Risk Factors for Sacral Insufficiency Fractures in Cervical Cancer After Whole Pelvic Radiation Therapy

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Abstract. *Aim: To evaluate the incidence and risk factors of sacral insufficiency fractures (SIFs), particularly dose–volume histogram (DVH) parameters, in patients with cervical cancer after whole pelvic radiation therapy (WPRT). Patients and Methods: The medical records of 61 patients with cervical cancer who underwent WPRT were retrospectively reviewed. The cumulative incidence of SIF, as well as the risk factors that could affect its incidence were assessed. Results: Of the 61 patients, 11 (18%) were diagnosed with SIF, as revealed by computed tomography. Multivariate analysis revealed that abnormal body mass index (BMI) (more than 25 kg/m² or below 18 kg/m²) and administration of five or more chemotherapy cycles were independently associated with SIF. A slight difference was observed in the D50% (the administered dose covering half of the sacrum) between patients with and those without SIF ($p=0.052$). Conclusion: Thus, the D50% of the sacrum should be particularly considered in patients with abnormal BMI and five or more cycles of chemotherapy.*

Whole pelvic radiation therapy (WPRT) or WPRT plus weekly cisplatin is essential for treating gynecological cancers (1, 2). The sacral bone is one of the primary sites affected by WPRT because it is within the central radiation field (3). However, various adverse events, including sacral insufficiency fractures (SIFs), remain relatively unexplored. SIFs are a subgroup of stress fractures resulting from normal or physiological stress applied to weakened bones. The exact incidence of SIF after WPRT remains undetermined; however, several studies have reported that the incidence of SIF is approximately 10-20% and relatively rare in patients

with gynecological, anal, and rectal cancer treated with WPRT (4-7). Previous studies reported that age, low body weight, osteoporosis, and co-medications, primarily corticosteroids and prior-radiotherapy, are risk factors for SIF (8, 9). Regarding radiotherapy, a few previous studies have demonstrated the relationship between the dose–volume histogram (DVH) in therapy with intensity-modulated radiation therapy (IMRT) and the risk for SIF in prostate and gynecological cancer (10-12). IMRT can be used to impose dose constraints on the sacrum; however, it may not be available at all institutions. Few studies that have been conducted using three-dimensional conformal radiation therapy (3D-CRT) comprising the 4-field box technique have established a relationship between DVH and SIF in patients with cervical cancer (7). Here, we aimed to evaluate the incidence and risk factors for SIF, particularly DVH parameters, in patients with cervical cancer after WPRT and when using the 4-field box technique.

Patients and Methods

Eligibility. The medical records of 61 patients with cervical cancer who received WPRT at the Nihon University Itabashi Hospital, Japan, between January 2012 and April 2018 and whose imaging and clinical data for an appropriate observation period (>6 months) were available were retrospectively reviewed. Patients with radiation fields smaller than small pelvic radiation therapy, *e.g.* “tumor plus margin”, as well as patients undergoing palliative radiotherapy and those with pre-existing bone metastases at any site were excluded. Data were retrieved once the detailed imaging and clinical results were included in the electronic medical records in 2012; this allowed for complete evaluation of the patients’ clinical course.

Radiotherapy. All patients underwent computed tomographic (CT) simulation. We conducted 3D-CRT comprising the 4-field box technique (anterior–posterior–right–left side) frequently combined with brachytherapy. IMRT was not used because our hospital has not yet adapted to IMRT for gynecological cancer. Moreover, classical anterior–posterior 2-field radiotherapy was not used because of its reduced effects on the small intestine. WPRT performed with 10-MV photon beams was delivered once daily for 5 days a week. The radiation doses were administered in fractions of 1.8 Gy with a total dose of 50.4 Gy, or of 2 Gy totaling a dose

