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# Pelvic fractures after definitive and postoperative radiotherapy for cervical cancer: A retrospective analysis of risk factors

Kasumi Yamamoto, Shoji Nagao *, Kazuhiro Suzuki, Ai Kogiku, Tokihiro Senda, Hiroko Yano, Miho Kitai, Takaya Shiozaki, Kazuko Matsuoka, Satoshi Yamaguchi

*Department of Gynecologic Oncology, Hyogo Cancer Center, 13-70 Kitaoji-cho, Akashi-city, Hyogo 673-8558, Japan*

## HIGHLIGHTS

- The incidence of pelvic fracture was 15.8% in women with cervical cancer received radiotherapy.
- Pelvic fracture was diagnosed after a median of 14 months from the completion of radiotherapy.
- The predisposing factors were postmenopausal status, rheumatoid arthritis, and brachytherapy.
- Active interventions are necessary for women with high-risk factors.

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## ABSTRACT

*Objectives.* This study clarified the incidence of and identified the risk factors for post-radiation pelvic insufficiency fractures (PIFs) in women who received postoperative definitive or adjuvant radiotherapy (RT) for cervical cancer.

*Patients and methods.* The medical records and data of imaging studies, including computed tomography scan and magnetic resonance imaging, of women with cervical cancer who received external-beam RT for the entire pelvic area between January 2003 and December 2012 at our institution were reviewed.

*Results.* A total of 533 patients with histologically diagnosed cervical cancer who received RT (298: definitive RT, 235: adjuvant RT) were included in this study. Eighty-four patients (15.8%) developed PIF in the irradiated field. Median age at onset of PIF was 72.5 years (range: 54–95 years), and 82 of them (98%) were postmenopausal women. Sixty-nine patients (80%) developed PIF within 3 years from the completion of RT. The median time for the development of PIF was 14 months (range: 1–81 months). The most commonly involved fracture site was the sacral bone. Postmenopausal state, coexistence of rheumatoid arthritis, and high-dose-rate intracavitary brachytherapy (HDR-ICBT) use were significant predisposing factors for the development of PIF, according to multivariate analysis.

*Conclusions.* The incidence rate of PIF among patients who received RT for locally advanced cervical cancer was 15.8%. The principal predisposing factors for post-radiation PIF were postmenopausal state, rheumatoid arthritis, and HDR-ICBT use. Active interventions, including bone density screening followed by medication, should be considered during the early stage of RT for women with high-risk factors of PIF.



## 1. Introduction

The incidence of radiotherapy (RT)-induced pelvic insufficiency fractures (PIFs) in patients with gynecologic cancer is 10%–29% [1–5]. PIF is a late-onset complication of RT in patients with cervical cancer. It may cause refractory pain and frequently impair the quality of life of patients for a prolonged period. Hence, RT-induced PIF in patients with cervical cancer is one of the urgent issues to be resolved.

The first step to preventing PIF is to appropriately identify high-risk women for PIF. However, most previous studies on PIF among patients with cervical cancer have confined their research to definitive RT-induced PIF. Information on PIF, including both adjuvant and definitive RT-induced PIF, is lacking.

The objective of this study was to clarify the incidence of and identify the risk factors for RT-induced PIF in patients who received definitive or postoperative adjuvant RT for locally advanced cervical cancer.

* Corresponding author.
*E-mail address:* nagao@hp.pref.hyogo.jp (S. Nagao).

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## 2. Patients and methods

### 2.1. Study population

After institutional review board approval was obtained, we reviewed the medical records of women with cervical cancer who had received external-beam RT (EBRT) for the entire pelvis between January 2003 and December 2012 at our institution. These women included both patients who received postoperative adjuvant RT and definitive RT. Patients with PIF at the beginning of RT were excluded. We reviewed the medical records and extracted the patient clinical information according to the STROBE statement [6].

### 2.2. Follow-up and diagnosis of PIF

After the completion of RT, all patients received radiological imaging tests, including computed tomography (CT) and magnetic resonance imaging (MRI), twice a year for the first 2 years and yearly for the next 3 years. We identified PIFs using the following diagnostic criteria: a bony lesion with an apparent fracture line with or without sclerotic changes within the irradiated field. Fractures secondary to bone metastasis were excluded.

### 2.3. Radiation therapy

The definitive RT protocol followed at our hospital comprises a combination of EBRT and high-dose-rate intracavitary brachytherapy (HDR-ICBT) using a remote afterloading system, concurrent with or without chemotherapy. A total dose of 30–41.4 Gy of EBRT administered at 1.8 Gy per fraction, followed by HDR-ICBT and EBRT with central shielding (CS) up to a total external dose of 50–50.4 Gy, was delivered over 5 to 6 weeks. Usually, EBRT was delivered using the four-field box technique, except for elderly or obese patients, in whom the anteroposterior/posteroanterior (AP/PA) field technique was used. Two-to-four fractions of HDR-ICBT at 5–6 Gy per fraction were administered to point A. Patients with normal organ function received 5–6 cycles of concurrent chemotherapy comprising weekly cisplatin (40 mg/m$^2$) or weekly nedaplatin (30 mg/m$^2$). Intravenous and oral steroids were administered before chemotherapy.

