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Hip fractures and pain following proton therapy for management of prostate cancer

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Abstract

Background. Proton therapy (PT) for prostate cancer reduces rectal and bladder dose, but increases dose to the femoral necks. We assessed the risk of hip fracture and pain in men treated with PT for prostate cancer. *Material and methods.* From 2006 to 2008, 382 men were treated for prostate cancer and evaluated at six-month intervals after PT for toxicities at University of Florida Proton Therapy Institute (UFPTI). The WHO Fracture Risk Assessment Tool (FRAX) generated annual hip-fracture risk for the cohort. The WHO FRAX tool was utilized to generate the expected number of patients with hip fractures and the observed-to-expected ratio; confidence intervals and p-value were generated with the mid-P exact test. Univariate analysis of hip pain as a function of several prognostic factors was accomplished with Fisher's exact test. *Results.* Median follow-up was four years (range, 0.1–5.5 years). Per FRAX, 3.02 patients were expected to develop a hip fracture without PT. Three PT patients actually developed fractures for a rate of 0.21 fractures per 100 person-years of follow-up. There was an observed-expected ratio of 0.99 (p-value not significant). Forty-eight patients (13%) reported new pain in the hip during follow-up; three required prescription analgesics. *Conclusion.* PT for prostate cancer did not increase hip-fractures in the first four years after PT compared to expected rates in untreated men.

Men with prostate cancer are often at risk for other age-related adverse events, such as hip fractures. The risk of hip fractures can be increased in men with prostate cancer because bone integrity may be compromised by androgen deprivation therapy (ADT), occult bone metastases, or both [1–4]. Radiotherapy (RT), which can compromise bone integrity, has also been associated with an increased risk of hip fracture. Using the Surveillance, Epidemiology, and End Results (SEER) database, Elliott et al. found a 76% increased risk of hip fracture in men with prostate cancer treated with pelvic three-dimensional (3D) conformal external-beam RT (EBRT) alone compared with patients treated with surgery alone [5]. The risk of hip fracture was even greater with the addition of short-course ADT to EBRT [5].

Currently, there is great interest in the use of proton therapy (PT) for managing prostate cancer. Because the entrance dose with PT is much less than the target dose and there is no exit dose, only two fields are required to deliver a sufficiently high radiation dose to the target with acceptably low doses to entrance tissues. The use of a two-field technique with opposed lateral beams permits significant avoidance and/or sparing of the rectum, a key tissue for potential radiation toxicity. However, because only two fields are used, there is a slightly higher dose delivered to the femoral neck and head than with a five- to seven-field intensity-modulated radiation therapy (IMRT) plan [6], leading to the speculation that there could be a higher risk of hip fracture with the currently popular PT technique than with sophisticated methods of x-ray-based RT [7].

The present study evaluates the risk of developing hip fractures in men treated at the University of Florida Proton Therapy Institute with PT for prostate cancer.

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Material and methods

Patients

The present study was approved by our Institutional Review Board and included men who were treated with PT at the University of Florida Proton Therapy Institute (UFPTI) for prostate cancer and enrolled on at least one of three treatment protocols, including PR01, a phase II study of treating low-risk prostate cancer patients to 78 CGE at 2 CGE/fraction, PR02, a phase I/II study in intermediate-risk patients of dose escalation from 78 to 82 CGE at 2 CGE/fraction, and PR03, a phase III study of concurrent weekly docetaxel with concurrent proton therapy to 78 CGE, all of which have been previously described, and an outcomes tracking protocol (OTP), between September 2006 and April 2008. Participants also had a minimum of six months of follow-up [8]. Eighteen of the 400 men evaluated were excluded because of treatment with both proton and photon RT for coverage of pelvic nodes (n = 15) or because of prior pelvic irradiation (n = 3), resulting in a total of 382 men included in the study.

Simulation, planning, and treatment

UFPTI's simulation, planning, and treatment guidelines for prostate cancer have previously been published [8]. The femoral heads of all patients were contoured prior to treatment planning; dose constraints to the femoral head were a V55CGE < 2 cm^3 (volume of the femoral head receiving 55 CGE should be less than 2 cm^3) and a V50CGE $< 15\%$ (volume of the femoral head getting 50 CGE is less than 15%). There were no dose constraints for the femoral necks. Patients with de novo prostate cancer were treated with 2 CGE per fraction to a total dose of 76–82 CGE (96%). Sixteen of the 382 patients were treated with PT in the adjuvant or salvage setting following laparoscopic, robotic, or radical prostatectomy (n = 12) or cryosurgery (n = 4) and received 70–74 CGE at 2 CGE per fraction.