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of 50 Gy. In addition, a 1.8-Gy dose with a total dose of 45 Gy in 25 fractions was administered to patients without nodal involvement (at low risk) or to those with poor general condition. The landmarks used to plan the 4-field box technique were as follows: Anterior and posterior fields, superior border at L5 (the small pelvis is the bifurcation of the iliac artery, almost at superior S1), lateral borders 1.5-cm lateral to the widest point of the pelvic cavity, and inferior border at the *obturator foramen* (lateral fields, posterior border to *pubic symphysis*). The posterior border was located in half of the sacrum as it covered the lymph node area of the anterior sacrum (the uterosacral region). Figure 1 depicts a typical WPRT field. In the patients who underwent combined brachytherapy, the center shield was inserted from approximately 30 Gy owing to a reduced rectal dose. Figures 2 and 3 illustrate the typical dose distribution of WPRT and WPRT with a center shield. Brachytherapy was conducted once a week with one tandem and two ovoids. The dose per fraction was primarily 6 Gy per week, and the total brachytherapy dose was 24 Gy. Regarding small pelvic irradiation, because the sacrum is included in the same range as the WPRT, the dose of the sacrum was dependent on the total dose. Four patients underwent nodal boost that was delivered distant from the sacrum.

Dose determination of SIF. Because the treatment planning system followed in our hospital was replaced in 2014, we only had access to the treatment plans of 47 out of the 61 patients. Three specific DVH parameters (namely the maximum dose, mean dose, and D50%) of the sacrum were selected for the correlational analysis between dose and SIF. D50% indicates the administered dose covering half of the sacrum volume and is relevant for assessing the overall burden of the dose to the bones. Because the dose to the sacrum provided *via* brachytherapy was difficult to calculate, we planned to analyze the total WPRT and brachytherapy doses separately in the future.

Follow-up and diagnosis of SIF. All patients were clinically examined by a gynecologist and radiotherapist every 3 months. CT scanning of the entire body was performed during routine follow-ups (average 6 months). Magnetic resonance imaging (MRI) was performed based on the patient's clinical indications, for example, when SIF and tumor recurrence were suspected. All patients with SIF were diagnosed using CT; three patients also underwent MRI scanning.

Statistical analysis. The cumulative incidence of SIF was estimated using the Kaplan–Meier method and was defined as the interval from the last day of WPRT until the date of development of sacral pain or the identification of imaging studies *via* reviewing of hospital records. In the case of pain onset prior to imaging, the onset of SIF was defined based on when pain occurred and not when it became clear *via* CT. The risk factors that might affect the incidence of SIF [*i.e.* age, radiation field, brachytherapy, number of births, menopause, body mass index (BMI), and chemotherapy cycle] were assessed using univariate and multivariate analyses. *p*-Values of less than 0.05 were considered statistically significant. DVH analysis results of the sacrum of the 47 available patients were compared using the Mann–Whitney *U*-test. SPSS 15.0 J statistical software (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.

Patient consent. This retrospective study evaluated patient characteristics, diagnoses, and treatment data retrieved from the electronic medical records. The present study was conducted in line

with the ethical guidelines of the 1964 Helsinki declaration and its later amendments or with other comparable ethical standards. Patient records and information were anonymized and de-identified prior to evaluation. Before the start of the treatment, the patients were informed that their data might be used in future investigations, even if they died. All the patients provided consent for their data to be used. The requirement for additional participant consent was waived off owing to the retrospective nature of the study.

Results

Patient characteristics and treatment. A total of 61 patients (median age=56 years; age range=29-83 years) with cervical cancer who were treated using the 4-field box technique were included. Table I summarizes the baseline patient characteristics. SIF did not occur in any patient either post-operatively or after receiving 45 Gy of WPRT. None of the patients with histories of rheumatoid arthritis and autoimmune disease were under corticosteroids. No patient received hormone therapy or *bisphosphonates* during WPRT and the observation period.

Incidence and characteristics of SIF. The median follow-up duration was 14 (range=6-75) months. Using CT, 11 (18%) out of the 61 patients were diagnosed with SIF. The median time from the end of WPRT to the diagnosis of SIF was 8 months (range=6-19 months). The cumulative incidence of SIF at 5 years was 27.2%. Specific fractures that coursed the vertical fracture line in the sacral *alae* parallel to the sacroiliac joint and bone sclerosis were considered diagnostic criteria for SIF (Figure 4). One patient experienced a *pubis* fracture in association with SIF. Three out of the 11 (27%) patients with SIF had symptomatic lesions; however, SIFs spontaneously healed with a conservative treatment regimen comprising non-steroidal anti-inflammatory drugs and rest.

