Androgen Deprivation Therapy for Localized Prostate Cancer and the Risk of Cardiovascular Mortality

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Background We investigated whether androgen deprivation therapy (ADT) use is associated with an increased risk of death from cardiovascular causes in patients treated for localized prostate cancer.

Methods From the Cancer of the Prostate Strategic Urologic Research Endeavor database, data on 3262 patients treated with radical prostatectomy and 1630 patients treated with external beam radiation therapy, brachytherapy, or cryotherapy for localized prostate cancer were included in this analysis. Competing risks regression analyses were performed to assess whether use of ADT was associated with a shorter time to death from cardiovascular causes after controlling for age (as a continuous variable) and the presence of baseline cardiovascular disease risk factors. All tests for statistical significance were two-sided.

Results The median follow-up time was 3.8 years (range = 0.1–11.3 years). Among the 1015 patients who received ADT, the median duration of ADT use was 4.1 months (range = 1.0–32.9 months). In a competing risks regression analysis that controlled for age and risk factors for cardiovascular disease, both ADT use (adjusted hazard ratio [HR] = 2.6; 95% confidence interval [CI] = 1.4 to 4.7; $P = .002$) and age (adjusted HR = 1.07; 95% CI = 1.02 to 1.1; $P = .003$) were associated with statistically significantly increased risks of death from cardiovascular causes in patients treated with radical prostatectomy. Among patients 65 years or older treated with radical prostatectomy, the 5-year cumulative incidence of cardiovascular death was 5.5% (95% CI = 1.2% to 9.8%) in those who received ADT and 2.0% (95% CI = 1.1% to 3.0%) in those who did not. Among patients 65 years or older treated with external beam radiation therapy, brachytherapy, or cryotherapy, ADT use was associated with a higher cumulative incidence of death from cardiovascular causes, but the difference did not reach statistical significance.

Conclusions The use of ADT appears to be associated with an increased risk of death from cardiovascular causes in patients undergoing radical prostatectomy for localized prostate cancer.

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Androgen deprivation therapy (ADT) serves an important role in the treatment of patients with prostate cancer. ADT is being used increasingly in combination with local therapy to treat patients with localized prostate cancer with adverse features (1). Randomized studies have demonstrated that the addition of ADT to external beam radiation therapy improves cancer-specific and overall survival in patients with locally advanced (2) and higher risk localized (3) prostate cancer. Although randomized trials (4–7) have not shown that short-course neoadjuvant ADT is beneficial to patients undergoing radical prostatectomy, investigators are exploring the combination of ADT with systemic cytotoxic chemotherapies as a new neoadjuvant approach (8).

However, ADT can lead to elevated body mass index, increased fat deposition, and decreased insulin sensitivity (9–(11). These conditions are part of the constellation of medical conditions that characterize the metabolic syndrome, which increases an individual's risk of developing type II diabetes mellitus and coronary artery disease. Analysis of a prospective cohort of patients revealed that, among patients in the general population, those with the metabolic syndrome are more likely to die from cardiovascular disease than those without the metabolic syndrome (12). Thus, concern exists that patients who develop the metabolic syndrome associated with ADT may be at an increased risk of cardiovascular death.

A recent large observational study noted that patients with locoregional prostate cancer that was treated with ADT are at an

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increased risk of developing incident diabetes and cardiovascular disease (13). Whether the metabolic changes induced by ADT might ultimately translate into an increased risk of death from cardiovascular disease has not been established. Because hormonal therapy continues to be an important component of the management of patients with localized prostate cancer with high-risk features, identifying potential risks associated with ADT use remains an important endeavor. Therefore, the purpose of this study was to investigate whether ADT use in patients treated for localized prostate cancer was associated with an increased incidence of cardiovascular and all-cause mortality.

CONTEXT AND CAVEATS

Prior knowledge

Androgen deprivation therapy (ADT) is increasingly being used in combination with local therapy to treat patients with high-risk localized prostate cancer. However, ADT can lead to conditions that are included in the metabolic syndrome, which increases the risk of coronary artery disease.

