

Falls and Physical Performance Deficits in Older Patients With Prostate Cancer Undergoing Androgen Deprivation Therapy

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OBJECTIVES	Men experience a decrease in lean muscle mass and strength during the first year of androgen deprivation therapy (ADT). The prevalence of falls and physical and functional impairment in this population have not been well described.
METHODS	A total of 50 men aged 70 years and older (median 78) receiving ADT for systemic prostate cancer (80% biochemical recurrence) underwent functional and physical assessments. The functional assessments included Katz's Activities of Daily Living (ADLs) and Lawton's Instrumental Activities of Daily Living (IADLs). Patients completed the Vulnerable Elder's Survey-13, a short screening tool of self-perceived functional and physical performance ability. Physical performance was assessed using the Short Physical Performance Battery. The history of falls was recorded. Of the 50 patients, 40 underwent follow-up assessment with the same instruments 3 months after the initial assessment.
RESULTS	Of the 50 men, 24% had impairment in the ADLs, 42% had impairment in the IADLs, 56% had abnormal Short Physical Performance Battery findings, and 22% reported falls within the previous 3 months. Within the Short Physical Performance Battery, deficits occurred within all subcomponents (balance, walking, and chair stands). On univariate analysis, age, deficits in ADLs and IADLs, and abnormal cognitive and functional screen findings were associated with an increased risk of abnormal physical performance. ADL deficits, the use of an assistive device, and abnormal functional screen findings were associated with an increased risk of falling.
CONCLUSIONS	The results of our study have shown that older men with prostate cancer receiving long-term ADT exhibit significant functional and physical impairment and are at risk of falls that is greater than that for similar-aged cohorts. Careful assessment of the functional and physical deficits in older patients receiving ADT is warranted. UROLOGY 72: 422–427, 2008. © 2008 Elsevier Inc.

Prostate cancer largely affects older men, with 75% of prostate cancer incidence and more than 90% of prostate cancer mortality occurring in men older than 65 years old.¹ Older men, including those with prostate cancer, are at risk of functional decline because of normal senescent changes. More than one half of men

with prostate cancer aged 75 years or older have at least one serious comorbidity and most will die with, not because of, their cancer.^{2,3} Luteinizing hormone-releasing hormone agonist therapy, the standard first-line androgen deprivation therapy (ADT) for recurrent or metastatic prostate cancer, reduces testosterone to castrate levels in almost all patients.^{4,5} The well-established toxicities of ADT include fatigue, muscle weakness and wasting, and osteoporosis. All these can be potentially harmful to a vulnerable subset of patients. Despite this, ADT is increasingly being used in older men, with 48% of men 80 years old and older receiving ADT within 6 months of their initial diagnosis.⁶ However, these men are often asymptomatic, and no definitive overall survival benefit to early vs late initiation of ADT has been demonstrated.⁷

The objective of this study was to estimate the prevalence of functional and physical impairment among older patients with prostate cancer receiving ADT using a comprehensive geriatric assessment (CGA) and to bet-

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ter describe the prevalence of falls in older patients with prostate cancer receiving ADT.

MATERIAL AND METHODS

Patient Population, Research Design, and Data

We report on a convenience sample of men aged 70 years and older who attended the University of Chicago Genitourinary Oncology clinics with histologically confirmed prostate cancer and were receiving ADT. The recruitment inclusions, exclusions, and methods have previously been reported in a validation study of Vulnerable Elder's Survey-13 (VES-13).⁸ In brief, eligible patients had nonprogressive systemic disease, which was defined as biochemical recurrence using standard criteria, or asymptomatic metastatic disease.⁹ All patients had received ADT for their prostate cancer for at least 3 months and were responding to treatment as determined by prostate-specific antigen criteria. Patients were English-speaking with at least an eighth grade education, had no other active cancer diagnosis, and no history of chemotherapy.

A total of 50 patients underwent a CGA at baseline, and 40 underwent the same assessments again after 3 months. We included a battery of functional measures, including Activities of Daily Living (ADLs, basic activities to care for oneself),¹⁰ Instrumental Activities of Daily Living (IADLs, ability to perform higher functions),¹¹ and VES-13 (self-reported geriatric screening tool used to identify patients at risk of functional decline).¹² The Short Physical Performance Battery (SPPB) assessed balance, quadriceps strength, and walking speed.^{13,14} A history of falls within the previous 3 months was obtained at the first assessment, and, at the second assessment, a history of any new falls since the previous assessment 3 months earlier was recorded. Other subsets of the CGA included the Short Portable Mental Status Questionnaire as a cognitive screen,¹⁵ Charlston Comorbidity Index,¹⁶ medication history, Medical Outcomes Study social support scale,¹⁷ Mini-Nutritional Assessment to identify geriatric patients at risk of malnutrition (using the determinants of appetite, weight loss, and body mass index),¹⁸ and the Medical Outcomes Study Short Form 36-item Health Survey to screen for fatigue.¹⁷ Abnormal findings in each of the tests included within the CGA are associated with an increased risk of morbidity and/or mortality and have been validated within the elderly population.⁸

Participation in the study was entirely voluntary, and the ethical standards for human subjects were strictly followed, including study approval by the University of Chicago's institutional review board.