Data collection

The charts of 382 men treated with PT for prostate cancer were reviewed to extract prospectively recorded medical events and interventions, including provider-assessed toxicity. Prior to treatment and at six-month intervals after PT, nurses and physicians recorded interim medical events and interventions and evaluated patients by using the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE) [9] to assess toxicities, including genitourinary (GU), gastrointestinal (GI), erectile function, and pain (including pain symptoms, pain location, pain scale, and medication use). Factors potentially associated with increased risk of hip fracture or pain were recorded from each patient's initial consultation and completion notes, and included ADT, steroid use, testosterone level, body mass index (BMI), previous fracture, smoking, excessive alcohol consumption, arthritis, osteoporosis, renal/liver disease, hyperparathyroidism, diabetes, and dosimetry details. The radiotherapy treatment start date and date of last physician assessment were obtained to calculate follow-up length.

The World Health Organization's (WHO) Fracture Risk Assessment tool (FRAX) [10] was applied to each patient to generate both an individual annual hip-fracture risk and an expected total number of patient fractures for the study population based on individual follow-up. A second calculation was made for patients with ADT, where these patients were assumed to have secondary osteoporosis for the purpose of risk calculation using the method by Saylor et al. [11]. Of note, the FRAX score is based on age, sex, weight, height, alcohol consumption, and smoking. We had 100% data for these components of the FRAX. Additionally, the FRAX score uses history of prior fracture, history of fracture in a parent, glucocorticoids use, rheumatoid arthritis, and secondary osteoporosis. Unless we had information to otherwise suggest a positive answer to these, we assumed patients did not have these problems. Furthermore, it was assumed that patients' parents did not have a fractured hip. These assumptions would provide us with the most conservative estimate (lowest risk of hip fracture score).

Based on application of the WHO FRAX tool to each patient in our study, the mean annual hip fracture risk by assuming ADT caused secondary osteoporosis per Saylor's method [12] was 0.13% (range, 0–1.6%) and was 0.10% (range, 0–1.6%) when not making that assumption. Based on each patient's own annual hip fracture risk and his follow-up time, in our patient population, 3.02 and 2.44 patients were expected to develop a hip fracture without PT (or other radiation) intervention by the Saylor method or not, respectively, with a median follow-up of four years (range, 0.7–5.5 years for surviving patients).

Statistics

JMP software was used for statistical analysis (SAS Institute, Cary, NC, USA). Univariate analysis of hip pain as a function of several prognostic factors was accomplished with Fisher's exact test. The WHO FRAX tool was utilized to generate the expected number of patients with hip fractures and the observed-to-expected ratio (OER); confidence intervals (CI) and p-value were generated with the mid-P exact test.

Results

Observed median follow-up for surviving patients was 4.0 years (range, 0.7–5.5 years). Patient- and treatment-specific details are summarized in Table I. In total, 83% and 98% of patients were seen for follow-up within the 12 months and 24 months prior to our analysis, respectively. Six percent (n = 23) of men died during follow-up for the following reasons: cardiovascular disease (n = 10), cancer other than prostate cancer (n = 8), unknown causes (n = 3), prostate cancer (n = 1), and dementia (n = 1). Of the patients who died from unknown causes, all had a prostate-specific antigen (PSA) < 1 at last follow-up.

Table I. Patient characteristics.

Patient characteristics	No. of patients	%
Age (years)		
< 60	66	17
60 to < 70	157	43
70 to < 80	135	35
80+	24	6
Body mass index		
< 30	284	74
30+	98	26
Ethnicity		
White	351	92
Black	25	7
Hispanic	5	1
Asian	1	< 1
Diabetes		
Yes	58	15
No	324	85
Previous fracture		
Yes	30	8
No	352	92
Hyperlipidemia		
Yes	212	56
No	170	44
Hypertension		
Yes	201	53
No	181	47
Arthritis		
Yes	70	18
No	312	82
Alcohol use		
≥ 7 drinks weekly	93	24
< 7 drinks weekly	289	76
Smoking history		
≥ 10 pack years	129	34
< 10 pack years	253	66
Glucocorticoid therapy		
≥ 1 month	32	8
< 1 month or none	350	92
Androgen deprivation therapy		
Yes	85	22
No	297	78
Proton dose		
70–74 CGE	16	4
76 CGE	1	< 1
78 CGE	216	57
80 CGE	39	10
82 CGE	110	29

CGE, Cobalt Gray equivalent.

In total, three patients actually developed fractures between nine and 33 months after PT for an OER of 0.99 (CI, 0.25–2.70; p = 0.99) accounting for the use of ADT or an OER of 1.23 (CI, 0.31–3.35; p = 0.67) when not accounting for the use of ADT. Two of these men had high-risk disease and received ADT with 78 CGE, but developed biochemical recurrences and may have had bone metastases to contribute to their risk for hip fractures. The other patient had recurrent prostate cancer following prostatectomy and received 70 CGE and ADT; he is currently disease-free. Additional patient characteristics are listed in Table II.

