Osteoporosis and fractures after androgen deprivation initiation for prostate cancer

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Introduction: *Androgen deprivation therapy (ADT) is widely utilized for treatment of localized and advanced prostate cancer (CaP). ADT is associated with increased rates of osteoporosis; however, its impact on fracture risk is not completely understood. We investigated incidence and predisposing factors for osteoporosis and fractures in a large, contemporary, single institution series of patients treated with ADT for CaP.*

Methods: *We retrospectively reviewed medical records of all patients who received ADT for CaP between 1/1989 and 7/2005. Primary endpoints of investigation were osteoporosis and non-pathologic fractures. Independent variables included age, race, body mass index (BMI), pretreatment serum PSA, Gleason sum, clinical stage, ADT type (medical versus surgical) and schedule (continuous versus intermittent), and receipt of calcium, vitamin D or bisphosphonate supplementation. Data were analyzed by Chi-square test, Student's t-test, Linear Regression, and Logistic Regression ($p < 0.05$ significant).*

Results: *A total of 395 patients were analyzed (mean age 71.7 years, 59% African American, 41% Caucasian/other). At mean follow-up of 66.1 months, 92 (23%) patients developed osteoporosis and 27 (7%) patients developed non-pathologic fractures. On univariate analysis, age, race, BMI, and ADT duration were significantly associated with osteoporosis development, while BMI, ADT duration, and presence of osteoporosis were significantly associated with fracture incidence. Regression analysis revealed that age > 70 at ADT initiation, continuous ADT, and increased treatment duration predicted osteoporosis development, while only osteoporosis was independently predictive of fracture development.*

Conclusions: *Patients receiving continuous ADT for CaP are at increased risk for developing osteoporosis which may lead to fractures, with an incidence of 7% in our study population.*

Key Words: prostate cancer, androgen deprivation therapy, hormonal therapy, complications, fractures, osteoporosis

Introduction

Prostate adenocarcinoma (CaP) is the most commonly diagnosed malignancy in men in the United States, with an expected 218 890 new cases and 27 050 deaths estimated in 2007.[1] Androgen deprivation therapy (ADT) is used broadly as a treatment for men with clinically localized and advanced stage prostate cancer. Current applications of ADT include neoadjuvant and adjuvant therapy in men undergoing primary external beam radiation therapy (EBRT) or brachytherapy for clinically localized CaP, adjuvant therapy in men with lymph node metastases, salvage therapy in men with rising PSA after primary surgical or radiation treatment for localized CaP, gland downsizing prior to prostate cryosurgery, and primary palliative therapy in select patients.[2,3]

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ADT is associated with a wide profile of adverse affects in the short term, including decreased libido, vasomotor flushing, fatigue, and anemia. In recent years, a growing body of literature has defined a profile of significant long term adverse effects, including osteoporosis, skeletal fractures, altered body composition, and impaired glycemic control.[2-7] A number of studies have reported increased rates of osteoporosis and fractures among patients treated with ADT, although the precise nature of these associations remains ill-defined.[5-7] We therefore investigated the incidence of osteoporosis and fractures in our series of patients treated with ADT for prostate cancer.

Materials and methods

After obtaining institutional review board approval, we performed retrospective chart review of all patients receiving ADT for CaP at a single center (Veterans Affairs Medical Center, Memphis, Tennessee, USA) at our institution between January 1989 and June 2005. ADT was defined as receipt of a GnRH agonist (Goserelin acetate depot, AstraZeneca PLC, London, UK), combined androgen blockade (GnRH agonist and anti-androgen), or bilateral orchiectomy. Patients with incomplete records and those receiving only adjuvant or neoadjuvant ADT were excluded. Primary endpoints of the chart review were development of osteoporosis and non-pathologic fracture. Osteoporosis was diagnosed by dual-energy x-ray absorptiometry (DXA) scan.[8] Bone density studies were ordered at the discretion of the treating physician, usually the primary care physician; the urology service did not institute a protocol for routine surveillance of bone density. Imaging for detection of fractures was obtained when there was clinical suspicion of a fracture event. Fractures were considered non-pathologic in the absence of imaging or histology proving otherwise. Each fracture event was reviewed for mode of injury, management, and associated morbidity and mortality. Clinicopathologic variables analyzed included age at ADT initiation, duration of treatment, race, BMI (kg/m^2), pre-treatment serum PSA, Gleason sum, clinical stage (AJCC 1992),[9] type of ADT (medical versus surgical), ADT schedule (continuous versus intermittent), and receipt of calcium, vitamin D, or bisphosphonate therapy.

