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Pelvic insufficiency fractures after whole pelvic irradiation for uterine cervical cancer

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Summary

Pelvic insufficiency fractures (PIFs) are not a rare complication among patients with uterine cervical cancer treated by radiotherapy. The authors evaluated the rates of and risk factors for PIF after radiotherapy for cervical cancer at their institution. They enrolled 97 patients in this retrospective study. The median prescribed dose to the whole pelvis was 45 (range, 39.6-50.4) Gy. The median follow-up period was 26 months. PIF was detected at 23 sites in 15 patients (15.5%). A total of six of the 15 PIF patients (40.0%) had pain due to PIF. The cumulative PIF rates at one, two, and three years after radiotherapy were 9.0%, 16.3%, and 18.7%, respectively. Prescribed dose was the only risk factor associated with PIF in multivariate analysis. In most PIF patients, with pain is mild and can be controlled with nonsteroidal anti-inflammatory drugs. Physicians should have sufficient knowledge about PIF in order to conduct an accurate medical interview.

Key words: Uterine cervical cancer; Radiotherapy; Insufficiency fractures; Adverse event.

Introduction

Radiotherapy plays an important role in the treatment of uterine cervical cancer. The outcomes of radiotherapy in patients with Stage I and II cervical cancer are comparable to the outcomes of surgery [1-2]. For patients with Stage I to II with bulky mass or patients with Stage III to IV cancer, concurrent chemoradiotherapy is effective [3]. After surgery, adjuvant radiotherapy is indicated for patients with certain risk factors [4-6]. Patients with cervical cancer have a relatively good prognosis compared to those with other types of cancer. Many patients with cervical cancer achieve long-term survival. Therefore, it is very important to reduce the risks of late adverse events in this population. Gastrointestinal disorders are the most common late adverse event in patients with cervical cancer who have received radiotherapy [7]. Pelvic insufficiency fracture (PIF) is another important adverse event. PIF is seen as an H-shaped pattern on bone scintigraphy [8]. On magnetic resonance image (MRI), PIF is seen as a high-intensity signal on T1-weighted images and a low-intensity signal on T2-weighted images [9].

The authors evaluated the rates of and risk factors for PIF after radiotherapy for cervical cancer at their institution.

Materials and Methods

Between February 2010 and September 2014, 140 patients with cervical cancer received radiotherapy at the present institution, of whom 97 had evaluable the post-radiotherapy images after six months of therapy and were enrolled in this retrospective study. This study was approved by the institutional review board. All patients provided informed written consent before radiotherapy. Thirty-four patients (35.0%) received definitive radiotherapy and 63 patients (65.0%) received surgery followed by postoperative radiotherapy. Patient characteristics are shown in Table 1. Radiotherapy was performed using a 10-MV photon beam. The four-field box technique was used.

In patients treated with definitive radiotherapy, the middle block (MB) was inserted from the mid-course of radiotherapy. In these cases, the anteroposterior/posteroanterior technique was used after MB insertion. The upper border of the irradiated field was the bifurcation of the common iliac arteries. The lower border was the bottom of the obturator foramen or two to three cm below the lowest extent of cervical or vaginal disease. The lateral borders were placed one to two cm beyond the lateral margins of the bony pelvis. The prescribed dose per fraction was 1.8 or 2.0 Gy, five times a week. If required, patients received weekly cis-diamminedichloroplatinum as concurrent chemoradiotherapy.

PIF was defined as follows: (1) demonstration of fracture lines or increased sclerosis without osteolytic lesions on computed tomography (CT), (2) findings of decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images without soft tissue mass on MRI (Figure 1).

