the difference in detectors and reconstruction methods. The present study did not include dose volume histogram. In some cases, both EBRT and IMRT were performed during the treatment period, and it was not possible to calculate the total pelvic irradiation dose simply by adding the irradiation doses. Therefore, it is possible that the prescribed dose was clarified by using the dose volume histogram. It has been reported that high irradiation dose is a risk factor for PIF (30). In the present study, it may have been possible to clarify whether the prescribed dose is a risk factor of developing PIF or not by analyzing the dose volume histogram.

In conclusion, the incidence of PIF after RT for cervical cancer was 20.8% in the present study. Age was significantly associated with the development of PIF. Furthermore, PET/MRI, which offers the advantage of decreased radiation exposure to the patient, may detect PIF at an earlier phase before patients develop symptoms, thus allowing them to undergo early counseling and treatment for bone health and to maintain a better quality of life after cervical cancer treatment. However, further trials and reports are required to establish the usefulness of PET/MRI in PIF cases.

Availability of data and materials

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

Authors' contributions

MA, MM, KS participated in data collection and analyzed and interpreted patient data. RS, YU nad MN analyzed and interpreted the radiological data. YT and MM confirm the authenticity of all the raw data. YT contributed to the study conception and design. MA and YT drafted the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by Kobe University Hospital Clinical and Translational Research Center (IRB no. B200206, October 23rd, 2020). Given that this study was an observational study using existing data, patient consent was waived. All patient data were analyzed retrospectively, and no tissues were examined. However, all study details were disclosed to patients, and they were given the option to refuse registration via e-mail.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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