Bone Complications Among Prostate Cancer Survivors: Long-Term Follow-Up From the Prostate Cancer Outcomes Study

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Abstract

BACKGROUND—To assess the relationship between ADT exposure and self-reported bone complications among men in a population-based cohort of prostate cancer survivors followed for 15 years after diagnosis.

METHODS—The Prostate Cancer Outcomes Study (PCOS) enrolled 3,533 patients diagnosed with prostate cancer between 1994 and 1995. This analysis included participants with non-metastatic disease at the time of diagnosis who completed 15-year follow-up surveys to report development of fracture, and use of bone-related medications. The relationship between ADT duration and bone complications was assessed using multivariable logistic regression models.

RESULTS—Among 961 surviving men, 157 (16.3%) received prolonged ADT (>1 year), 120 (12.5%) received short-term ADT (1 year), and 684 (71.2%) did not receive ADT. Men

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receiving prolonged ADT had higher odds of fracture (OR 2.5, 95% CI 1.1–5.7), bone mineral density testing (OR 5.9, 95% CI 3.0–12), and bone medication use (OR 4.3, 95% CI 2.3–8.0) than untreated men. Men receiving short-term ADT reported rates of fracture similar to untreated men. Half of men treated with prolonged ADT reported bone medication use.

CONCLUSIONS—In this population-based cohort study with long-term follow-up, prolonged ADT use was associated with substantial risks of fracture whereas short term use was not. This information should be considered when weighing the advantages and disadvantages of ADT in men with prostate cancer.

Introduction

Prostate cancer is the most common non-cutaneous malignancy in men in the United States.[1] Androgen deprivation therapy (ADT), through orchiectomy or the use of gonadotropin-releasing hormone agonists or antagonists, is the most frequently used systemic therapy for prostate cancer. At present, over 600,000 prostate cancer survivors with various states of the disease are receiving ADT in the United States.[2] Although widely used and considered safe by oncology standards, ADT is not without complications. Recognizing the risks from and managing the complications of ADT exposure have become critical components of survivorship care for men with prostate cancer.

Bone-related complications of ADT include loss of bone mineral density and an increased risk of fractures.[3] The consequences of hip fractures for survivors of prostate cancer are especially grave, given that the risk of death at one year after hip fracture is 31–35% for men, as compared to 17–22% for women.[4] Bone-related complications of ADT have been reported in retrospective studies of large administrative databases, as well as smaller prospective studies.[3, 5–9] However, these studies are limited by relatively short follow-up, and, when based on Surveillance, Epidemiology, and End Results (SEER) Medicare linked data, only include men over age 65 at diagnosis. Assessing men exposed to ADT across an array of age groups is crucial as the risk of ADT-associated fragility fracture is associated with duration of exposure to ADT in men of any age.[3] Additionally national guideline recommendations regarding bone mineral density testing and bone-targeted medications are not age dependent. The Prostate Cancer Outcomes Study (PCOS) is a population-based cohort of men diagnosed with prostate cancer in 1994–5, identified by one of 6 SEER tumor registries, and followed for up to 15 years after diagnosis. As such, the PCOS may allow us to overcome some of the limitations of prior studies and provide a more generalizable portrait of the long-term complications of ADT use in men with prostate cancer.

The goal of our study was to investigate long-term bone complications associated with ADT in a population-based cohort of prostate cancer survivors followed for up to 15 years after diagnosis. We assessed patient-reported bone health outcome measures, including the development of fracture, the frequency of bone mineral density testing, and the use of bone-targeted medications for osteoporosis treatment or fracture prevention. We hypothesized that men treated with prolonged ADT would report fracture, bone mineral density testing, and bone-targeted medication use more commonly than untreated men, and that short-term ADT exposure would not be associated with these outcomes.

Materials and Methods

Study Design

The PCOS enrolled incident prostate cancer patients age 39–89 from 6 participating SEER sites (Connecticut, Utah, New Mexico, and the metropolitan areas of Atlanta, Georgia, Los Angeles, California, and Seattle-Puget Sound, Washington) between October 1, 1994, and October 31, 1995, randomly sampling 5,672 subjects from 11,137 eligible prostate cancer cases. A rapid case ascertainment system was used to identify patients as close to diagnosis as possible. A pre-specified sampling strategy was employed that oversampled younger men, Hispanics, and African Americans (to ensure a representative population of United States prostate cancer patients), while maintaining adequate sample size to address key research questions.[10–11] Institutional Review Boards (IRB) at all participating sites approved the study.