The time until the detection of PIF was calculated from the time of completion of radiotherapy. The incidence of PIF was calculated using the Kaplan-Meier method. The Cox proportional hazard model was performed as both univariate and multivariate analyses to evaluate the risk factors for PIF. The independent variables were age, sex, body weight, serum calcium level before radiotherapy, number of childbirths (less than two versus more than three), prescribed dose, and presence or absence of concurrent chemotherapy. Multivariate analysis was performed for variables with a p-value of < 0.10 in univariate analysis. A p-value of < 0.05

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Table 1. — *Patient characteristics (n = 97 patients).*

Median age (range) (years)		57 (29-89)
Aim of radiotherapy	Definitive	34
	Postoperative	63
Median body weight (range) (kg)		50.9 (32.0-107.0)
Histology	Squamous cell carcinoma	77
	Adenocarcinoma	14
	Others	6
T classification	T1b1	30
	T1b2	18
	T2a	11
	T2b	27
	T3a	0
	T3b	7
	T4	4
Serum calcium at the beginning of radiotherapy (range) (mg/dl)		9.2 (7.9-11.1)
Numbers of delivery	Two or fewer	70
	Three or more	27
Median prescribed dose (range) (Gy)		45 (39.6-50.4)

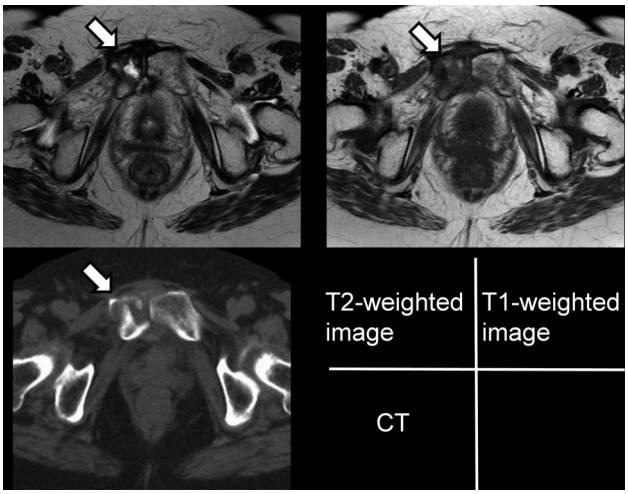

Figure 1. — Pelvic MRI shows a high-intensity signal in the T2-weighted image and a low-intensity signal in the T1-weighted image in the right pubis. Pelvic CT shows cortical fractures in the right pubis.

Table 2. — *Summary of univariate analysis.*

Parameters	Hazard Ratio (95% CI†)	*p* value
Age	1.030 (0.997-1.064)	0.0724
Body weight	0.959 (0.905-1.016)	0.1593
Serum calcium	1.008 (0.347-2.930)	0.9881
Numbers of delivary (<3 *vs*. ≥3)	2.937 (1.057-8.157)	0.0387
Pathology (SCC *vs*. others)	0.737 (0.234-2.316)	0.6015
Prescribed dose	1.384 (1.123-1.706)	0.0023
Concurrent chemotherapy (yes *vs*. no)	2.566 (0.721-9.132)	0.1455

†CI: confidential interval, SCC: squamous cell carcinoma.

Table 3. — *Summary of multivariate analysis.*

Parameters	Hazard Ratio (95% CI†)	*p* value
Age	1.023 (0.985-1.062)	0.2465
Numbers of delivary (<3 *vs*. ≥3)	2.183 (0.760-6.277)	0.1472
Prescribed dose	1.356 (1.094-1.679)	0.0053

†CI: confidential interval.

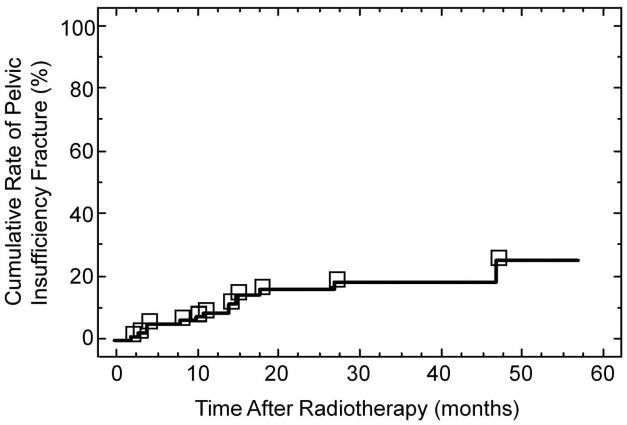

Figure 2. — Overall incidence of pelvis insufficiency fracture after radiotherapy in patients with cervical cancer.

was considered significant.