Five additional patients underwent hip-replacement surgery for severe arthritis without evidence of hip fractures. All five patients had reported hip pain with a diagnosis of arthritis prior to treatment with proton therapy and had intense activity in the involved hip on pretreatment bone scan. One of these patients had surgery already scheduled at the time of PT. Hip replacements in these patients occurred at 8, 15, 19, 25, and 27 months after PT.

A total of 60 patients (16%) reported pain in the hip, groin, or thigh. Twelve of these patients reported pain prior to PT; thus, only 13% of men (n = 48) developed new pain. Pain was mild and typically described as bursitis-type pain with burning and aching on the outer part of the thigh when lying on the specific hip at night or pain after rising from a prolonged sitting position. Only 16 men required medications for pain control, including 13 who used non-steroidal anti-inflammatory drugs (NSAIDs) and three who required prescription analgesics or narcotics. The median time to reporting pain after PT was nine months (range, 1–45 months).

Univariate analyses were performed to identify risk factors for hip pain (data not shown). No factors were associated with increased risk of hip pain.

Discussion

In the present study, three patients developed hip fractures following PT. Importantly, all three of these patients were on ADT for high-risk or recurrent prostate cancer. ADT is known to cause a decrease in bone mineral density [11] and, therefore, patients who receive ADT should be assumed to have secondary osteoporosis when calculating fracture risk using the FRAX tool [11]. All three patients had a significantly increased hip fracture risk per the FRAX tool. The average calculated annual hip fracture risk for our cohort was 0.22%, which is much lower than

Table II. Characteristics of three patients who experienced hip fractures.

Patient characteristics	Patient 1	Patient 2	Patient 3
Age (years)	77	77	79
Body mass index	23.2	28.3	21.1
Past medical history	Prior fracture, smoker	Robotic prostatectomy	Arthritis, osteoporosis, degenerative joint disease, steroid use
Disease characteristics	T2cN0M0, Gleason 8, PSA 23.5	Relapse following prostatectomy	T2bN0M0, Gleason 9, PSA 11.6
Disease progression	Yes	No	Yes
Androgen deprivation therapy use	Yes	Yes	Yes
Radiotherapy dose	78 CGE	70 CGE	78 CGE
Time to fracture after radiotherapy	18 & 29 months	33 months	9 months
10-year fracture risk	11%	6.40%	15%
Max/mean femoral neck dose	Right- 36 CGE/33 CGE Left- 35 CGE/32 CGE	31 CGE/27 CGE	36 CGE/34 CGE

CGE, Cobal Gray equivalent; PSA, prostate-specific antigen.

annual risks of 0.64%, 1.1%, and 1.5% for the three patients who actually developed hip fractures. Based on the hip fracture risk for the whole patient cohort by the FRAX calculator there would have been an expected 2.44 patients suffering fractures (or 3.02 accounting for use of ADT), which is similar to what we observed (three patients). New hip pain was reported by 13% of patients following PT, but it was generally mild with only 3% using NSAIDS and 0.7% using prescription analgesics or narcotics.

Currently, there are limited clinical data available in the literature about hip and pelvic bone complications after PT. Elliot et al. [5] recently conducted a study to evaluate the risk of hip fractures after pelvic EBRT in men with prostate cancer. A review of the records of 45,665 men aged >62 years and diagnosed with prostate cancer out of the SEER-Medicare database revealed a 76% increase in the risk of developing fractures after EBRT delivered by 3D conformal radiotherapy (CRT) compared with prostatectomy. The risk of developing hip fractures after 3DCRT and ADT was 145% greater than for men who received radical prostatectomy alone. This study reported a cumulative incidence of hip fractures of 2.5% at 40 months of follow-up for patients receiving EBRT at similar doses to patients in our study. In our study, the rate of hip fractures was 0.75%, which is less than that reported in the Elliot et al. study at 40 months after treatment. Interestingly, the three patients who developed hip fractures in our study would have been excluded from evaluation in the Elliot study since patients with relapsed disease following radiotherapy and patients receiving postoperative radiotherapy were not eligible due to the additive risk of bone metastases.

A more recent study presented by Sheets et al. [13], also evaluating hip fracture in a propensity-score matched population from the SEER Medicare population, demonstrated an increased risk of hip fracture among patients getting 3DCRT ($n = 6666$) compared with IMRT ($n = 6310$) (1 vs. 0.8 fractures per 100 patient-years; $p = 0.006$). In this same analysis, a comparison of hip fractures following IMRT ($n = 684$) compared with PT ($n = 684$) demonstrated no significant difference in fracture risk (0.8 vs. 0.7). Although this study does not compare PT, IMRT, or 3DCRT patients to the general population or to prostatectomy patients, it does highlight that PT does not appear to increase the risk of fracture over other types of external-beam radiotherapy.