Eligible men were asked to complete a self-administered baseline survey within approximately 6 months after diagnosis. This survey included items on clinical and sociodemographic factors, co-morbid conditions (modified from the Charlson Comorbidity Index), health-related quality of life (HRQOL), age at diagnosis, race/ethnicity, marital status, income level, education level, and insurance type.[12–13] Information regarding treatment for prostate cancer (surgery, radiation, hormonal therapy, no therapy, or any combination of therapies), and tumor characteristics (Gleason score, highest diagnostic prostate specific antigen (PSA) level, disease stage) was collected from a detailed 1-year medical record review as described previously and was coded according to SEER guidelines.[10–14] Participants were contacted again at 1, 2, 5, and 15 years following diagnosis and asked to complete a survey containing items on further prostate cancer treatment, including past or current use of ADT, incident co-morbid conditions, clinical outcomes, and HRQOL. The long-term (15 years after diagnosis) survey included specific items on bone health.

Study Population

To be included in this analysis, PCOS participants must have had non-metastatic disease at the time of diagnosis and completed a long-term (15 year) patient survey. Specific questions in the survey assessed whether men had developed bone metastases or fracture, as well as receipt of a bone mineral density test or bone medications. Of the initial 3,533 PCOS participants who completed a baseline survey, 1782 were alive at the time of 15-year follow-up. Of these, 998 (56%) completed the fifteen year survey. Thirty-seven of these men had metastatic disease at diagnosis and were excluded from our analysis, resulting in an analytic cohort of 961 men. Twelve men with metastatic disease at the time of the long-term survey were excluded from the fracture analysis as we were unable to distinguish between pathologic fractures due to metastatic disease and fragility fractures due to low bone mineral density. Patient non-response resulted in missing data for fracture (7), bone mineral density test (107), and bone medications (34). Missing data was counted as not reporting fracture, receipt of a bone mineral density test, or bone medication use.

Statistical Analysis

Independent Variables—We categorized participants into the following exposure subgroups based on 1-year medical record review data and self-report of receipt of ADT at 6 months, 1, 2, 5 and 15 years after diagnosis: no ADT, short-term ADT (total ADT duration of 1 year or less), and prolonged ADT (total ADT duration of more than 1 year). Short-terms ADT was defined as 1 year of ADT exposure because this duration has been used in previous studies to define ADT duration, and was more reliably defined from our survey data than other commonly used durations like 4–6 months.[15–17] ADT exposure was defined in the survey question as treatment with GnRH agonist therapy, antiandrogen medications, or a combination of these. We included the following covariates in our models: age at diagnosis, race, and Charlson comorbidity score marital status, and Gleason score. All covariates included in the multivariable analysis were chosen based on perceived clinical relevance prior to univariable analysis.

Dependent Variables

<u>**Fracture, Bone Mineral Density Testing, and Bone Medication Use:**</u> Patients were specifically queried regarding the development of fracture, and the use bone mineral density testing or bone targeted medications, including calcium, vitamin D, zoledronic acid, alendronate, risedronate, calcitonin, and parathyroid hormone, in the long-term survey.

Statistical Methods—We computed descriptive statistics to compare distributions of patient baseline characteristics and outcome variables across ADT exposure groups. We assessed the relationship between reported duration of ADT exposure and reported development of fracture receipt of bone mineral density testing, and bone-medication use using univariable logistic regression. We then assessed the association between ADT exposure and fracture, receipt of bone mineral density testing, and bone-medication use using weighted multivariable logistic regression adjusted for ADT exposure, age at diagnosis, race, marital status, Gleason score, and Charlson comorbidity score. Sample weights were calculated as the inverse of the sampling proportions within each region–race– age group stratum. To account for 333 subjects with missing Gleason score data, we extrapolated the score from World Health Organization grade for 237 men who had such data available from SEER abstraction and incorporated this into the multivariable model. For 96 men without Gleason score and WHO grade, we performed single imputation to account for missing data. All tests of statistical significance were two-sided, and *P* values of less than 0.05 were considered statistically significant. We used R statistical software version 2.15.1 and the associated survey package for our analyses.[18–20]