Statistical Analysis

The primary objectives of the study and method have been previously reported.⁸ The sample size was designed to provide a suitably precise estimate of the proportion scoring at or greater than the "vulnerable" score on the VES-13. Specifically, a sample size of 50 participants would provide a confidence interval within 13% of the true prevalence value, assuming a true prevalence value of 40%. Standard descriptive statistics (eg, frequencies and relative frequencies) and summary statistics (eg, mean, median, standard deviations, and/or range) were used as appropriate. The percentage of persons who met the predetermined cutoff score for impairment on each individual test was recorded. Using logistic regression analysis, univariate associations between patient characteristics and impairment on the

Table 1. Baseline patient and disease characteristics

Characteristic	Value
Patients enrolled (n)	50
Age (y)	
Median	78
Range	70-92
Education (y)	
Median	14
Range	8-20
Race (%)	
White	64
African American	36
BMI (kg/m ²)	
Median	29.6
Range	28.5-38.1
Albumin	
Median	4.1
Range	3.2-5
Hemoglobin	
Median	12.8
Range	7.8-15.9
Gleason score	
Median	7
Range	5-9
Disease status (%)	
Biochemical recurrence	80
Overt metastatic disease	20
Previous local therapy (%)	
RT	68
Surgery	16
None	16
ADT interval (mon)	
Median	36
Range	3-96

BMI = body mass index; RT = radiotherapy; ADT = androgen deprivation therapy.

SPPB and the risk of falls were evaluated to determine whether any significant predictor variables existed. Multivariate regression analysis was not performed due to concern about the instability of parameter estimates with a limited sample size. Stata, version 9.0 (StataCorp, Chicago, IL) was used for all statistical analyses.

RESULTS

Sample

A total of 58 patients agreed to participate in the study. Of the 58 patients, 50 completed the surveys and physical performance assessment at baseline and were included in this analysis. Of these 50 patients, 40 completed the follow-up assessments at 3 months, with 10 patients lost to follow-up. No significant differences were noted in patient-level characteristics between the 8 patients who did not complete the baseline assessment and the 50 patients who completed the study procedures (data not shown).

Patient and Disease Characteristics

The patient characteristics are listed in Table 1. The median patient age was 78 years, the patients were primarily married and well-educated, and 36% were African

Table 2. Abnormalities on comprehensive geriatric assessment

Test	Geriatric Domain	Score Range	Cutoff Point Associated with Adverse Outcomes*	Median (Range)	Impaired (%)
VES-13	Functionally based screening measure	0-10	≥ 3	2.5 (0-9)	50.0
ADLs	Function	0-16	<14 (dependence in any ADL)	16 (4-16)	24.0
IADLs	Function	0-14	<12 (dependence in any IADL)	13 (2-14)	42.0
CALGB Charlson Comorbidity Score	Comorbidity	0-54	>10 or ≥ 2 comorbidities that "somewhat interfere" with daily function	15 (0-48)	34.0
Medications (n)	Comorbidity/toxicity potential from side effects, drug interactions	0- ∞	≥ 5	4 (0-11)	46.0
Rand Medical Social Support Scale	Social support/access to medical care and support	0-5	<4	5 (0-5)	18.0
SPMSQ	Cognition/risk of dementia	0-10	≥ 3 errors	1 (0-6)	24.0
MNA	Nutritional assessment	0-14	≤ 11	11 (8-13)	8
SF-36: Did you feel worn out (during previous 4 wk)?	Fatigue	0-5	≤ 2	4 (1-5)	14
Summary of deficits within physical performance measures					
SPPB	Objective evaluation of physical performance	0-12	≤ 9	9 (0-12)	56.0
Falls within past 3 mo (n)	Objective evaluation of Physical Performance	0- ∞	>0	0 (0-4)	22.0
Physical disability assessment within VES-13	Self-perceived physical health	0-2	>0	0 (0-2)	52.0

VES-13 = Vulnerable Elders Survey-13; ADLs = Activities of Daily Living; IADLs = Instrumental Activities of Daily Living; CALGB Charlson Comorbidity Score = Cancer and Leukemia Group B adaptation of Charlson Comorbidity Score; SPMSQ = Short Portable Mental Status Questionnaire; MNA = Mini-Nutritional Assessment; SF-36 = Medical Outcomes Study Short Form 36-item Health Survey; SPPB = Short Physical Performance Battery.