Statistical data analysis was conducted to describe factors which are significantly associated with, and/or predictive for, the development of osteoporosis and fracture during ADT treatment. Data were analyzed using univariate and multivariate statistics. Student's t-test and Chi-square test were utilized for univariate analysis, while Linear Regression and Multivariate Stepwise Logistic Regression statistics, utilizing the forward procedure, were used for multivariate analysis, whereby all potential explanatory covariates were incorporated into the model as independent variables with fracture or osteoporosis as the dependent variable.

Potential independent variables including age, Gleason sum, pretreatment serum PSA level, and BMI were modeled as both continuous and dichotomous variables as follows: age ≤ 70 versus > 70 years, Gleason sum < 7 versus ≥ 7, PSA < 10 versus ≥ 10 ng/dL, and BMI < 30 versus ≥ 30 kg/m^2. Other categorical variables included race (African American or Caucasian/other), castration type (surgical or medical), pattern of ADT treatment (continuous or intermittent), use of combined androgen blockade (CAB), osteoporosis, calcium/vitamin D supplementation, and bisphosphonate supplementation. Independent variables were included in the regression models if $p \leq 0.10$ in univariate analysis. The proportion of patients surviving fracture-free or osteoporosis-free was assessed by Kaplan-Meier analysis. Cox Proportional Hazards models were used to determine risk factors for osteoporosis. Survival data were analyzed by age, race and BMI.

All reported p-values were based on two-sided tests of significance, with $p < 0.05$ considered statistically significant. Statistical analysis was carried out using SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

Results

Demographic and clinicopathologic data are summarized in Table 1. A total of 395 patients were included in the analysis with a mean age at ADT initiation of 71.7 years (median: 73.1, range: 47-89). Of these, 233 (59%) were African American, while 162 (41%) were Caucasian/other. Mean pretreatment serum PSA value was 130.8 ng/dL (median: 15.4, range: 0.4-6031.0) and mean follow-up time was 66.1 months (median: 60.1, range: 10.7-208.2). Three hundred seventy-one (94%) men received pharmacologic ADT while 24 (6%) underwent bilateral orchiectomy. In total, 264 (67%) men underwent ADT as salvage therapy after failing initial curative attempts while 131 (33%) elected to undergo ADT as primary therapy for CaP. Three hundred fifty-nine (91%) men received continuous ADT while 36 (9%) received intermittent ADT.