Analysis of risk factors. In multivariate analysis, abnormal BMI (*i.e.* more than 25 kg/m² or below 18 kg/m²) [hazard ratio (HR)=9.301; 95% confidence interval (CI)=2.303-37.566; *p*=0.002] and receipt of five or more chemotherapy cycles (HR=5.569; 95% CI=1.089-28.476; *p*=0.039) were independently associated with SIF (Table II). Menopausal status when receiving WPRT was slightly associated with SIF in the univariate analysis (*p*=0.081), but not significantly in the multivariate analysis. Age, dose, brachytherapy, and parity were not significantly associated with SIF either in the univariate or multivariate analyses. It was impossible to statistically evaluate the association between the total dose (45 Gy *vs.* 50 or 50.4 Gy) and treatment methods (WPRT plus brachytherapy *vs.* WPRT after operation) because none of the patients (45 Gy, WPRT after operation) developed SIF.

DVH analysis. Because the treatment planning system followed in our hospital was replaced in 2014, we evaluated

Figure 1. The 4-field box technique plan. Anterior defined superior border at L5, lateral borders at 1.5-cm lateral to the widest point of the pelvic cavity, and inferior border at the obturator foramen on digitally reconstructed radiography (left). The irradiation field from the anterior and posterior sides completely covered the sacrum; therefore, the dose to the sacrum could not be adjusted. Lateral fields comprised anterior border to the posterior surface of the pubic symphysis (right). The posterior border was positioned to 50% of the sacrum to cover the lymph node area of the anterior sacrum (i.e. the uterosacral region). Only the lateral beam was able to adjust the dose to the sacrum.

Figure 2. Dose distribution of whole pelvic radiation therapy (WPRT). Isodose lines of 95% (yellow), 80% (light green), and 50% (blue) of WPRT on computed tomographic imaging (left and right).

Figure 3. Dose distribution of whole pelvic radiation therapy (WPRT) with center shield. The caudal portion of the sacrum is shielded when using a short center shield (left). When using a long center shield, only the central part of the sacrum is shielded (right). The majority of sacrum insufficiency fractures are located near the sacroiliac joint, which is not covered by the center shield.

Table I. Baseline clinical characteristics of patients (n=61).

Characteristic	Value	Number of SIFs
Age, years		
Median (range)	55 (29-83)	
<55	31 (51)	3
≥55	30 (49)	8
PS		
0	5 (8)	1
1	55 (90)	10
2	1 (2)	0
Stage ^a		
Ib	8 (13)	1
IIa	6 (10)	0
IIb	5 (8)	1
IIIa	5 (8)	2
IIIb	30 (49)	5
IVa	2 (4)	1
IVb	5 (8)	1
Total dose (Gy)		
45	19 (31)	0
50 or 50.4	42 (69)	11
Radiation field		
Small pelvis	5 (8)	1
Whole pelvis	56 (92)	10
Brachytherapy		
Yes	46 (75)	10
No	15 (25)	1
Number of births		
0-1	26 (43)	5
≥2	35 (57)	6
Operation		
Yes	19 (31)	0
No	42 (61)	11
Menopause		
Yes	34 (56)	9
No	27 (44)	2
BMI		
<18	10 (16)	4
>25	8 (13)	3
18-25	43 (71)	4
Chemotherapy cycles		
≥5	28 (46)	8
<5	33 (54)	3

PS: Performance status, BMI: body mass index, SIF: sacrum insufficiency fractures. ^aTNM classification 7th edition.

only 47 out of the 61 patients. The median sacral volume was 215 cc (range=164-337 cc). DVH analysis of the sacrum derived from the CT datasets revealed median maximum and mean doses as well as D50% of 51.0 Gy (range=45.3-57.5 Gy), 39.7 Gy (range=32.5-45.4 Gy), and 41.5 Gy (range=33.9-52.7 Gy), respectively. Seven out of the 47 patients were diagnosed with SIF. The Mann-Whitney *U*-test revealed no significant differences between the mean and maximal sacral doses between patients with and those without SIF. The median D50% was 41.1 Gy for the patients

Table II. Analyses of the risk factors for sacral insufficiency fractures as revealed by univariate and multivariate analyses.