Study design

Observational retrospective study using data from the Cancer of the Prostate Strategic Urologic Research Endeavor registry of patients with biopsy-proven prostate adenocarcinoma.

Contribution

ADT use appears to be associated with a statistically significantly increased risk of death from cardiovascular causes among patients aged 65 years or older undergoing radical prostatectomy for localized prostate cancer. The 5-year cumulative incidence of cardiovascular death was 5.5% among patients who received ADT and 2.0% among those who did not. Among patients aged 65 years or older treated with external beam radiation therapy, brachytherapy, or cryotherapy, ADT use was associated with an increased cumulative incidence of death from cardiovascular causes, but the increase was not statistically significant.

Implications

Careful cardiovascular evaluation and intervention are advisable before initiating ADT in patients with localized prostate cancer.

Limitations

The study had a relatively short follow-up with few fatal cardiovascular events observed. All possible risk factors for cardiovascular death could not be controlled for because of the study's retrospective nature.

Patients and Methods

The Cancer of the Prostate Strategic Urologic Research Endeavor Database

The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) is a nationwide longitudinal, observational disease registry of patients with biopsy-proven prostate adenocarcinoma. The CaPSURE registry contains demographic, clinical, treatment, and outcome data for more than 13 000 patients from 31 urology practices, including 25 community-based practices, three academic medical centers, and three US Department of Veterans Administration hospitals. Patients are treated according to the usual practice of their physicians. An approved and signed Internal Review Board informed consent form is obtained from all patients who choose to enroll in the CaPSURE data registry. The details of the project methodology have been reported previously (14).

The accuracy of the data in CaPSURE is maintained through the use of extensive quality assurance measures that are incorporated into the data collection and entry processes. Data are entered into the registry through a computer-based interface that uses built-in logic checks for each data stream to allow end users to identify and reconcile entries that are flagged as illogical or invalid. The CaPSURE study investigators initially performed random audits of medical records during routine on-site visits and have moved toward performing end-of-study reviews on all subjects that withdraw from the study or die. The purpose of the review is to verify the veracity of reported data and to add any key data elements that are missing. All source documents on prostate biopsies, anatomic surgical pathology, and bone scan results are obtained when available.

On enrollment in the CaPSURE registry, each patient completes a baseline questionnaire that includes a checklist of preexisting medical comorbidities (i.e., arthritis or joint/bone disease, hypertension, heart disease, stroke or neurologic conditions, diabetes, lung disease, cancer [other than prostate cancer], kidney disease, blood disease, stomach or intestinal disease, and urinary tract diseases). Study subjects are also able to write in conditions that do not fit in one of the above categories. From the written answers in this questionnaire, six additional comorbidity categories were created to include eye diseases and vision problems; ear, nose, and throat conditions; diseases of other internal organs, including liver, gallbladder, spleen, or pancreas; chronic or major infectious diseases; endocrine diseases; and mental health conditions.

Patients are followed until the time of death or withdrawal from the study. CaPSURE receives notification of the death of the subject from several sources, including family, clinician, or on-site research coordinators, and electronic searches of either the Social Security Death Index or the National Death Index, which is sponsored by the National Center on Health Statistics. When a death is verified, the cause of death is determined in an unblinded fashion from either the official state death certificate or, less commonly, the National Death Index.

Patient Selection and Treatment

As of July 31, 2006, 13 124 patients had been enrolled in the CaPSURE disease registry. When the registry was queried for patients with localized prostate cancer [i.e., T1–3a, NX/N0, MX/M0 (15)] diagnosed between January 1, 1995, and December 31, 2004, 7832 patients were identified. Of these 7832 patients, 1367 were excluded because they did not undergo definitive local therapy (radical prostatectomy, external beam radiation therapy, brachytherapy, or cryotherapy) or were treated with diethylstilbestrol, finasteride, chemotherapy, orchiectomy, or transurethral microwave therapy. An additional 1573 patients were excluded from the analysis because of missing data regarding the use of ADT and the presence of baseline heart disease, hypertension, or diabetes. Thus, the final study cohort consisted of 4892 patients. Of this study cohort, 3262 patients underwent initial treatment with radical

prostatectomy and 1630 patients underwent initial treatment with the nonsurgical options of external beam radiation therapy, brachytherapy, or cryotherapy.