TABLE 1. **Demographic and clinicopathologic data**

Variable	
Number of patients	395
Age at ADT initiation (years)	
Mean	71.7
Median (range)	73.1 (46.7-89.3)
Pretreatment serum PSA level (ng/dL)	
Mean	130.8
Median (range)	15.4 (0.4-6031.0)
Gleason grade sum (mean [median, range])	6.9 (7.0, 3.0-10.0)
Primary Gleason grade	3.4 (3.0, 2.0-5.0)
Secondary Gleason grade	3.5 (3.0; 1.0-5.0)
BMI (kg/m^2)	
Mean	26.9
Median (range)	26.7 (12.5-52.4)
Race (n/%)	
African American	233 (59.0)
Caucasian/other	162 (41.0)
Castration type (n/%)	
Medical	371 (93.9)
Surgical	24 (6.1)
ADT therapy type (n/%)	
Primary	131 (33.2)
Salvage	264 (66.8)
EBRT/Brachytherapy	199 (50.3)
RRP	32 (8.1)
TCAP	13 (3.3)
EBRT/TCAP	2 (0.5)
RRP/EBRT	18 (4.6)
ADT administration schedule (n/%)	
Continuous	359 (90.9)
Intermittent	36 (9.1)
Clinical stage (n/%)	
T1a/b	5 (3.8)
T1c	163 (41.1)
T2a	42 (10.6)
T2b/c	22 (5.6)
T3a/b/c	7 (1.8)
N+	8 (2.0)
M+	14 (3.5)
Unknown	125 (31.6)
Vitamin D supplementation (n/%)	
Yes	12 (3.0)
No	383 (97.0)
Bisphosphonate therapy	
Yes	18 (4.6)
No	377 (95.4)
Follow-up time (months)	
Mean	66.1
Median (range)	60.1 (10.7-208.2)

Outcomes are summarized in Table 2. At a mean follow-up of 66.1 months, 92 (23%) patients developed osteoporosis and 27 (7%) patients developed non-pathologic fractures. Fractures occurred in ribs (4), hip/pelvis (15), humerus (3), wrist (4), ankle (1), tibia (2), and spine (12). Excluding one pedestrian-struck patient who suffered tibial fractures, all fractures were the result of minor trauma associated with same level falls or were subacute at the time of diagnosis. Twenty-nine (71%) fractures were managed nonoperatively with splints, casts, or observation, and twelve (29%) fractures were managed operatively by either the orthopedic or neurosurgery services. The urology service was consulted for urinary retention during the post-operative course of one patient who underwent surgical management of a hip fracture, but otherwise the urology service was not involved directly or indirectly in the diagnosis or management of any fracture events; in only five instances was a fracture event noted in the urologic record. Two patients who were admitted for operative management of hip fractures died as a result of perioperative complications.

TABLE 2. **Osteoporosis and fractures - outcomes and complications**

Outcome	**Number (total n = 395)**
Patients with osteoporosis	92 (23%)
Patients with nonpathologic fractures	27 (7%)
Fracture location	
Hip/pelvis	15
Spine	12
Wrist	4
Humerus	3
Ribs	4
Tibia	2
Ankle	1
Fracture management	
Operative	12 (29%)
Non-operative	29 (71%)
Inpatient	23 (56%)
Outpatient	18 (44%)
Complications associated with fractures	
Pneumonia	2
Thromboembolism	1
Cerebrovascular accident/ cerebral hemorrhage	1
Myocardial Infarction	1
Death	2

Univariate analyses of potential explanatory covariates for osteoporosis and fracture incidence are summarized in Table 3 and Table 4, respectively. Variables significantly associated with development of osteoporosis include age, BMI, duration of therapy, and race. Advanced age at the time of ADT initiation was positively associated with osteoporosis on analysis both as a continuous and as a categorical (≤ 70 years versus > 70 years) covariate ($p = 0.04$; $p \leq 0.001$). Lower BMI was positively associated with osteoporosis on analysis both as a continuous and as a categorical (< 30 versus ≥ 30) covariate ($p = 0.04$; $p \leq 0.025$). Development of osteoporosis was significantly associated with increased duration of therapy (mean treatment duration: 87.6 months) compared to cases without osteoporosis (mean treatment duration: 60.6 months) ($p < 0.001$). The incidence of osteoporosis among Caucasian/other patients (31%) was higher than among African American patients (18%) ($p \leq 0.01$). Differences in the incidence of osteoporosis according to the continuity of ADT (continuous versus intermittent) or use of combined androgen blockade were not statistically significant. Only 12 patients were given calcium/vitamin D supplementation, and only 18 patients were given bisphosphonates. Although these covariates were positively associated with osteoporosis and fractures, a review of timeline data showed that in almost every case supplements were started after the diagnosis of osteoporosis or fracture.