Results

Study Population

Baseline characteristics of the 961 men diagnosed with non-metastatic prostate cancer who provided patient-reported outcomes 15 years following diagnosis are included in Table 1. In this population, 684 did not report ADT use, 120 men reported 1 year ADT, and 157 reported > 1 year of ADT exposure (Table 1). Rates of survey completion were similar among ADT exposure groups, with 86% of no ADT and 85% of the short-term and

prolonged ADT groups returning surveys at all time points. There were small but significant differences between participants in different treatment groups in terms of age at diagnosis, race, and education level. A greater percentage of men reporting ADT use had high grade disease (Gleason scores of 8–10), were treated with radiation rather than prostatectomy, and had slightly higher comorbidity scores than men not reporting ADT.

Study Outcome

The risk of self-reported fracture was 10% in the entire cohort, 9.5% in untreated men, 9% in men reporting treatment with short-term ADT (1 year), and 15% among men reporting treatment with prolonged ADT (> 1 year) (p = 0.18). The overall reported frequency of bone mineral density testing in the cohort was 27%, with 28% of men reporting short term ADT exposure, and 49% among men reporting prolonged ADT exposure also reporting bone mineral density testing (p < 0.001). On univariable analysis men reporting short-term ADT exposure (1 year) did not have an increased probability of reporting fracture, bone mineral density testing, or bone medication use compared with men not reporting treatment with ADT (Table 2). Men reporting treatment with prolonged ADT had increased odds of reporting fracture, bone mineral density testing, and bone medication use compared to men not reporting treatment with ADT (Table 2).

Bone medication use varied by duration of exposure to ADT and medication type. Among men reporting prolonged ADT, 50.3% reported treatment with bone medications, compared to 24.7% and 31.7% of men not reporting treatment with ADT and men reporting short-term ADT treatment, respectively (p < 0.001). Of men reporting bone medication use, 94% reported calcium or vitamin D use and 6% reported bisphosphonate use (including intravenous and oral formulations) (p < 0.001).

We used weighted logistic regression to assess the association between reported ADT treatment duration and reported development of fracture at 15 years accounting for patient-level covariates (Table 3). Men reporting short-term use of ADT did not have increased odds of fracture or bone medication use compared to men reporting no treatment with ADT, although there was a trend towards increased odds of fracture in this group when compared to men who did not receive any ADT (p=0.08). Men reporting treatment with prolonged ADT had significantly increased risk of fracture (OR 2.5, 95% CI 1.1–5.7) and bone medication use (OR 4.3, 95% CI 2.3–8.0) compared to men who denied treatment with ADT. Bone mineral density testing was more likely among men reporting treatment with both short-term and prolonged ADT than among men not reporting ADT treatment (OR 2.6, 95% CI 1.2–5.8 for short-term ADT; OR 5.9, 95% CI 3.0–12 for prolonged ADT). A sensitivity analysis performing the same analysis while excluding patients who experienced fracture yielded virtually identical results (data not shown).

Age, marital status, comorbidity, and Gleason grade were not associated with risk of fracture at 15 years, but African Americans had a lower risk of fracture compared to Caucasians (OR 0.15, 95% CI 0.04–0.60). Participants were more likely to report bone mineral density testing as they aged (OR 1.5 per 10 years, $P = 0.04$), but less likely to report testing with increasing comorbid illness, with adjusted ORs of 0.18 ($P < 0.001$) for Charlson score 2 and 0.24 ($P = 0.009$) for Charlson score 3, using persons with a score of 0 as the reference

group (data not shown). Compared to participants not exposed to ADT, those with long-term ADT use had significantly increased likelihood of bone-medication use with an adjusted OR of 4.3 (p<0.001). There were no significant associations between bone medication use and any other independent variables including age, marital status, comorbidity, race or Gleason grade (data not shown).

Discussion

Results from the PCOS provide important insights into the issue of bone health and patterns of preventive care in prostate cancer survivors who are receiving ADT. The odds of fracture, bone mineral density testing, and bone medication use were higher among men treated with prolonged (> 1 year) ADT compared to men not receiving ADT. The corresponding associations for short-term ADT use (1 year) were generally in the same direction, but far less pronounced.

