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CLINICAL INVESTIGATION **Prostate**

INSUFFICIENCY FRACTURES AFTER PELVIC RADIOTHERAPY IN PATIENTS WITH PROSTATE CANCER

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Purpose: To assess the incidence, predisposing factors, and clinical characteristics of insufficiency fractures (IF) in patients with prostate cancer, who received pelvic radiotherapy as part of their definitive treatment.
Methods and Materials: The charts of 134 prostate cancer patients, who were treated with pelvic radiotherapy between 1998 and 2007 were retrospectively reviewed. IF was diagnosed by bone scan and/or CT and/or MRI. The cumulative incidence of symptomatic IF was estimated by actuarial methods.
Results: Eight patients were identified with symptomatic IF after a median follow-up period of 68 months (range, 12–116 months). The 5-year cumulative incidence of symptomatic IF was 6.8%. All patients presented with lower back pain. Insufficiency fracture developed at a median time of 20 months after the end of radiotherapy and was managed conservatively without any need for hospitalization. Three patients were thought to have metastatic disease because of increased uptake in their bone scans. However, subsequent CT and MR imaging revealed characteristic changes of IF, avoiding any further intervention. No predisposing factors for development of IF could be identified.
Conclusions: Pelvic IF is a rare complication of pelvic radiotherapy in prostate cancer. Knowledge of pelvic IF is essential to rule out metastatic disease and prevent unnecessary treatment, especially in a patient cohort with high-risk features for distant spread. © 2010 Elsevier Inc.

Insufficiency fracture, Pelvic radiotherapy, Androgen deprivation, Prostate cancer, Complication.

INTRODUCTION

Insufficiency fracture (IF) is a subgroup of stress fracture. Unlike the other subtype (*i.e.,* fatigue fracture), IF results from normal or physiologic stress applied to weakened bone. Underlying conditions that decrease the elastic resistance of bone and predispose it to IF include osteoporosis, Paget disease, hyperparathyroidism, rheumatoid arthritis, and irradiation. Specific fractures that course vertically in the sacral alae, parallel to the sacroiliac joint, are the diagnostic criterion of IF. This particular distribution is believed to be produced by the weight of the upper body and spine being transmitted to the sacrum (1).

Although the actual incidence of IF after pelvic radiotherapy is unknown, it has been regarded as a rare complication. Even with small sample sizes, IF has been described after irradiation for gynecologic (2–4), anal (5), and rectal cancer (6, 7). Recent studies reported the incidence of IF in gynecologic patients as 8%–20% (8–10). Data in prostate cancer patients is rare and limited to some case reports (11, 12).

In this study, we report our experience with eight cases of symptomatic IF occurring in patients being treated with pelvic radiotherapy for carcinoma of the prostate and investigate the incidence, clinical characteristics, and risk factors for development of IF.

METHODS AND MATERIALS

Patient selection

In our database, we retrospectively identified 610 patients who were definitively treated for prostate cancer between 1998 and 2008. One hundred and thirty-four of these patients who were treated with whole pelvic radiotherapy (WPRT) as part of their definitive treatment and had a minimum follow-up of 12 months were enrolled in this study (Table 1). Between 1998 and 2005, the initial 115 patients were treated with pelvic fields designed with

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Table 1. Patient characteristics (*n*: = 134)

Median age (range)	65 years (44-–83)
Stage	
T1c	4 (3%)
T2a-–b	45 (34%)
T3a-–b	85 (63%)
Gleason score	
≤ 6	28 (21%)
7	62 (46%)
8-–10	44 (33%)
Median PSA (range)	20.5 ng/mLl (2.5-–170)
Androgen deprivation	
None	6 (5%)
Short term (≤6 months)	28 (21%)
Long term (>6 months)	100 (74%)

Abbreviation: PSA = prostate-specific antigen.

three-dimensional conformal radiotherapy (3D-CRT). From 2005 through 2007, the next 19 patients were treated with intensity-modulated radiotherapy (IMRT) to the whole pelvis. One hundred and eighteen patients had an estimated risk of lymph node (LN) involvement >15%, based on the equation +LN = (2/3) prostate-specific antigen (PSA) + [(GS – 6) × 10] (13), and 16 patients had LN involvement, determined by imaging or biopsy. The median age of the cohort was 65 years (range, 44–83 years). Clinical stage at presentation was locally advanced in 63% of cases. All of the patients had a diagnosis of adenocarcinoma. The majority had high-grade pathology with Gleason score ≥7 in 79% of the patients. Median pretreatment PSA was 20.5 ng/mL (range, 2.5–170 ng/mL). Before, during, or after radiotherapy, 86% received androgen deprivation therapy (ADT) for a median of 24 months (range, 6–36 months).