On univariate analysis, fracture incidence among patients differed significantly according to BMI, duration of therapy, and presence of osteoporosis, but not by age or race, Table 4. Mean BMI was lower in patients with fractures (23.6 kg/m^2) than in those without fractures (27.4 kg/m^2) ($p = 0.001$). Duration of ADT was, on average, 49% longer in patients with fractures (mean treatment duration: 96.6 months) than in those without fractures (mean treatment duration: 64.7 months) ($p \leq 0.001$). Predictably, the development of osteoporosis was positively associated with the development of fractures ($p \leq 0.001$).

Table 5 summarizes the results of multivariate analysis of osteoporosis and fracture incidence and potential explanatory covariates. Regression analysis demonstrated three factors that were significantly associated with the development of osteoporosis: advanced age, continuity of ADT, and increased treatment duration. Patients greater than 70 years of age at the time of ADT initiation were more likely to develop osteoporosis compared to younger patients (OR, 2.489, $p = 0.025$). Patients receiving continuous androgen deprivation therapy were more likely to

TABLE 3. **Osteoporosis and potential explanatory covariates**

Variable	Categorical subsets	Osteoporosis Yes	Osteoporosis No	Total	P value
ADT pattern	Continuous	88	271	359	≤ 0.1
	Intermittent	4	32	36	
Age (continuous)		73.1*	71.2*		0.04†
Age (categorical)	≤ 70	23	134	157	≤ 0.001
	>70	69	169	238	
Bisphosphonate	No	81	296	377	≤ 0.001
	Yes	11	7	18	
BMI (continuous)		26.0*	27.4*		0.04†
BMI (categorical)	< 30	76	213	289	≤ 0.025
	≥ 30	16	90	106	
CAB	No	56	210	266	≤ 0.2
	Yes	36	93	129	
Calcium/vit D	No	82	301	383	≤ 0.001
	Yes	10	2	12	
Castration type	Medical	89	282	371	≤ 0.20
	Surgical	3	21	24	
Duration of therapy (continuous)		87.6 mos*	60.6 mos*		< 0.001†
Gleason sum	< 7	23	62	85	≤ 1
	≥ 7	44	156	200	
PSA (continuous)		102.7*	137.7*		0.66†
PSA (categorical)	< 10	18	87	105	≤ 1
	≥ 10	41	153	194	
Race	African American	42	191	233	≤ 0.01
	Caucasian/other	50	112	162	

*mean
† Student's t-test

develop osteoporosis compared to those receiving intermittent therapy (OR, 2.144, p = 0.032). Finally, increased treatment duration was predictive for the development of osteoporosis (OR, 3.521, p = 0.001). On multivariate analysis of fracture events and potential explanatory covariates, only the presence of osteoporosis was statistically significant (OR, 3.264, p = 0.006).

The mean duration of treatment for the study was 66.1 months. However, Caucasian and African American patients differed in terms duration of treatment. White patients received treatment up to a maximum of 208.66 months compared to African American patients who received treatment at a maximum of 184.67 months. Because of these differences, Kaplan Meier analysis covered a range for treatment duration from 0 to 184.67 months, which includes data on 375 patients. A total of 286 (76%) of

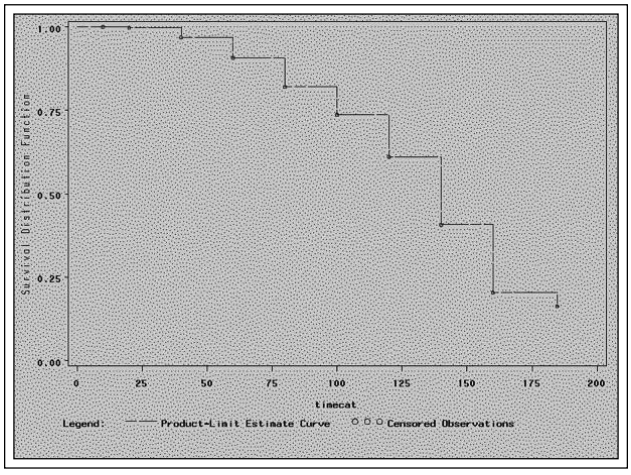

Figure 1. Androgen deprivation and osteoporosis free survival.