Our data are consistent with several previously reported studies describing the effects of ADT on the risk of fracture. Several small prospective clinical trials with brief follow-up (12–24 months) demonstrate an association between exposure to ADT and declining bone mineral density, but do not describe the long-term risk of fracture.[5–8] This analysis demonstrated that men treated with ADT for more than one year had an increased risk of fracture compared to men not receiving treatment with ADT, while men treated with short-term ADT had a risk of fracture that was similar to that of untreated men. Although the rates of fracture were lower than those reported in fracture prevention trials that assess for asymptomatic fractures via scheduled skeletal surveys, the rate of fracture in this long-term, prospective study is consistent with evidence from previously reported Medicare analyses.[3,9] Among various patient-related factors, only African American race was associated with decreased odds of fracture (OR 0.15 compared to Caucasians), an observation that was consistent with a recent study which suggested that African Americans may have a lower risk of fracture as compared to Caucasians after two years of treatment with ADT (two-year incidence of any fracture was 9.8% in Caucasian men and 2.9% in African-American men, *P* = 0.07).[21] Findings from the PCOS cohort provide much-needed prospective data and long-term follow-up to confirm previously reported findings from these short-term prospective studies and retrospective database analyses.

The frequency of bone mineral density (BMD) testing and factors that influenced testing differed in this study from previously reported SEER-Medicare analyses. Men treated with prolonged ADT in the PCOS received BMD testing more commonly than men treated with greater than 1 year of ADT in the SEER-Medicare population (49% vs. 10.2%).[22] Frequency of BMD testing was also higher in the PCOS cohort overall (27%). In contrast to the SEER-Medicare analysis, men in the PCOS were more likely to report BMD testing as they aged, while men 85 years of age or older in the SEER-Medicare analysis were less likely to undergo BMD testing than men aged 66–69 years (OR 0.76, 95% CI 0.65–0.89).[22] These differences may be due to selection and response bias, as men choosing to participate in this study 15 years after their initial treatment for cancer may be more likely to engage in positive health care behaviors and advocate for BMD testing as they age. This difference may also be due to regional variability detected in the SEER-Medicare analysis, as PCOS

only sampled men from 6 of the available SEER regions. Importantly, the higher frequency of BMD testing in the aging PCOS cohort appears to reflect appropriate medical care, as a recent analysis found that the risk of fracture increases with age, with 98.8% of men over 80 years of age meeting criteria for pharmacologic therapy for fracture prevention.[23]

Our analysis is the first to report that the use of bone medications was significantly more common among men treated with prolonged ADT compared to untreated men, possibly indicating that practitioners are increasingly implementing appropriate osteoporosis and fracture prevention strategies, and counseling these high-risk patients. The majority of men who reported use of bone medications used either calcium or vitamin D, both of which are easily accessible over the counter. Utilization of bisphosphonates for prevention of fragility fractures in prostate cancer survivors at high risk of fracture, recommended for several years prior to the administration of the 15-year survey, was less common.[24] This may reflect poor understanding of the survey question by participants, slow uptake of national guideline recommendations, or low estimation of patient fracture risk by providers.

While our study reports multiple clinically relevant findings, we acknowledge that it has several limitations. First, the analysis cohort is approximately 27% of the original sample of men due to death or drop out from the study, as described elsewhere.[25] Because of this, the assessed cohort may represent a healthier "survivor" cohort without high rates of bone complications, resulting in under-reporting of those rates. However, one may expect similar or greater numbers of "survivor" participants in the no ADT or short-term ADT groups given their less aggressive prostate cancer, meaning the association demonstrated would bias towards the null. Secondly, we rely on patient report of long-term bone-related outcomes, possibly underestimating the frequency of fracture and bone mineral density testing. Finally, our analysis does not reflect physician recommendations that may have been disregarded by patients with poor adherence. Despite these limitations, the noteworthy strengths of these data are the length of the follow-up period and the diverse population that included younger men and a substantial proportion of minorities.