* Score that is prospectively associated with morbidity and mortality.^{8,12,18,37}

American. Approximately one half were anemic (hemoglobin less than 13 mg), a known side effect of ADT.⁴ Of the 50 patients, 75% were overweight or obese (body mass index greater than 25 kg/m²). Most patients (84%) had received primary local tumor therapy. Continuous ADT in the form of a luteinizing hormone-releasing hormone agonist was used for all patients. Most patients (80%) had biochemical recurrence, and the remainder had asymptomatic, painless bone metastases. The median time of ADT was 36 months (range 3-96; Table 1).

Abnormal Findings in CGA

Patients demonstrated a high degree of functional and physical impairment on the CGA (Table 2). One half of patients scored 3 or more on the VES-13.¹² In addition, 34% had two or more comorbidities, and nearly one half were taking five or more medications. Also, 24% of patients had three or more errors on the Short Portable Mental Status Questionnaire, suggestive of underlying cognitive impairment.¹⁹ Finally, 14% reported fatigue on the Medical Outcomes Study Short Form 36-item Health Survey, and 8% were nutritionally deficient according to the findings from the Mini-Nutritional Assessment.

Abnormalities in Physical Performance Measures

The men demonstrated a high degree of impairment on the assessments of physical performance (Table 2). Of

the 50 men, 56% had abnormal scores on the SPPB, an objective measure of balance, walking speed, and quadriceps strength. The mean score on the SPPB was 7.9 of 12, with deficits noted in all three areas of assessment on this examination (Table 3). Also, 22% reported falls during the previous 3 months at the baseline assessment, with 10% reporting two or more falls during the previous 3 months. Supporting this finding, 52% of men reported impairment in their self-perceived physical health on this portion of the VES-13.

Predictors of Abnormal Physical Performance and Falls

Univariate analyses were conducted to explore the potential factors that could be associated with abnormal physical performance or falls in older men on ADT. Age, ADL deficit, IADL deficit, abnormal scores on the Short Portable Mental Status Questionnaire and VES-13, and the use of an assist device (cane/walker) were all associated with an increased risk of having abnormal physical performance as measured by the SPPB (Table 4). An ADL deficit, use of an assist device, and abnormal VES-13 score were associated with an increased risk of falls. In this small sample, the interval of ADT was not associated with an increased risk of abnormal physical

Table 3. Baseline Short Physical Performance Battery Scores by category

Test	Points Accumulated (Per Scoring Instructions)	Frequency (n = 50)
Stands* (measure of balance)		
Side-by-side stand		
Not attempted or unable to complete for 10 s	0	0.20
Held for 10 s	1	0.80
Semi-tandem stand		
Not attempted or unable to complete for 10 s	0	0.28
Held for 10 s	1	0.62
Tandem stand		
Not attempted or held for < 3 s	0	0.38
Held for 3-9 s	1	0.10
Held for 10 s	2	0.52
Measured 4-m walk (s) (walking speed)		
Unable to do walk	0	0.08
Time ≥ 6.52	1	0.10
Time > 4.66-6.52	2	0.16
Time > 3.62 or < 4.65	3	0.34
Time ≤ 3.62	4	0.32
Chair stands† (quadriceps strength)		
Unable to complete 5 chair stands	0	0.20
Chair stand time > 16.6 s	1	0.00
Chair stand time 13.7-16.6 s	2	0.18
Chair stand time 11.2-13.6 s	3	0.18
Chair stand time < 11.2 s	4	0.44

* Side by side stand, stand with feet side by side for 10 s; Semi-tandem stand, stand with side of heel of 1 foot touching big toe of other foot for 10 s; tandem stand, stand with heel of 1 foot in front of and holding toes of other foot for 10 s.

† Time to stand from chair 5 times without using arms.

Table 4. Univariate analysis of odds of falling or having abnormal SPPB score according to predictor variables

Variable	Abnormal SPPB Score (≤9)		Falls (Any)	
	OR	P Value	OR	P Value
Age	1.20	.002	0.91	.13
ADL deficit	*	*	4.71	.04
IADL deficit	21.11	<.001	8.31	.14
Comorbidity	6.33	.011	1.39	.66
≥5 Medications	2.85	.08	2.04	.33
Poor social support	0.57	.44	0.84	.85
Cognitive impairment	13.59	.017	1.47	.62
Score ≥ 3 on VES-13	7.18	.002	5.41	.05
MNA ≤ 11	0.77	.80	4.75	.15
Patient stage (metastatic vs BCR)	2.11	.33	5.79	.07
ADT duration (mon)	1.00	.40	1.02	.15
Use of assist device	†	†	7.07	.01

BCR = biochemical recurrence; ADT = androgen deprivation therapy; other abbreviations as in Table 2.