TABLE 4. **Fractures and potential explanatory covariates**

Variable	Categorical subsets	Fracture		Total	P value
		Yes	No		
ADT pattern	Continuous	25	334	359	≤ 1
	Intermittent	2	34	36	
Age (continuous)		71.8*	71.6*		0.93†
Age (categorical)	≤ 70	12	145	157	≤ 1
	> 70	15	223	238	
Bisphosphonate	No	23	354	377	≤ 0.01
	Yes	4	14	18	
BMI (continuous)		23.6*	27.4*		0.001†
BMI (categorical)	< 30	24	265	289	≤ 0.1
	≥ 30	3	103	106	
CAB	No	16	250	266	≤1
	Yes	11	118	129	
Calcium/vit D	No	23	360	383	≤ 0.001
	Yes	4	8	12	
Castration type	Medical	26	345	371	≤ 1
	Surgical	1	23	24	
Duration of therapy (continuous)		96.6 mos*	64.7 mos*		≤ 0.001†
Gleason sum	< 7	4	81	85	≤1
	≥ 7	12	188	200	
Osteoporosis	No	13	290	303	≤ 0.001
	Yes	14	78	92	
PSA (continuous)		184*	128*		0.7†
PSA (categorical)	< 10	6	99	105	≤1
	≥ 10	9	185	194	
Race	African American	12	221	233	≤0.2
	Caucasian/other	15	147	162	

*mean
†Student's t-test

patients in the study survived osteoporosis-free over the duration of ADT treatment, Figure 1. Osteoporosis-free survival varied significantly by age, race and combination of race with BMI. African American patients (log rank p = 0.0072) and patients 70 years of age or younger (log rank p = 0.0040) were more likely to survive osteoporosis-free over the duration of ADT treatment. Also, African American patients with a BMI greater than 30 (log rank p = 0.0142) were more likely to survive osteoporosis-free over the duration of ADT. A total of 351 (94%) of patients survived fracture-free over the duration of ADT treatment, Figure 2. Fracture-free survival did not vary significantly by race, BMI or age. However, fracture-free survival was highest amongst African American patients with a BMI greater than 30 (98% fracture-free survival).

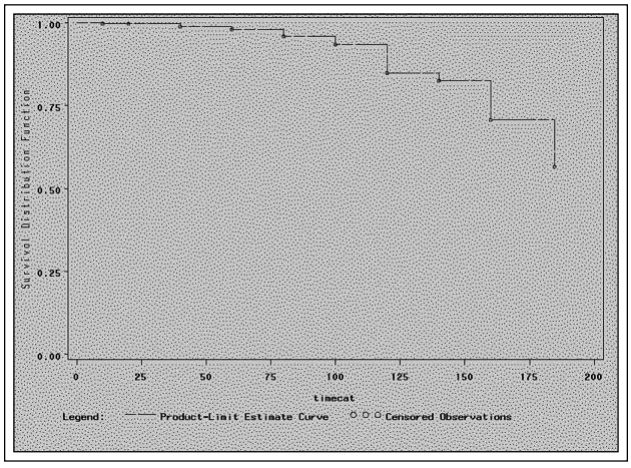

Figure 2. Androgen deprivation and fracture free survival.