Conclusion

Men treated with prolonged ADT had significantly higher odds of fracture over a 15 years period after diagnosis than men not treated with ADT. Men receiving prolonged ADT also reported more frequent screening and treatment for bone-related complications, with 50% reporting use of bone medications. Notably, men receiving short-term ADT had a similar risk of fracture to men not receiving ADT, suggesting that short durations of adjuvant ADT therapy may not appreciably increase the risk of this complication. African-American men reported fewer fractures but underwent bone density testing at a similar frequency to Caucasian participants. Continued efforts to reduce skeletal complications for men receiving ADT should focus on reducing overtreatment of men with ADT when possible, and addressing skeletal health screening and complication prevention in men receiving prolonged ADT.

Acknowledgments

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Table 1

Baseline characteristics of men with localized prostate cancer by ADT treatment group.

	N (%)	No ADT N (%)	1 Year ADT N (%)	> 1 Year ADT N (%)
Total	961 (100)	684 (71.2)	120 (12.5)	157 (16.3)
Age in years (at diagnosis)				
				P = 0.001[2]
<50	33 (3)	28 (4)	3 (3)	2 (1)
50–59	315 (33)	238 (35)	31 (26)	46 (29)
60–69	439 (46)	315 (46)	58 (48)	66 (42)
70–79	170 (18)	102 (15)	27 (23)	41 (26)
80	4 (0)	1 (0)	1 (1)	2 (1)
Race				
				P = 0.037[1]
Non-Hispanic white	725 (75)	528 (77)	91 (76)	106 (68)
Non-Hispanic black	115 (12)	70 (10)	15 (12)	30 (19)
Hispanic	121 (13)	86 (13)	14 (12)	21 (13)
Marital status				
				P = 0.028[2]
Married	848 (88)	610 (89)	109 (91)	129 (82)
Unmarried	108 (11)	71 (10)	11 (9)	26 (17)
Unknown	5 (1)	3 (0)	0 (0)	2 (1)
SEER region				
				P = 0.10[1]
Connecticut	145 (15)	97 (14)	22 (18)	26 (17)
New Mexico	69 (7)	53 (8)	3 (2)	13 (8)
Seattle, Washington	117 (12)	88 (13)	11 (9)	18 (11)
Utah	191 (20)	133 (19)	22 (18)	36 (23)
Atlanta, Georgia	124 (13)	99 (14)	14 (12)	11 (7)
Los Angeles, California	315 (33)	214 (31)	48 (40)	53 (34)
Median household income incensus tract of residence				
				P = 0.50[1]
$10,000	28 (3)	20 (3)	3 (2)	5 (3)
$10,000–$20,000	83 (9)	59 (9)	8 (7)	16 (10)
$20,000–$40,000	236 (25)	159 (23)	30 (25)	47 (30)
$40,000–$75,000	306 (32)	217 (32)	42 (35)	47 (30)
> $75,000	233 (24)	179 (26)	24 (20)	30 (19)
Unknown/refused	75 (8)	50 (7)	13 (11)	12 (8)
Education level				
				P = 0.015[2]
Quartile 1 (<high school)	111 (12)	73 (11)	20 (17)	18 (11)
Quartile 2 (high school/some college)	408 (43)	276 (40)	48 (40)	84 (54)