ADT was defined as treatment with a gonadotropin-releasing hormone agonist and/or an antiandrogen either neoadjuvantly (initiated before the start of local therapy) or adjuvantly (initiated up to 6 months after the start of local therapy). The duration of ADT use was determined by the clinical practice of the treating physician. Overall, 1015 patients were treated with ADT in conjunction with their local therapy and 3877 patients were not treated with ADT. Among the patients who underwent radical prostatectomy, 266 were treated with ADT, and among those who received nonsurgical treatment, 749 were treated with ADT.

The primary endpoint of this study was death from cardiovascular causes. A cardiovascular death was defined as a death from acute myocardial infarction, sudden cardiac arrest or death, coronary artery disease, cardiac ischemia, malignant arrhythmia, or thromboembolic disease such as pulmonary embolism or cerebrovascular accident. A total of 131 patients who were included in this study cohort died of cardiovascular causes.

Statistical Analysis

The baseline demographics of patients who were and patients who were not treated with ADT were compared by use of the Wilcoxon two-sample test for continuous variables and the chi-square test for categoric variables. For the time-to-endpoint analyses, time zero was defined as the start date of definitive therapy, not the start date of ADT. Competing risks methods (16) were used to account for competing causes of mortality when analyzing the endpoint of time to death from cardiovascular causes. Separate competing risks analyses were performed for the 3262 patients who underwent initial radical prostatectomy and the 1630 patients who received nonsurgical treatments to account for potential treatment selection biases. Competing risks regression analyses (17) that were controlled for age in years as a continuous variable and the presence or absence of heart disease or diabetes at baseline were performed to assess the association between ADT use and the time to death from cardiovascular causes. In a univariable analysis, the presence of hypertension was not statistically significantly associated with death from cardiovascular causes and was, therefore, excluded from the multivariable competing risks analysis.

Cox multivariable regression analysis (18) was used to assess the association between ADT use and time to death from any cause. The data were tested and found to meet the assumptions of the Cox analysis by use of time-dependent covariate methodology (18). A stepwise selection process was used to determine which variables to include in the model, with a selection entry criterion of a P value of less than or equal to .1 and a selection stay criterion of a P value of less than or equal to .1. Using these criteria, we selected the variables of age in years (continuous variable), presence of baseline diabetes (categoric variable, yes or no), biopsy Gleason score (categoric variable, ≤ 7 or ≥ 8), and clinical tumor stage category (categoric variable, T1–2 or T3–4) as covariates. In addition, because of their statistical significance in the univariable analysis and their clinical relevance, the presence of heart disease (categoric variable, yes or no) and pretreatment prostate-specific antigen level (continuous variable) were also included in the model.

The adjusted hazard ratios (HRs) and associated 95% confidence intervals (CIs) of death from cardiovascular causes and death from any cause were estimated on the basis of the coefficients from the competing risks and Cox regression models, respectively. For the purpose of illustration, estimates of death from cardiovascular causes after initial local therapy were calculated by the cumulative incidence method (16) and graphically displayed. The cumulative incidences of death from cardiovascular causes were calculated and graphically displayed separately for patients younger than 65 years and for patients 65 years or older for both treatment cohorts of radical prostatectomy and nonsurgical therapy (i.e., external beam radiation therapy, brachytherapy, or cryotherapy). The age of 65 years was selected as the cut point on the basis of a published randomized study of radical prostatectomy versus watchful waiting that found that prostate cancer treatment may not be beneficial for patients aged 65 years or older (19). Given that ADT may contribute to the toxicity of therapy, evaluating the cumulative incidence of cardiovascular mortality in patients aged 65 years or older is clinically relevant. Comparisons of the cumulative incidence estimates of death from cardiovascular causes after initial therapy were made by use of Gray's K-sample test (20), which accounts for competing causes of mortality. For the 3- and 5-year point estimates of the cumulative incidences of death from cardiovascular causes, the associated 95% confidence intervals were calculated and reported. All tests for statistical significance were two-sided.