TABLE 5. Regression analysis of predictive factors

	Osteoporosis		Fracture	
Variable	**Odds ratio**	**P value**	**Odds ratio**	**P value**
ADT pattern (continuous versus intermittent)	2.144	0.032	1.320	0.822
Age (> 70 versus ≤ 70)	2.489	0.025	0.612	0.531
Bisphosphonate (yes versus no)	0.263	0.110	3.762	0.220
BMI (< 30 versus ≥ 30)	1.018	0.961	1.036	0.969
CAB (yes versus no)	0.637	0.098	1.447	0.653
Calcium/vit D (yes versus no)	0.079	0.033	4.078	0.041
Castration type (medical versus surgical)	0.476	0.218	1.195	0.865
Gleason sum (≥ 7 versus < 7)	1.884	0.071	1.804	0.525
Increased treatment duration*	3.521	0.001	0.986	0.138
Osteoporosis (yes versus no)	3.264	0.006		
PSA (≥ 10 versus < 10)	1.325	0.481	2.900	0.176
Race (Caucasian/other versus African American)	0.822	0.590	2.451	0.206

*continuous variable

Discussion

Among 395 patients treated with ADT for a mean treatment duration of 66 months, we identified a 23% cumulative incidence of osteoporosis and a 7% cumulative incidence of nonpathologic fractures, Tables 1 and 2). Our findings are generally consistent with previously published studies pertaining to osteoporosis and fracture prevalence in men treated with ADT.[10-12] A number of prospective and retrospective studies have demonstrated accelerated bone loss in men with prostate cancer treated with ADT.[7,13-16] Most studies report a 3%-5% annual decrease in bone mineral density (BMD) during initial androgen deprivation therapy with a subsequent decrease in annual bone loss during long-term treatment.[17] However, the overall prevalence of osteoporosis in men with prostate cancer is unknown. Bruder et al reported a 27% prevalence of osteoporosis in a retrospective study of 125 men treated with ADT.[18] In two smaller studies, Berruti et al reported significant bone loss in 26% to 31% of patients in a prospective study of 35 patients treated with ADT,[7] while Modi et al described a 38% prevalence of osteoporosis in 26 men treated with ADT for at least 1 year.[19] Not all men with prostate cancer treated with ADT will develop osteoporosis, due to variability in clinical and pathologic factors; however an overall osteoporosis prevalence of at least 23% can be anticipated with long term ADT.

In addition to hypogonadism, known risk factors for osteoporosis include advanced age, alcohol abuse, chronic glucocorticoid therapy, smoking, slender body habitus, and decreased physical activity.[20] It is not currently known how these and other clinicopathologic factors modulate the osteoporosis-inducing effect of ADT. Our multivariate regression analysis demonstrated that advanced age (> 70) at the time of ADT initiation, continuous as opposed to intermittent ADT, and increased duration of ADT were independent factors significantly associated with development of osteoporosis, Table 5. In prior studies, increased duration of ADT has consistently demonstrated independent predictive value for development of osteoporosis.[15,16] While the effect of intermittent androgen deprivation on BMD has not previously been well studied; it seems plausible that with intervals of "ADT holiday," bone mineral density could be better maintained over the long term.

Our multivariate analysis failed to show a significant independent predictive value for BMI or race, Table 5. Indeed, the effects of BMI as well as advanced age on development of osteoporosis have not been demonstrated with consistency across published studies.

Daniell et al noted that average bone loss after castration was 50% greater in obese men and men younger than 75.[13] On the other hand, Berruti et al found no significant relationship between age and changes in bone mineral density in a prospective study of 35 patients treated with LHRH analogue for 12 months.[7] The impact of race on development of osteoporosis during ADT is also uncertain. Oefelein et al demonstrated that African American racial background was an independent protective factor against development of osteoporosis,[21] while our data failed to show racial background as an independent predictor for development of osteoporosis, Table 5, (although on univariate analysis a significantly smaller proportion of African Americans developed osteoporosis than Caucasians/other [Table 3]). Racial distribution within a study cohort has been shown to have a significant impact on measured outcomes, with a selection bias toward groups that may be underrepresented.[22] Our patient cohort included a larger number and proportion of African Americans than Oefelein et al's, (59% versus 30%, respectively),[21] thus decreasing the potential for a selection bias due to racial disparities of number. Nevertheless, prospective studies are needed to resolve these discrepancies.