	N (%)	No ADT N (%)	1 Year ADT N (%)	> 1 Year ADT N (%)
Quartile 3 (college)	174 (18)	132 (19)	24 (20)	18 (11)
Quartile 4 (advanced degree)	260 (27)	198 (29)	28 (23)	34 (22)
Unknown/refused	8 (1)	5 (1)	0 (0)	3 (2)
Insurance				
				P = 0.44[2]
Medicare	279 (29)	187 (27)	41 (34)	51 (32)
Private or military	572 (60)	415 (61)	66 (55)	91 (58)
Medicaid or other	18 (2)	12 (2)	4 (3)	2 (1)
No insurance	5 (1)	4 (1)	1 (1)	0 (0)
Unknown/refused	87 (9)	66 (10)	8 (7)	13 (8)
Tumor grade (Gleason)				
				P < 0.001[1]
Gleason 6	738 (77)	553 (81)	82 (68)	103 (66)
Gleason 7	160 (17)	100 (15)	24 (20)	36 (23)
Gleason 8	63 (7)	31 (5)	14 (12)	18 (11)
Charlson comorbidity score				
				P = 0.01[1]
0	465 (48)	348 (51)	49 (41)	68 (43)
1	317 (33)	225 (33)	45 (38)	47 (30)
2	123 (13)	78 (11)	14 (12)	31 (20)
3	56 (6)	33 (5)	12 (10)	11 (7)
Baseline comorbid disease				
Diabetes[3]	64 (7)	34 (5)	15 (12)	15 (10)
Congestive heart failure	20 (2)	13 (2)	4 (3)	3 (2)
Stroke	20 (2)	13 (2)	2 (2)	5 (3)
Heart attack	45 (5)	26 (4)	10 (8)	9 (6)
Hypertension	285 (30)	191 (28)	39 (32)	55 (35)
Chronic pulmonary disease	16 (2)	12 (2)	1 (1)	3 (2)
Depression[2]	57 (6)	28 (6)	13 (11)	6 (4)
Primary treatment[4]				
Radical prostatectomy	697 (73)	538 (79)	78 (65)	81 (52)
Radiation therapy	158 (16)	97 (14)	27 (23)	34 (22)
Hormonal therapy	26 (3)	0 (0)	13 (11)	13 (8)
Watchful waiting	80 (8)	49 (7)	2 (2)	29 (18)

[1] P-value calculated by Pearson Chi-squared test.

[2] P-value calculated by Pearson Chi-squared test after collapsing neighboring categories to account for empty cells.

[3] Diabetes (P = 0.003) and depression (P = 0.04) were the only baseline comorbidities that significantly varied in prevalence between ADT treatment groups. P-values calculated by Pearson Chi-squared test (not shown).

[4] Treatment groups were divided as follows: Radical prostatectomy includes men who reported prostatectomy alone, prostatectomy plus radiation, prostatectomy plus hormonal therapy (ADT or orchiectomy), and prostatectomy plus radiation and hormonal therapy; Radiation includes men who

reported radiation alone, and radiation plus hormonal therapy; Hormonal therapy includes only men who reported definitive hormonal therapy as their primary treatment; Watchful waiting includes men who reported watchful waiting or no treatment.

Table 2

Odds ratios for bone-related complications 15 years after diagnosis by ADT treatment group (univariable analysis).

	N/Total	OR	95% Confidence Interval	P-Value[1]
Fracture[1]				
No ADT	65/611	Ref		
1 year ADT	11/107	0.97	0.5 – 1.9	0.92
> 1 year ADT	23/125	1.7	1.0 – 2.9	0.04*
Bone mineral density testing[1]				
No ADT	150/465	Ref		
1 year ADT	34/76	1.4	0.9 – 2.2	0.15
> 1 year ADT	77/52	4.6	3.1 – 6.8	< 0.001*
Bone medication use[1]				
No ADT	169/495	Ref		
1 year ADT	38/76	1.5	0.96 – 2.2	0.08
> 1 year ADT	79/70	3.3	2.3 – 4.8	< 0.001*

[1]P-value calculated by logistic regression

*Statistically significant result.

Table 3

Multivariable analysis of the adjusted association between ADT duration and the development of fracture 15 years after diagnosis.

	OR	95% Confidence Interval	P-Value[2]
No ADT	Reference		
1 year ADT	2.5	0.9 – 7.0	0.08
> 1 year ADT	2.5	1.1 – 5.7	0.033[*]
Age at Diagnosis (by 10 yrs)	1.6	0.9 – 2.7	0.10
Race			
Caucasian	Reference		
Black	0.15	0.04 – 0.6	0.008[*]
Hispanic	1.0	0.5 – 2.3	0.97
Marital Status			
Married	Reference		
Single	1.1	0.4 – 2.6	0.88
Comorbidity Index			
0	Reference		
1	0.4	0.2 – 1.0	0.05
2	0.6	0.2 – 1.7	0.33
3+	0.8	0.1 – 5.0	0.85
Gleason score			
6	Reference		
7	0.9	0.4 – 2.1	0.84
8–10	0.8	0.2 – 3.4	0.79

[1] Multivariable model adjusts for ADT treatment, age, race, marital status, comorbidity index and Gleason score.

[2] P-value calculated by multivariable logistic regression incorporating sampling weights.

[*] Statistically significant result.