Results

Baseline Patient Characteristics

The median follow-up time for the study population was 3.8 years (range = 0.1–11.3 years). The median follow-up times for patients treated with radical prostatectomy and nonsurgical techniques were 3.9 and 3.5 years, respectively ($P = .003$). The baseline patient, tumor, and treatment characteristics of the 4892 patients in the study cohort are summarized in Table 1. The median age of the entire study cohort was 64 years (range = 39–86 years). Patients treated with radical prostatectomy and ADT had a median age of 63 years, and patients treated with radical prostatectomy without ADT had a median age of 62 years ($P<.001$). Patients who received external beam radiation therapy, brachytherapy, or cryotherapy in combination with ADT had a median age of 71 years, and patients who received one of these therapies but did not receive ADT had a median age of 69 years ($P<.001$).

A total of 1015 patients received ADT in conjunction with their local therapy with a median duration of 4.1 months (range = 1.0–32.9 months). The median duration of ADT use among patients who received ADT in the radical prostatectomy group was 4.0 months (range = 1.0–32.9 months). The median duration of ADT use among those who received ADT in the nonsurgical group was 4.3 months (range = 1.0–31.4 months). The proportions of patients with baseline heart disease and hypertension were similar between those who did and those who did not use ADT, regardless of type of local therapy. Among patients treated with external beam radiation therapy, brachytherapy, or cryotherapy, the proportion of patients with baseline diabetes was statistically significantly higher in patients using ADT than in patients not using ADT ($P = .004$).

Table 1. Baseline characteristics of the study population*

Characteristic	Radical prostatectomy group†			Non–radical prostatectomy group†		
	No ADT, No. (%)	ADT, No. (%)	*P* value‡	No ADT, No. (%)	ADT, No. (%)	*P* value‡
Age, y						
<65	1978 (66)	145 (55)		239 (27)	139 (19)	
≥65	1018 (34)	121 (45)	<.001	642 (73)	610 (81)	<.001
Primary local therapy						
Radical prostatectomy	2996 (100)	266 (100)		–	–	
EBRT	–	–		262 (30)	410 (55)	
Brachytherapy	–	–		509 (58)	267 (36)	<.001
Cryotherapy	–	–		110 (12)	72 (10)	
Pretreatment PSA, ng/mL						
≤4	473 (16)	26 (10)		144 (16)	56 (7)	
>4 to 10	2069 (69)	146 (55)	<.001	586 (67)	408 (54)	<.001
>10 to 20	365 (12)	62 (23)		119 (14)	180 (25)	
>20	89 (3)	32 (12)		32 (4)	105 (14)	
Biopsy Gleason score						
≤6	2204 (74)	143 (54)		690 (78)	391 (52)	
7	670 (22)	82 (31)	<.001	154 (17)	244 (33)	<.001
8–10	122 (4)	41 (15)		37 (4)	114 (15)	
Tumor category§						
T1	1595 (53)	98 (37)		448 (51)	339 (45)	
T2	1370 (46)	158 (59)	<.001	420 (48)	383 (51)	.004
T3	31 (1)	10 (4)		13 (1)	27 (4)	
Heart disease at baseline						
No	2692 (90)	233 (88)		694 (79)	587 (78)	
Yes	304 (10)	33 (12)	.2	187 (21)	162 (22)	.8
Diabetes at baseline						
No	2813 (94)	247 (93)		817 (93)	664 (89)	
Yes	183 (6)	19 (7)	.5	64 (7)	85 (11)	.004
Hypertension at baseline						
No	2080 (69)	187 (70)		573 (65)	467 (62)	
Yes	916 (31)	79 (30)	.8	308 (35)	282 (38)	.3

* ADT= androgen deprivation therapy; EBRT = external beam radiation therapy; PSA = prostate-specific antigen.

† Percentages may not sum to 100% because of rounding errors.

‡ Chi-square test. All statistical tests were two-sided.

§ Tumor categories are as described previously (15).

