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Pelvic Fractures After Radiotherapy for Cervical Cancer:

Implications for Survivors

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Abstract

BACKGROUND—The incidence of pelvic fractures and associated risk factors was determined in women treated with curative-intent radiotherapy for cervical cancer.

METHODS—The records of 516 women treated with curative-intent radiotherapy for cervical cancer between 2001 and 2006 at the University of Texas M. D. Anderson Cancer Center were reviewed. Among these, 300 patients had at least 1 post-treatment computed tomography scan or magnetic resonance imaging study available for review, and they comprised our study population. All imaging studies were re-reviewed by a single radiologist to evaluate for fractures.

RESULTS—Pelvic fractures were noted in 29 of 300 patients (9.7%). Fracture sites included sacrum (n = 24; 83%), sacrum and pubis (n = 3; 10%), iliac crest (n = 1; 3%), and sacrum and acetabulum (n = 1; 3%). Thirteen patients (45%) were symptomatic, with pain being the most common presenting symptom. The median time from the completion of radiotherapy to the detection of fractures on imaging studies was 14.1 months (range, 2.1–63.1 months), with 38% of patients diagnosed within 1 year and 83% diagnosed within 2 years of completing therapy. The median age of the patients at diagnosis was higher in the women who developed a fracture compared with the women who did not (56.5 years vs 46.7 years; $P = .04$). A higher number of women with a fracture were postmenopausal (62% vs 37%; $P = .03$). The median body mass index was lower in the women who had a fracture (26.0 kg/m² vs 28.0 kg/m²; $P = .03$).

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

CONCLUSIONS—Pelvic fractures were detected in a substantial proportion of women after radiotherapy for cervical cancer. Bone mineral density screening and pharmacologic intervention should be considered in these women.

Keywords

cervical cancer; radiotherapy; pelvic fractures; survivorship; bone mineral density

Radiotherapy has become an essential component of either definitive or adjuvant therapy for patients with cervical cancer. Advances in such treatment have resulted in substantial improvements in preventing disease recurrence and in overall survival for these patients.^{1–6} However, despite these advances, focus on the long-lasting effects of therapy and survivorship has lagged behind. On the basis of anecdotal observations, we became concerned about an apparent increased risk of pelvic fractures in patients treated with definitive radiotherapy for cervical cancer. These observations prompted us to perform the current study.

Pelvic fractures, particularly hip fractures, are a major source of morbidity and mortality with significant public health implications. In the general population, adults who sustain a fracture are 50% to 100% more likely to have another fracture of a different type.^{7,8} Previous studies have demonstrated that pelvic irradiation results in demineralization of bone matrix, with a pelvic fracture rate of 2% to 89% reported among women undergoing radiotherapy for gynecologic malignancies.^{9–17} However, given the limited sample size of previous studies and the paucity of information regarding associated risk factors, we sought to determine the incidence of pelvic fractures in women treated with curative-intent radiotherapy for cervical cancer and their associated risk factors.

MATERIALS AND METHODS

After approval from the Institutional Review Board, our study population was identified through a search of the Gynecologic Oncology and Radiation Oncology databases at the University of Texas M. D. Anderson Cancer Center. Between January 2001 and December 2006, 516 women with cervical cancer were treated with curative-intent radiotherapy. Three hundred of these patients had at least 1 post-treatment computed tomography (CT) scan ($n = 220$; 73%) or magnetic resonance imaging (MRI) study ($n = 80$; 27%) available for review, and they comprised the current study population. There were no patients with pre-existing pelvic fractures, pelvic fractures diagnosed on pretreatment imaging, or bony metastases.

Patient medical records were reviewed for age at cancer diagnosis, ethnicity, body mass index (BMI), menopausal status, and smoking history. Pathologic characteristics including cancer stage, histology, and tumor grade were also obtained. The radiotherapy records were reviewed for the type and duration of radiotherapy. All available pretreatment and post-treatment CT scans and MRI studies were re-reviewed by a single radiologist to evaluate for fractures (R.I.).

The characteristics of the women who developed a fracture were compared with those who did not. Comparisons of categorical variables between groups were performed using chi-

square and Fisher exact tests if necessary. Comparisons of continuous variables between groups were evaluated using the Mann-Whitney *U* test. A value of $P < .05$ was considered to be statistically significant. All analyses were performed using SPSS statistical software (version 16.0; SPSS Inc, Chicago, Ill).