* Deficit in ADL predicted outcome perfectly.

† Use of assist device predicted outcome perfectly.

performance or falls. All patients who fell noted significant fatigue.

Change in Physical Performance and Falls During 3-Month Period

Forty patients completed the follow-up assessments at 3 months. Of the 40 patients, 20% had worsening SPPB scores during this period (a decrement of 2 or more points). Of those with a previous history of falls (n = 9), 56% experienced additional falls. Of those with no history of falls (n = 31), 12% experienced a new fall during those 3 months. Finally, 15% of patients reported worsening physical disability.

COMMENT

The results of this study have demonstrated that older men with prostate cancer receiving long-term ADT exhibit significant functional and physical impairment and are at risk of falls. Nearly one half of men were impaired according to the IADLs and VES-13 scores, which portend an increased risk of mortality.^{11,12} We also found significant impairment in physical performance measures.^{13,14} The mean score on SPPB was 7.9, lower than the mean of 10.4, which has been reported elsewhere in similarly aged men not receiving ADT.²⁰ The impairments were noted for all measures of the SPPB: balance,

walking speed, and chair stands. In addition, 22% reported falls during the previous 3 months, more than double the 6.6%-9.0% of older men who reported falls within 3-4 months in general outpatient geriatric populations.^{21,22} It is plausible that the combination of low bone density and increased falls could contribute to the increased risk of fractures noted in this population. Our results suggest that a vulnerable cohort of elderly patients receiving ADT who are seen routinely in clinics. Larger prospective trials are needed to clarify the relationship of ADT to physical disability and falls in this patient population.

Only a few other studies have reported the prevalence of objective physical disability in older patients with prostate cancer, and none of these studies reported on the prevalence of falls. In a sample of patients with prostate cancer at any stage, significant functional and physical disabilities were reported.²³ However, this was a heterogeneous population with advanced prostate cancer and many had received treatments other than ADT. In this sample, 50% of patients had abnormal scores on the Performance-Oriented Assessment of Mobility, indicating a risk of falls, although the prevalence of falling was not reported.²⁴ Another study reported no significant differences in physical function between patients with nonmetastatic prostate cancer receiving ADT and controls.²⁵ Physical function was tested with the 6-meter walk²⁶ and the Timed Up and Go test.²⁷ However, the age of patients was much younger (50% of the prostate cancer group was younger than 73 years old).

This study did have limitations. First, this was a small convenience sample, limiting our ability to generalize our findings. Second, confounding factors were present that could have contributed to our findings that were not evaluated in our study, such as vitamin D deficiency.²⁸ Vitamin D deficiency is prevalent in older men, especially in those who are African American, and has been associated with decreased muscle strength and an increased risk of falling.^{29,30} However, in our cohort, all patients were recommended to take calcium (1000-1500 mg) and vitamin D (800 IU),³¹ and most scored well on the nutritional assessment. Third, objective measures of muscle mass were not performed; thus we were unable to comment on the correlation of muscle mass to our findings of impairment in this patient population. Also, because of the short follow-up, we were unable to draw significant conclusions on the change in physical performance and falls with time in this patient population. Finally, this was a cross-sectional study; thus we could not establish a temporal relationship between ADT use and abnormal physical performance and falls. Nevertheless, the greater prevalence of falls and physical performance abnormalities in our study, compared with the general geriatrics population, is concerning.

This concern is especially noteworthy given the increasing attention to the high-risk geriatric state of "frailty." Frailty is a well-characterized syndrome that can

be measured with simple clinical and physiologic markers that develops over time as a result of accumulated stressors.³² Frailty is predictive of incident falls, worsening mobility, increased hospitalizations, and greater mortality in the general geriatric population.³³ Given the marked mobility and physical deficit problems found in older men with prostate cancer receiving ADT, we have hypothesized that ADT might "induce" frailty in these patients.³⁴

It is tempting to hypothesize that men with prostate cancer and undergoing ADT develop frailty, in part, because of the accelerated muscle atrophy resulting from the treatment. Studies have shown that ADT is an independent contributor to the loss of lean muscle mass, with decreased muscle mass and strength demonstrated within the first few weeks of therapy.³⁵⁻³⁷ We acknowledge that the relative contribution of ADT to falls, physical disability, and frailty has not been determined in our uncontrolled study. The underlying cause of these abnormalities is complex and often multifactorial. Still, we did find that, whatever the underlying cause, older men undergoing ADT are falling at high rates and are markedly physically disabled.

Recognizing the morbidity and mortality associated with fractures, physicians caring for this patient population should consider routinely screening for abnormal physical performance and falls. Additional controlled studies are necessary to determine the effect ADT has on the development of frailty and physical disability. In addition, further study of the effect of interventions on preventing or reducing falls and physical dysfunction in elderly men undergoing ADT is imperative.

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