Overall, patients who used ADT in conjunction with their local therapy were more likely to present with higher pretreatment levels of prostate-specific antigen (*P*<.001), higher biopsy Gleason scores (*P*<.001), and more clinically advanced tumors (*P*<.001 for radical prostatectomy group and *P* = .004 for non–radical prostatectomy group) than patients who did not use ADT. The number of prostate cancer deaths in each clinical risk group (21), stratified by treatment with or without ADT, is shown in Table 2.

Competing Risks Regression Analysis for Time to Death From Cardiovascular Causes

A competing risks regression analysis that controlled for age, presence of heart disease, and presence of diabetes was performed to assess whether the use of ADT at the time of initial therapy was associated with a shorter time to death from cardiovascular causes than nonuse of ADT. As shown in Table 3, among patients treated initially with radical prostatectomy, both ADT use (adjusted HR = 2.6; 95% CI = 1.4 to 4.7; *P* = .002) and older age (continuous variable) (adjusted HR = 1.07; 95% CI = 1.02 to 1.1; *P* = .003) were associated with statistically significantly increased risks of death from cardiovascular causes, whereas the presence of baseline heart disease (adjusted HR = 1.1; 95% CI = 0.5 to 2.4; *P* = .8) or diabetes (adjusted HR = 1.3; 95% CI = 0.5 to 3.2; *P* = .6) was not. Among patients treated with external beam radiation therapy, brachytherapy, or cryotherapy, only older age (adjusted HR = 1.07; 95% CI = 1.02 to 1.1; *P* = .004) was associated with an increased risk of death from cardiovascular causes, whereas use of ADT (adjusted HR = 1.2; 95% CI = 0.8 to 1.9; *P* = .4) and the presence of baseline heart disease (adjusted HR = 1.2; 95% CI = 0.7 to 2.1; *P* = .4) or diabetes (adjusted HR = 1.6; 95% CI = 0.8 to 3.2; *P* = .2) were not (Table 3).

Table 2. Prostate cancer deaths stratified by clinical risk group*

Risk group†	No ADT (n = 3877)		ADT (n = 1015)	
	No. of patients (%)	No. of PC deaths (%)	No. of patients (%)	No. of PC deaths (%)
Low	1968 (51)	1	293 (29)	3
Intermediate	1385 (36)	7	343 (34)	4
High	524 (13)	7	379 (37)	8

* ADT = androgen deprivation therapy; PC = prostate cancer; PSA = prostate-specific antigen.

† Low = T1–2a, PSA of 10 ng/mL or lower, and biopsy Gleason score ≤6; intermediate = T2b, PSA of 10–20 ng/mL, or biopsy Gleason score 7; high = T2c or higher, PSA of 20 ng/mL or higher, or biopsy Gleason score 8–10.

Table 3. Competing risks regression analysis for death from cardiovascular causes in patients in the study cohort

Variable	No. of patients	No. of events	Unadjusted HR (95% CI)	*P* value†	Adjusted HR (95% CI)‡	*P* value†	Adjusted HR (95% CI)§	*P* value†
Radical prostatectomy group								
Age (continuous), y	3262	61	1.07 (1.03 to 1.1)	<.001	1.07 (1.03 to 1.1)	.001	1.07 (1.02 to 1.1)	.003
ADT								
No	2996	46	1.0 (reference)				1.0 (reference)	
Yes	266	15	2.9 (1.6 to 5.2)	<.001	–	–	2.6 (1.4 to 4.7)	.002
Heart disease at baseline								
No	2925	52	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Yes	337	9	1.4 (0.7 to 2.8)	.4	1.1 (0.5 to 2.4)	.7	1.1 (0.5 to 2.4)	.8
Diabetes at baseline								
No	3060	55	1.0 (reference)				1.0 (reference)	
Yes	202	6	1.6 (0.7 to 3.6)	.3	1.4 (0.6 to 3.3)	.5	1.3 (0.5 to 3.2)	.6
External beam radiation therapy, brachytherapy, or cryotherapy group								
Age (continuous), y	1630	70	1.07 (1.02 to 1.1)	.003	1.07 (1.02 to 1.1)	.003	1.07 (1.02 to 1.1)	.004
ADT								
No	881	34	1.0 (reference)				1.0 (reference)	
Yes	749	36	1.3 (0.8 to 2.2)	.2	–	–	1.2 (0.8 to 1.9)	.4
Heart disease at baseline								
No	1281	50	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Yes	349	20	1.3 (0.8 to 2.2)	.3	1.2 (0.7 to 2.1)	.4	1.2 (0.7 to 2.1)	.4
Diabetes at baseline								
No	1481	60	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Yes	149	10	1.7 (0.9 to 3.3)	.1	1.7 (0.9 to 3.2)	.1	1.6 (0.8 to 3.2)	.2

* HR = hazard ratio; CI = confidence interval; ADT = androgen deprivation therapy.