In patients with gynecologic cancer who also received radiation dose to the femoral neck and head, Grigsby et al. [14] found elevated risk of femoral neck fractures following groin irradiation with risks of 11% at five years and 15% at 10 years among 207 patients. Importantly, no femoral neck fracture developed if the radiation dose to the hip was less than 42 Gy. In the three patients who developed hip fractures, none received a dose >40 CGE. Thus, influence from ADT and possible metastatic disease from recurrence may have contributed more to the risk of fracture than the PT.

Most studies evaluating fractures following RT have looked at pelvic insufficiency fractures (PIFs), a subclinical problem usually found during follow-up imaging for cervical cancer. Table III summarizes a list of studies evaluating pelvic and hip fractures following RT.

There are no studies in the literature assessing the risk of hip or femoral neck fractures after IMRT or PT. The studies in Table III suggest that pelvic, hip, and femoral neck fractures are common complications in patients receiving pelvic irradiation and take a median time of 13 to 20 months to develop. Studies regarding radiation-induced effects on bone suggest that bone may be most susceptible to fracture

Table III. Pelvic and hip fractures after pelvic irradiation for gynecologic malignancies or prostate cancer.

Study	No. of patients	Cancer site	RT Field	Pelvic fracture rate	Fracture site	Time to fracture
Grigsby et al., Mallinckrodt Institute of Radiology, 1995 [14]	207	Vagina, vulva, cervix, and endometrium	WPRT + groin	11% at 5 years; 15% at 10 years	Femoral neck	N/A
Kwon et al., Samsung Medical Center, 2008 [16]	510	Cervix	WPRT + brachytherapy boost	45.2% at 5 years	PIF	17 months
Oh et al., Samsung Medical Center, 2008 [17]	557	Cervix	WPRT ± brachytherapy boost	19.7% at 5 years	PIF	13 months
Igdem et al., Istanbul Bilim University, 2010 [15]	134	Prostate	WPRT + prostate	6.8% at 5 years	PIF	20 months
Elliot et al., University of Minnesota, 2011 [5]	13,396	Prostate	prostate ± WPRT	8% at 10 years	Hip	N/A
	6974		prostate ± WPRT + ADT	9% at 10 years		N/A

ADT, androgen deprivation therapy; N/A, not available; WPRT, whole-pelvis radiotherapy.

around one year after RT [18–20]. Based on this information, a significantly increased fracture risk should become evident within the 40 months of follow-up in the present study.

Hip pain following RT has not been discussed in the literature. However, PT to the pelvis could incite an inflammatory response, resulting in osteoarthritis, tendonitis, or bursitis. These different problems can cause similar types of pain, which respond to NSAIDS, and complicate diagnosis. Furthermore, these conditions can be incited by a number of different medical problems typically plaguing men in the same age category as those developing prostate cancer. In fact, in the National Health and Nutrition Examination Survey (NHANES) III study, which prospectively evaluated patient-reported hip pain, the incidence of reported hip pain among men aged 60 years and older was found to be 12.4% [21]. This rate resembles the 13% of patients in our database who reported new hip pain after starting PT. The pain found in the NHANES III study was generally mild with only 3% requiring NSAIDS and 0.7% requiring prescription medications. Given the similar rates of hip pain in our study and NHANES, it does not seem likely that PT has increased the risk of hip pain in our patient population.

Several limitations exist in the present study. Patients were followed only by clinical exam and PSA and did not have routine hip imaging. Thus, only clinically evident hip fractures and hip pain were reported and silent PIFs may have been missed. Additionally, accuracy of patient recall may have had some impact on reporting minor hip pain, especially since patients were asked for the toxicity assessment if they had 'any pain' and 'where it was located,' not specifically if they had hip pain. Nevertheless, it is unlikely that, if the hip pain was significant, it would have been missed. Recall accuracy is unlikely to have been a problem for hip fracture, given accuracy rates reported in other studies [22]. Further, we likely underestimated the hip fracture risk in the control population when using the FRAX tool as we assumed patients' parents did not have a history of hip fractures. We then calculated the fewest number of expected hip fractures possible. If we had all of a patient's information regarding their parent's prior hip fracture and other questions, the expected number of hip fractures would have only increased, which would not have changed our conclusions. Lastly, the follow-up data are limited, with only four years of follow-up.

PT for prostate cancer does not appear to increase either the risk of hip fracture or hip pain in the first four years of follow-up compared to expected rates in an untreated population of men. Longer follow-up is needed to confirm these findings.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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