RESULTS

The patient characteristics of the current study population are shown in Table 1. The median age at cancer diagnosis was 47.4 years (range, 21.6–90.9 years). The majority of patients (54%) were Caucasian. Approximately 40% of the patients were premenopausal before the initiation of therapy. The median BMI was 27.6 kg/m² (range, 15.5–58.2 kg/m²). Approximately 43% of patients were former or current smokers. The majority of patients had squamous cell carcinoma (73%) or adenocarcinoma (14%). Approximately 43% of patients had stage I disease, 26% had stage II disease, 21% had stage III disease, and 7% had stage IV disease (grading determined according to the International Federation of Gynecology and Obstetrics staging system).

A total of 258 patients (86%) received primary radiotherapy with external beam therapy to the whole pelvis using parallel opposing anteroposterior/posteroanterior (AP/PA) fields (n = 249; 97%) or intensity-modulated radiotherapy (IMRT) (n = 9; 3%). The median external beam radiation dose was 45.0 grays (Gy) (range, 38.8–68.3 Gy), and was followed by 2 intracavitary implants with low-dose-rate brachytherapy in the majority of patients (n = 241; 93%). Thirty-six patients (12%) received postoperative radiotherapy after undergoing either radical hysterectomy (n = 26) or simple hysterectomy (n = 10). These patients received a median of 45.0 Gy (range, 45.0–66.0 Gy) of external beam radiotherapy using a 4-field technique (n = 25; 69%) or IMRT (n = 11; 31%), followed by intracavitary treatments with high-dose-rate brachytherapy in 25 patients (69%). Six patients (2%) underwent preoperative radiotherapy with 45.0 Gy of external beam radiotherapy using AP/PA fields followed by a completion hysterectomy. A radiation boost to the pelvis after external beam treatment was given in 143 patients (48%). All patients in the study received similar radiation doses to the sacrum. Approximately 90% of patients (n = 269) received concomitant chemotherapy with weekly cisplatin (n = 222), cisplatin and 5-fluorouracil (5-FU) (n = 39), or other combinations (n = 8).

The median follow-up for all patients was 20.9 months and the median time from the end of treatment to last imaging was 7.4 months. Pelvic fractures were noted in 29 of 300 patients (9.7%). The most common fracture site was the sacrum (Table 2). Fractures were noted on CT scan in 21 patients (72%) and on MRI in 8 patients (28%). Thirteen patients (45%) were symptomatic, with 12 patients (92%) presenting with pain and 1 patient (8%) with lower extremity swelling. None of the patients required surgery or other orthopedic intervention due to the fractures.

Of the 29 patients who developed fractures, 23 (79%) were treated with primary radiotherapy, 5 (17%) with postoperative radiotherapy, and 1 (4%) with preoperative radiotherapy. Twenty-seven patients (93%) received concomitant chemotherapy with cisplatin (n = 23) or cisplatin and 5-FU (n = 4). A pelvic boost was given to 17 of the 29

patients (59%). The median time from the completion of radiotherapy to the detection of fractures on imaging studies was 14.1 months, with a standard deviation of 11.9 months and range of 2.1 to 63.1 months. Eleven of the fractures (38%) were diagnosed within 1 year of the completion of therapy, and 24 (83%) were diagnosed within 2 years of completing therapy (Fig. 1) (Table 2).

The clinical and pathologic characteristics of women who developed a fracture were compared with those of women who did not (Table 3). The median age at cancer diagnosis was significantly higher in the fracture group compared with the nonfracture group (56.5 years vs 46.7 years; $P = .04$). Approximately 62% of the women diagnosed with a fracture were postmenopausal at the time of cancer diagnosis, compared with only 37% in the nonfracture group ($P = .03$). In addition, the median BMI was lower in the women who developed a fracture compared with the women who did not (26.0 kg/m² vs 28.0 kg/m²; $P = .03$). There were no statistically significant differences noted with regard to ethnicity, smoking history, histology, stage of disease, tumor grade, radiation type, radiation dose, use of concomitant chemotherapy, or pelvic boost between the 2 groups.