Conformal planning and treatment

All patients underwent CT simulation and were treated supine. The pelvic lymph node volumes were contoured to include obturator, external iliac, internal iliac, and common iliac lymph nodes up to the vertebral body level of L5–S1. These were defined by outlining their adjacent blood vessels with a 0.5- to 1-cm margin.

Landmarks used to define the four-field 3D-CRT plans were defined as follows: anterior and posterior fields, superior border at L5–S1, lateral borders 2 cm lateral to the widest point of the bony pelvic inlet margin, and inferior border 1.5 cm below prostate on CT images; lateral fields, anterior border to anterior surface of pubic symphysis and posterior border to middle of the sacrum, including at least a posterior 0.75-cm margin on the prostate and seminal vesicles. External irradiation was delivered using a 6–18 MV linear accelerator with a daily dose of 1.8 Gy. A total dose of 45–50.4 Gy was delivered to the pelvis. The patients with a high estimated risk of nodal involvement received a conformal boost to 70.2–75.6 Gy to the prostate and seminal vesicles, whereas the N1 patients were only treated to 66.6 Gy.

IMRT plans were delivered with the simultaneous integrated boost technique. The nodal PTV was treated to 56 Gy in 1.4-Gy fractions, whereas the prostate and seminal vesicle PTV received 76–78 Gy in 2-Gy fractions for a total of 38–39 fractions.

Because of the treatment planning system was replaced in 2002, we only have access to the treatment plans of 49 patients. In each CT data set, sacral alae are contoured to identify minimum, maximum, and mean doses delivered to this structure.

Diagnostic criteria of IF

All imaging studies of the symptomatic patients were reviewed. Three patients had bone scans, along with CT and MRI scans. The remaining five patients were diagnosed only with MRI. Bone scans showed regionally increased activity of sacroiliac joint or sacrum or other pelvic bone. T1 hypointense and T2 hyperintense lesion without soft tissue mass was diagnostic on MRI (Fig. 1). Demonstration of fracture lines or sclerotic changes without osteolytic lesion on CT was characteristic of IF (Fig. 2). No patient had any evidence of bone metastases during the clinical course.

Outcome analysis

The cumulative incidence of IF was calculated with the Kaplan-Meier method. Clinical characteristics, including distribution of lesions and development of pain, were identified by review of hospital records and imaging studies.

Risk factors that could affect the incidence of symptomatic IF (age, diabetes mellitus, time on androgen ablation, photon energy, ischemic disease, radiotherapy technique, and dose to the pelvis) were assessed by log-rank test (univariate analysis) and Cox regression analysis with hazards model (multivariate analysis). Factors with a difference at the 0.05 level were considered significant.

Dose–volume histogram (DVH) analysis of the sacrum of the available 49 patients were compared with the Mann-Whitney *U* test.

RESULTS

Incidence

After a median follow-up of 68 months (range, 12–116 months), 8 patients were diagnosed with symptomatic IF. The cumulative incidence of symptomatic IF at 5 years was 6.8% (Fig. 3). The median time from the end of radiotherapy to the diagnosis of IF was 20 months (range, 5–52 months). IF was diagnosed when patients were disease free. Their median PSA level at the time of the diagnosis of IF was 0.04 ng/mL (range, 0.01–6.5 ng/mL).

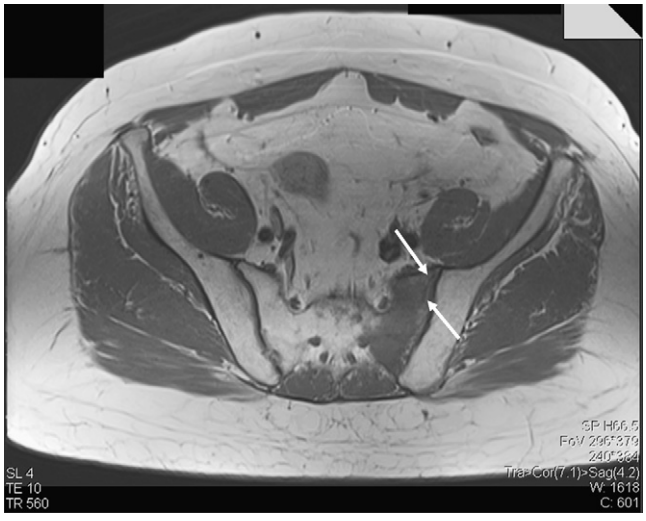

Fig. 1. MR image demonstrating hypointense fracture line (white arrows) with surrounding medullary edema neighbouring sacroiliac joint.