Results

The median follow-up period was 26 months. PIF was detected at 23 sites in 15 patients (15.5%). The most frequent site of PIF was the sacrum. Five patients (33.3%) developed multiple PIFs. Although six of 15 patients (40.0%) with fracture had pain due to PIF, the degree of pain was mild.

The median time from the completion of radiotherapy until the detection of PIF was 11 (range, 2-47) months. The cumulative PIF rates at one, two, and three years after radiotherapy were 9.0%, 16.3%, and 18.7%, respectively (Figure 2).

In univariate analysis, the number of childbirths and prescribed dose were significantly correlated with the PIF rate (Table 2). The variables with *p*-values < -0.10 in univariate analysis were included in the multivariate analysis, which showed that prescribed dose was the only risk factor associated with PIF (Table 3).

Discussion

PIF developed in 15.5% of patients in the present study. Previously reported PIF rates after radiotherapy for cervical cancer ranged from 1.7% to 35.6% [9-16], which is in line with the present results. The cumulative PIF rate in this study was also similar to these reported rates. The median time until the detection of PIF was 11 months; most PIFs occurred within two years after the completion of radiotherapy. However, the latest occurrence of PIF in this study was approximately four years after completion of radiotherapy. There is a previous report of PIF that occurred seven years after the completion of radiotherapy [9]. Therefore, long-term follow-up assessment is needed. The incidence of PIF with pain ranges from 43% to 82% [9-11]. The incidence of PIF with pain was 40.0% in the present study and was assessed by carefully checking the medical charts. However, most patients had mild pain and might not have reported it to their physicians. Most pain due to PIFs can be managed with rest and nonsteroidal anti-inflammatory drugs.

In univariate analysis, the number of childbirths and the prescribed dose were significantly associated with the PIF rate. Estrogen acts through high-affinity estrogen receptors in osteoblasts and osteoclasts to restrain bone turnover. When estrogen levels decrease, there is less restraint of bone turnover [17]. Slemenda *et al.* reported that bone loss was significantly associated with lower estrogens levels [18]. However, there are reports that estrogen levels are not associated with fracture risk [19-20]. In a study conducted in postmenopausal women, Maataoui *et al.* reported that the number of years since menopause is the best predictor of vertebral fractures [21]. This suggests that a long-term low-estrogen state increases the risk of fracture. In the current study, patients with longer periods of low estrogen levels might have been at higher risk of PIF. In multivariate analysis, the prescribed dose to the whole pelvis was the only significant risk factor.

This study has some limitations. In patients who were treated with definitive radiotherapy, the MB was inserted at the mid-course of radiotherapy, and these patients received high-dose-rate intracavitary radiotherapy. Because the dose irradiated to the bone was unclear, it was not considered in this study. This study was retrospective in nature and was performed by carefully checking medical charts. As mentioned previously, patients with mild pain might not have reported this pain to their physicians. Therefore, the actual rate of painful PIF in the present study could have been higher. Furthermore, the effect of lactation was not analyzed.

Conclusion

PIF is not a rare adverse event in patients with cervical cancer who have received radiotherapy. In most PIF patients who report pain, it is mild. However, these patients might not report this pain to their physicians, which means that a treatment opportunity could be missed. Most cases of PIF can be controlled with nonsteroidal anti-inflammatory drugs. Physicians are required to have sufficient knowledge about PIF in order to conduct an accurate medical interview.

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