DISCUSSION

The key finding from the current study is that a substantial proportion of patients develop pelvic fractures after definitive radiotherapy for cervical cancer. Because radiotherapy is a curative treatment for many of these patients, the long-lasting effects of therapy- and survivorship-related issues such as osteoporosis and pelvic fractures need further attention.

In our cohort, we noted a 9.7% fracture rate. The majority of fractures (83%) were diagnosed within 2 years of the completion of treatment. Our findings are supported by previous studies (Table 4). Blomlie et al¹⁰ prospectively studied 18 Norwegian women treated with radiotherapy for advanced cervical cancer. They performed pre- and post-treatment MRI studies and detected pelvic insufficiency fractures in 89% of patients. A retrospective cohort study by Baxter et al¹² evaluated American women aged ≥ 65 years with pelvic malignancies using the Surveillance, Epidemiology, and End Results (SEER) cancer registry data linked to Medicare claims data. Among 1139 cervix cancer patients, they noted a pelvic fracture rate of 8.2%; for women treated with radiotherapy, compared with 5.9% for those who were not treated with radiotherapy. A subsequent study by Ikushima et al¹⁴ reported a fracture rate of 11% among 158 patients with gynecologic malignancies treated with radiotherapy, with 78% of the fractures occurring within 1 year of therapy. A recent study by Kwon et al¹⁵ retrospectively evaluated post-treatment MRI studies on 510 women treated with radiotherapy for cervical cancer. Pelvic insufficiency fractures were noted in 20% of patients at a median of 17 months after treatment.

An interesting finding in the above-mentioned studies, as well as in the current study, is the short interval between treatment with radiotherapy and the development of fractures. Although to the best of our knowledge there is currently limited information available regarding the effects of radiotherapy on the bone remodeling processes, radiation has been shown to directly affect osteoblasts, osteoclasts, and osteocytes, resulting in a net reduction in bone matrix production. In addition, radiation to the vascular supply of bone has been

reported to cause microcirculation occlusion and further compromise of osteoblast function.¹⁸ Further study is needed to examine the alterations in levels of selected markers of bone turnover with regard to risk for radiation-related fractures.

In the current study, pelvic fractures were associated with lower BMI. Similarly, a study by Ogino et al¹³ reported a weight of <49 kg to be associated with sacral insufficiency fractures among 335 Japanese women treated with radiotherapy for advanced cervical cancer. In addition, Oh et al¹⁶ noted a weight <55 kg to be a significant predisposing factor for pelvic insufficiency fractures among Korean women treated with pelvic radiotherapy. In the general population, lower BMI is associated with decreased bone mass and identified as a risk factor for osteoporosis and pelvic fractures.¹⁹ This is likely due to these individuals having lower stores of body fat and lower circulating estrogen levels, which help prevent loss of bone tissue. It remains unclear what the added effects of radiotherapy are in women with a low BMI.

In the current study, none of the patients developed serious complications associated with the fractures. However, in the general population, a personal history of a fracture is the most significant risk factor for developing another fracture. A limitation of our study is that the data were collected retrospectively. Accurate information regarding the use of hormone replacement therapy and other medications affecting bone mineral density was not available. In addition, post-treatment imaging studies were not performed consistently or at specified intervals, likely underestimating the incidence and time to fracture. Follow-up in the current study was limited, and therefore the long-term morbidity and mortality associated with osteoporosis and pelvic fractures is not fully known in this population and may reflect an underestimate of the true fracture rate in patients receiving pelvic radiotherapy. To further address this issue, we have initiated a study prospectively evaluating the incidence of pelvic fractures as well as changes in bone mineral density and serum markers of bone turnover among women being treated with radiotherapy for gynecologic malignancies.

In conclusion, pelvic fractures were detected in approximately 10% of women after definitive radiotherapy for cervical cancer. The current study is unique in that the majority of previous studies were performed in Asia, with little information currently available concerning postradiation pelvic fractures among American women. In addition, to our knowledge, there are few data available regarding pelvic fractures and osteoporosis in premenopausal women undergoing treatment for gynecologic malignancies. Our findings suggest that bone mineral density screening and pharmacologic intervention should be considered in women undergoing pelvic radiotherapy for cervical cancer. Further prospective study is needed to better understand the risk factors for the development of fractures in this population and to develop novel preventive and therapeutic strategies. The prevention of osteoporosis and pelvic fractures may result in improved survivorship in women undergoing radiotherapy for gynecologic malignancies.