For postoperative adjuvant therapy, patients with a high risk of pelvic recurrence received 50.4 Gy at 1.8 Gy per fraction of EBRT for the entire pelvic field, using the four-field box technique. Patients with a high risk of vaginal stump recurrence received 30.6 Gy at 1.8 Gy per fraction of EBRT using the four-field box technique, followed by 19.8 Gy at 1.8 Gy per fraction of EBRT using the AP/PA field technique for the same field, with CS and 24 Gy at 6 Gy per fraction of HDR-ICBT to point A. In patients with positive para-aortic nodes, the RT fields were extended up to the levels of the involved lymph nodes. Chemotherapy was administered concurrently in patients with positive pelvic nodes, pathological parametrial invasion, and non-squamous cell carcinoma histology.

### 2.4. Data analysis

We calculated the temporal rates of PIF using the Kaplan–Meier method. Risk factors for PIF, including age, menopausal status, diabetes mellitus, rheumatoid arthritis, RT technique, chemotherapy use, and HDR-ICBT use, were assessed using the log-rank test (univariate analysis) and Cox regression analysis with hazard models (multivariate analysis). Factors with a difference in $p$-values of $<0.005$ were considered significant. Statistical analysis was performed using IBM SPSS statistics Version 22.0 (IBM Corp.; Armonk, New York, USA).

## 3. Results

Of 561 patients with cervical cancer who underwent whole pelvic radiation therapy at Hyogo Cancer Center between January 2003 and December 2012, 533 patients were included in this study. Twenty-eight patients who received CT or MRI only once during the follow-up period were excluded from the study. Among the study patients, 298 received definitive RT and 235 received adjuvant RT after surgery. Patient characteristics are shown in Table 1. Eighty-four (15.8%) of 533 patients developed PIF in the irradiated field during a median follow-up period of 49 months (range: 6–143 months). The median age of the patients who developed PIF was 72.5 years (range: 54–95 years), and 82 of them (98%) were postmenopausal women. By contrast, the median age of patients without PIF was 55 years. No fracture occurred in patients who received hormone replacement therapy. Only 39% of non-fracture cases received definitive RT, whereas 70% of the fracture cases received definitive RT. In total, 30 patients underwent irradiation for the enlargement of para-aortic lymph nodes.

PIF was diagnosed after a median of 14 months (range, 1–81 months) from the completion of RT (Fig. 1). Sixty-nine patients (82.1%) developed PIF within 3 years. The distribution of PIFs (includes overlap cases) was as follows: sacrum in 39 (46.4%), pubis in 27 (32.1%), lumbar spinal vertebra in 25 (29.8%), sacroiliac joint in 22 (26.2%), ilium in 11 (13.1%), and femoral head in 4 (4.8%) women. Multiple fractures developed at initial diagnosis in 51(60.7%) patients.

In 84 women with PIF, 25 (29.7%) required NSAIDs and 20 (23.8%) required an opioid combined with NSAIDs. These 45 women (53.5%) may have suffered from pain. Furthermore, 6 (9.4%) of 84 women required hospitalization for pain control.

No woman underwent surgical treatment. In contrast, 16 women with PIF, identified base on imaging findings, had no symptoms relevant to PIF-induced pain.

In the univariate analysis using the log-rank test, age ≥ 70 years ($p < 0.0001$), postmenopausal state ($p < 0.0001$), HDR-ICBT use ($p < 0.0001$), history of previous delivery ($p = 0.0260$), body mass index ≥20 kg/m$^2$

**Table 1**
Patient characteristics.

| | Non-PIF ($N = 449$) | PIF ($N = 84$) | $p$-Value |
|---|---|---|---|
| Median age (range) | 55.0 (25–89) | 72.5 (54–95) | <0.0001 |
| Median body mass index (range) | 21 (14–36) | 22 (15–31) | 0.290 |
| Postmenopausal state | 250 (57%) | 82 (98%) | 0.737 |
| Prior HRT | 33 (7%) | 0 (0%) | 0.014 |
| Smoking | | | |
| Current/past | 91 (20%) | 9 (11%) | |
| Never | 250 (56%) | 61 (72%) | 0.014 |
| Unknown | 108 (24%) | 14 (17%) | |
| Medical history | | | |
| Diabetes mellitus | 24 (5%) | 12 (14%) | 0.897 |
| Rheumatoid arthritis | 3 (1%) | 5 (6%) | 0.768 |
| FIGO stage | | | |
| I | 151 (34%) | 9 (11%) | |
| II | 152 (34%) | 34 (40%) | 0.004 |
| III | 97 (22%) | 28 (33%) | |
| IV | 49 (10%) | 13 (16%) | |
| Histopathology | | | |
| Squamous cell carcinoma | 328 (73%) | 65 (78%) | |
| Adenocarcinoma | 71 (17%) | 6 (7%) | |
| Adenosquamous carcinoma | 11 (2%) | 3 (4%) | 0.408 |
| Neuroendocrine carcinoma | 10 (2%) | 1 (1%) | |
| Unknown | 29 (6%) | 9 (10%) | |
| Radiation therapy | | | |
| Adjuvant RT | 96 (21%) | 9 (11%) | |
| Adjuvant CCRT | 177 (40%) | 16 (19%) | |
| Definitive RT | 44 (10%) | 21 (25%) | <0.0001 |
| Definitive CCRT | 132 (29%) | 38 (45%) | |
| HDR-ICBT | 178 (40%) | 60 (71%) | <0.0001 |

PIF: pelvic insufficiency fracture, HRT: hormone replacement therapy, RT: radio therapy, CCRT: concurrent chemoradiotherapy, HDR-ICBT: high-dose-rate intracavitary brachytherapy.

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