Variable	Univariate analysis <i>p</i> -Value	Multivariate analysis		
		HR	95% CI	<i>p</i> -Value
Age				
<55 Years	0.174	1	0.203-7.668	0.811
≥55 Years		1.248		
Radiation field				
Small pelvis	0.937	1	0.025-7.937	0.579
Whole pelvis		2.265		
Brachytherapy				
No	0.295	1	0.016-5.848	0.433
Yes		3.248		
Number of births				
0-1	0.419	1	0.093-2.088	0.302
≥2		2.269		
Menopause				
No	0.081	1	0.022-1.602	0.126
Yes		5.374		
BMI				
18-25 kg/m ²	0.006	1	2.303-37.566	0.002
<18 or >25 kg/m ²		9.301		
Chemotherapy cycles				
<5	0.126	1	1.089-28.476	0.039
≥5		5.569		

BMI: Body mass index, HR: hazard ratio, CI: confidence interval.

without SIF and 43.7 Gy for those with SIF. A borderline significant difference in D50% was noted between those with SIF and those without (*p*=0.052).

Discussion

SIF is a type of fracture that occurs when physiological stress is applied to weakened bones and is characterized by cytoplasmic swelling and decreases in bone marrow cells and elastic resistance of bone matrix (4, 13). Incorrect diagnosis can lead to unnecessary clinical examinations and treatments being performed. It is particularly important to investigate the characteristics and risk factors of SIF after WPRT. The reported incidence of SIF after WPRT varies from 10% to 40% mainly due to differences in diagnostic examination methods, criteria of diagnosis, presence or absence of symptoms, and frequency/timing of follow-up scans (3, 10, 14, 15). Ogino *et al.* reported an estimated 5-year cumulative risk of 17.9% of symptomatic SIF in patients who underwent WPRT for cervical cancer (7). In previous studies, SIF was identified by bone scanning in 34% cases and by MRI in 25% cases; 89% of the results differed owing to differences in the diagnostic methods and criteria for gynecological cancer (14, 16). In the present study, the occurrence of SIF, both symptomatic and asymptomatic, was 18% (11/61),

Figure 4. Sacral insufficiency fractures on computed tomography (CT) image. CT scan demonstrating fracture lines with sclerosis of the sacral alae at the level of the mid-sacrum with window settings adjusted for bone visualization (left). In another patient, CT images show loss of cortical bone integrity in the left portion of S1 (white arrow, right).

which is lower than that previously reported using primarily MRI; this is because diagnostic examinations in our study were performed using only CT. MRI has a high sensitivity in demonstrating bone edema and frequently reveals a fracture line in a typical location associated with SIF (16, 17). We conducted MRI for only three patients who had lower pelvic pain. However, in patients without signs of recurrence or pelvic pain, we conducted examinations using CT as well as tumor markers and did not use MRI. In clinical practice, it is unreasonable to perform MRI alone for the evaluation of SIF. Cabarrus *et al.* evaluated SIF and found the overall sensitivities of MRI and CT to be 100% and 74.6%, respectively (18). However, in the presence of a fracture line, the detection rates of both CT and MRI were approximately the same (MRI, 95.3%; CT, 89.7%). Evidently, MRI is superior to CT; however, CT may also be sufficient if SIF is doubtful and if careful observation is performed. Pelvic pain was reported in approximately 40% of the patients with SIF (3, 19). In our study, only three (27%) out of the 11 patients evaluated for SIF reported symptoms, fewer than those reported in a previous study (3, 19). Some past studies reported that symptomatic SIF spontaneously healed with conservative treatment (20, 21). If the interval of medical examination is long, mild pelvic pain may spontaneously heal and the patient may not notice or report it at the time of medical examination.

SIF frequently occurs in post-menopausal women with osteoporosis (22). Other risk factors for SIF include rheumatoid arthritis, corticosteroid usage, diabetes mellitus, parity, Paget's

disease, hyperparathyroidism, low body weight, and radiation therapy; these factors reduce the elastic resistance of the bone matrix (4, 13, 23). Of these factors, WPRT is the most common in elderly post-menopausal women (24).