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Figure 1.
Cumulative incidence of pelvic fractures after radiotherapy for cervical cancer is shown.

Table 1

Clinical and Pathologic Characteristics (N = 300 Patients)

Age at cancer diagnosis, y	
Median	47.4
Range	21.6–90.9
Ethnicity	
White	162 (54%)
Hispanic	86 (29%)
Black	48 (16%)
Asian	4 (1%)
BMI, kg/m²	
Median	27.6
Range	15.5–58.2
Menopausal status	
Premenopausal	119 (40%)
Postmenopausal	178 (59%)
Unknown	3 (1%)
Smoking status	
Smoker	127 (43%)
Nonsmoker	169 (56%)
Unknown	4 (1%)
Histology	
Squamous	219 (73%)
Adenocarcinoma	42 (14%)
Neuroendocrine	13 (4%)
Adenosquamous	8 (3%)
Other	18 (6%)
Stage	
I	130 (43%)
II	76 (26%)
III	63 (21%)
IV	22 (7%)
Unknown	9 (3%)

BMI indicates body mass index.

Table 2

Fracture Characteristics (N = 29)

Fracture sites	
Sacrum	24 (83%)
Sacrum and pubis	3 (10%)
Iliac crest	1 (3.5%)
Sacrum and acetabulum	1 (3.5%)
Time from treatment completion to fracture, mo	
Median	14.1
Standard deviation	11.9
Range	2.1–63.1
Fractures diagnosed within 1 y of therapy	11 (38%)
Fractures diagnosed within 2 y of therapy	24 (83%)

Table 3

Clinical, Pathologic, and Treatment Characteristics Associated With Fractures

Patient Characteristic	Fracture Group (N = 29)	No Fracture Group (N = 271)	P
Median age, y	56.5	46.7	.04
Menopausal status			.03
Premenopausal	11 (38%)	171 (63%)	
Postmenopausal	18 (62%)	100 (37%)	
Median BMI, kg/m ²	26.0	28.0	.03
Ethnicity			.19
White	18 (62%)	144 (53%)	
Hispanic	4 (14%)	82 (30%)	
Black	6 (21%)	42 (15%)	
Asian	1 (3%)	3 (2%)	
Smoking status			.86
Smoker	12 (41%)	115 (43%)	
Nonsmoker	17 (59%)	152 (57%)	
Type of radiotherapy			.27
Primary	23 (79%)	235 (87%)	
Postoperative	5 (17%)	31 (11%)	
Preoperative	1 (4%)	5 (2%)	
Concomitant chemotherapy			.75
Yes	27 (93%)	242 (89%)	
No	2 (7%)	29 (11%)	
Pelvic boost			.21
Yes	17 (59%)	126 (46%)	
No	12 (41%)	145 (54%)	

BMI indicates body mass index.

Table 4
Summary of the Literature Regarding Pelvic Fractures After Radiotherapy for Cervical Cancer

Reference	Country	No. of Patients	Menopausal Status	Fracture Rate	Time From Completion of Radiotherapy to Fracture
Blomlie 1996 ¹⁰	Norway	18	Pre and post	89%	Median: NA Range: 3–24 mo
Huh 2002 ¹⁷	Korea	463	Post	2%	Median: 12 mo Range: 7–19 mo
Ogino 2003 ¹³	Japan	335	Post	17%	Median: 8 mo Range: 3–59 mo
Baxter 2005 ¹²	United States	1139	Post	8.2%	NA
Ikushima 2006 ¹⁴	Japan	158	NA	11%	Median: 6 mo Range: 3–51 mo
Kwon 2008 ¹⁵	Korea	510	NA	20%	Median: 17 mo Range: 1–87 mo
Oh 2008 ¹⁶	Korea	557	NA	20%	Median: 13 mo Range: 5–44 mo
Current study	United States	300	Pre and post	10%	Median: 14 mo Range: 2–63 mo

Pre indicates premenopausal; post, postmenopausal; NA, not available.