We identified a nonpathologic fracture incidence of 7% in our study population, Table 2. This fracture incidence, although lower than reports from large epidemiological studies,[11,23] is comparable to results from previously published, single center, retrospective studies.[6,21,24] Hatano et al reported that 14 (6%) of 218 patients developed nonpathologic skeletal fractures after a mean of 28 months of androgen deprivation.[24] Oefelein et al reported that nonpathologic fractures occurred in 9 (5%) of 181 patients at a median duration of 47 months of ADT.[21] Townsend et al reported a 4.9% incidence of nonpathologic skeletal fractures in 224 patients treated with ADT for 96 months.[6] Of note, both Oefelein and Townsend reported a general lack of awareness of fracture events in the urologic medical records,[6,21] and we also found that fracture events were infrequently noted in the urologic records in our patient cohort. We did not have a control group in our study, and therefore relative fracture risk for patients in the ADT cohort cannot be estimated with any real precision. Previously published studies have estimated relative fracture risks ranging from 1.21 to 2.5.[10,23,25]

Fractures events in our study population were associated with minor to moderate trauma. The morbidity associated with fractures was significant, and although most fractures were managed nonoperatively, inpatient management was required in the majority of cases, Table 2. Of the 27 patients who developed fractures, 13 developed hip fractures (2 patients suffered asynchronous bilateral hip fractures). Two of the 13 patients who developed hip fractures died in the hospital after an extended, complicated, post-operative course. In general, about one-fifth of elderly individuals with hip fractures die from thromboembolic events, infection, or other complications[26] with higher mortality rates in men than in women.[27]

It should be pointed out that published investigations have demonstrated clinically significant means to limit the osteoporosis inducing effects of androgen deprivation therapy. Bisphosphonates at various dosing intervals have proven effective in limiting the rate of bone loss and increasing bone mineral density in prospective trials with men initiating androgen deprivation therapy for nonmetastatic prostate cancer.[28,29,30] In contrast, oral calcium and vitamin D supplements alone appear to be insufficient to prevent loss of bone mineral density in men initiating androgen deprivation therapy. Clinical practice surveys suggest that a minority of urologists actually screen for or prescribe bisphosphonate therapy for prevention of osteoporosis in men initiating androgen deprivation for prostate cancer.[31]

The retrospective nature of this investigation, the lack of a control group (i.e., men with prostate cancer who were on surveillance protocols or who received only primary localized therapy for prostate cancer) and potential selection bias with respect to initiation of ADT are all major methodological factors that limit the strength of our findings. Furthermore, while the electronic medical records system of the Veterans Administration Medical Centers (VAMC) allows access to comprehensive medical management records across all specialties and VAMC localities, any medical care provided outside of the VAMC system was not included in our analysis. To an uncertain degree, these study limitations almost certainly lead to an underestimation of the effects of long-term ADT on osteoporosis and skeletal fractures. However, the results of this investigation are bolstered by the size of the study population and the duration of follow-up. To our knowledge, this is the largest single-center series of patients evaluated for osteoporosis and fractures in the setting of ADT for prostate cancer reported to date. The follow-up period is substantial, with a mean duration of therapy of 66 months at an equal access health care center (the Veterans Affairs health care system).[22,32] Age and prostate disease characteristics in our study cohort are representative of the larger United States prostate cancer population, while race, lifestyle, and general health characteristics may reflect regional trends (Memphis, Shelby County, Tennessee).[33]

Conclusions

Patients receiving ADT for CaP are at increased risk for developing osteoporosis which may lead to fractures. Fracture incidence in our study population was 7% and was associated with significant morbidity and measurable mortality, which was often not appreciated by the treating urologist. These factors should be considered when starting patients with prostate cancer on androgen deprivation therapy, and appropriate patient counseling should precede the initiation of long-term androgen deprivation. □

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