Damage to the sacrum considerably depends on the radiation field and brachytherapy, total dose, fractionation and treatment duration (8, 25). Several studies have reported that the incidence of SIF increases when the dose is increased above the threshold of 40 Gy (15, 26). In the present study, an external dose (45-50.4 Gy) was delivered to the sacrum using the 4-field box technique. The median D50% was 41.1 Gy for patients without SIF and 43.7 Gy for those with; this difference was of borderline significance. There was no significant difference between the maximal and mean sacral dose between the two groups. These results indicate that SIF is not caused by a high dose to a small part of the sacrum, rather it is caused by an increased dose to the entire sacrum. The irradiation field from the anterior and posterior sides completely covers the sacrum; therefore, the dose to the sacrum cannot be adjusted. It is the lateral beam that affects the dose to the sacrum. In order to completely cover the lymph node area in the front of the sacrum (*i.e.* the uterosacral region) without administering lower doses, 50% of the sacrum was included in the irradiation field in our study. IMRT can be used to impose dose constraints on the sacrum; however, it may not be available at all institutions. Therefore, we suggest that the lateral beam of WPRT using the 4-field box technique, which shields 50% of the posterior portion of the sacrum, should be used to reduce the sacral

D50% without under-dosage. In the case of patients who underwent WPRT and brachytherapy, anterior–posterior to opposing irradiation used approximately 20-30 Gy of radiation with a center shield. The center shield reduces not only the rectal dose but also that to the sacrum. However, depending on how much of the center shield was inserted, the sacrum may be shielded in the caudal portion and not lead to reduction in sacral D50%. Furthermore, only the central part of the sacrum is shielded by the center shield; the majority of SIFs are located near the sacroiliac joint, which is not covered by the center shield. Therefore, we conclude that use or not of a center shield does not affect the occurrence of SIF.

Low body weight is reportedly related to SIF owing due to risk of osteoporosis (7). However, in this study, an abnormal BMI, which indicates not only low body weight but also obesity, was considered an important risk factor for SIF. SIFs assumedly occur due to the weight of the upper body and the spine transmitting this weight to the sacrum (27). Previous studies reported that several SIFs were located in near the sacroiliac joint, which may reflect the distribution of the weight-bearing strain of the sacrum (11). These studies indicate that if the weight of the upper body is large, the burden on the sacrum also increases, resulting in SIF. SIF influences pubic fractures owing to an increased anterior arch strain secondary to the initial failure of the posterior arch. Several studies have revealed that pubic fractures are associated with SIF in approximately 30% of cases (4, 28). In our study, one out of the 11 (9%) patients with SIF had complications related to asymptomatic pubic bone fractures. This frequency is low compared with that reported in a previous study and can be attributed to the small number of patients with SIF using CT as the only diagnostic technique. Upon detecting SIF, attention needs to be drawn to the possibility of pubic bone fractures.

In the present study, receipt of five or more chemotherapy cycles was considered an important risk factor for SIF. However, the influence of chemotherapy on SIF remains controversial. The extent of cellular and sacral damage depends on concomitant or adjuvant chemotherapy (8, 25). Gondi *et al.* reported a relationship between SIF and the administration of chemotherapy (29). Some other studies did not find any significant relation between the administration of chemotherapy and SIF (4, 30, 31). Although it was difficult to interpret significant differences in the chemotherapeutic cycles in our study, it is possible that SIF may be affected by long-term anticancer drug administration, thereby resulting in poor nutritional status and decreased bone mass. Moreover, age, number of births, radiation field, brachytherapy, and menopause were evaluated as potential predictors of SIF; however, we did not identify any significant association among these factors, probably due to the small number of events involved.

The key limitations of this study include its retrospective design and the small number of patients who underwent WPRT. Because the treatment planning system followed at our hospital was replaced in 2014, we were only able to verify the DVH treatment plans of 47 patients. Due to the retrospective nature of this study, the protocols for follow-up and medical examinations were variable. Because routine follow-up CT scanning was usually performed at 6-month intervals, the incidence of asymptomatic SIF may have been underestimated and the period until the appearance of a fracture may have been unclear. These limitations should be addressed in future studies.

Conclusion

In summary, 11 out of the 61 (18%) patients who underwent WPRT were diagnosed with SIF by CT alone. Therefore, we suggest reducing the dose to the sacrum using the lateral beam in the 4-field box technique without underdosing the uterosacral region, particularly in those patients at risk due to abnormal BMI and receiving five or more cycles of chemotherapy.

Competing Interests

The Authors have no financial disclosures.

Conflicts of Interest

The Authors declare no conflicts of interest in regard to this study.

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