† Gray's *P* value. All statistical tests were two-sided.

‡ Adjusted for age, heart disease, and diabetes.

§ Adjusted for age, ADT use, heart disease, and diabetes.

In the patients initially treated with radical prostatectomy, the increased risk of death from cardiovascular causes was evident in both younger (<65 years; $P = .02$) and older (≥65 years; $P = .01$) patients. As illustrated in Fig. 1, A, among patients in the radical prostatectomy group who were younger than 65 years, the 5-year cumulative incidence estimates of death from cardiovascular causes were 3.6% (95% CI = 0.0% to 7.2%) in patients using ADT and 1.2% (95% CI = 0.5% to 1.8%) in patients not using ADT. Patients aged 65 years or older who were initially treated with radical prostatectomy and ADT also had higher 5-year estimates of death from cardiovascular causes (5.5%; 95% CI = 1.2% to 9.8%) than patients in the same age group treated with radical prostatectomy alone (2.0%; 95% CI = 1.1% to 3.0%) (Fig. 1, B).

The plots of the cumulative incidences of death from cardiovascular causes among patients treated with external beam radiation therapy, brachytherapy, or cryotherapy who were younger than 65 years, stratified by treatment with and without ADT, are shown in Fig. 1, C. The corresponding cumulative incidence plots for patients aged 65 years or older are shown in Fig. 1, D. In patients younger than 65 years, the estimates of death from cardiovascular causes at 5 years were similar in the groups treated with ADT (2.9%, 95% CI = 0.0% to 7.0%) and not treated with ADT (2.3%, 95% CI = 0.3% to 4.3%). Among patients aged 65 years or older, the 5-year estimates of death from cardiovascular causes were higher for patients treated with ADT (8.4%; 95% CI = 5.1% to 11.7%) than for patients treated without ADT (5.7%; 95% CI = 3.2% to 8.1%), although the entire distributions of the cumulative incidence estimates of death from cardiovascular causes in these two cohorts were not statistically significantly different ($P = .2$).

Cox Regression Analysis for Time to Death From Any Cause

Separate Cox regression analyses were performed to analyze the association between ADT use and the time to death from any cause for patients treated with radical prostatectomy and those treated with external beam radiation therapy, brachytherapy, or cryotherapy. As shown in Table 4, in an analysis of patients treated with radical prostatectomy that controlled for age, presence of baseline heart disease and diabetes, and known prostate cancer prognostic factors, ADT use (adjusted HR = 2.2; 95% CI = 1.4 to 3.5; $P<.001$) remained associated with statistically significant increase in the risk of death from any cause. Older age (continuous variable) (adjusted HR = 1.07; 95% CI = 1.04 to 1.1; $P<.001$), biopsy Gleason score 8 or higher compared with a lower Gleason score (adjusted HR = 2.3; 95% CI = 1.4 to 4.1; $P = .002$), and presence of baseline diabetes compared with the absence of diabetes (adjusted HR = 1.9; 95% CI = 1.1 to 3.3; $P = .03$) were also associated with an increased risk of death from any cause. When the same analysis was performed among patients who did not undergo radical prostatectomy, a shorter time to all-cause mortality was not associated with ADT use (adjusted HR = 0.9; 95% CI = 0.7 to 1.3; $P = .7$) but was statistically significantly associated with advancing age (adjusted HR = 1.06; 95% CI = 1.03 to 1.09; $P<.001$), more advanced clinical tumor category (adjusted HR = 2.4; 95% CI = 1.2 to 5.2; $P = .02$), and

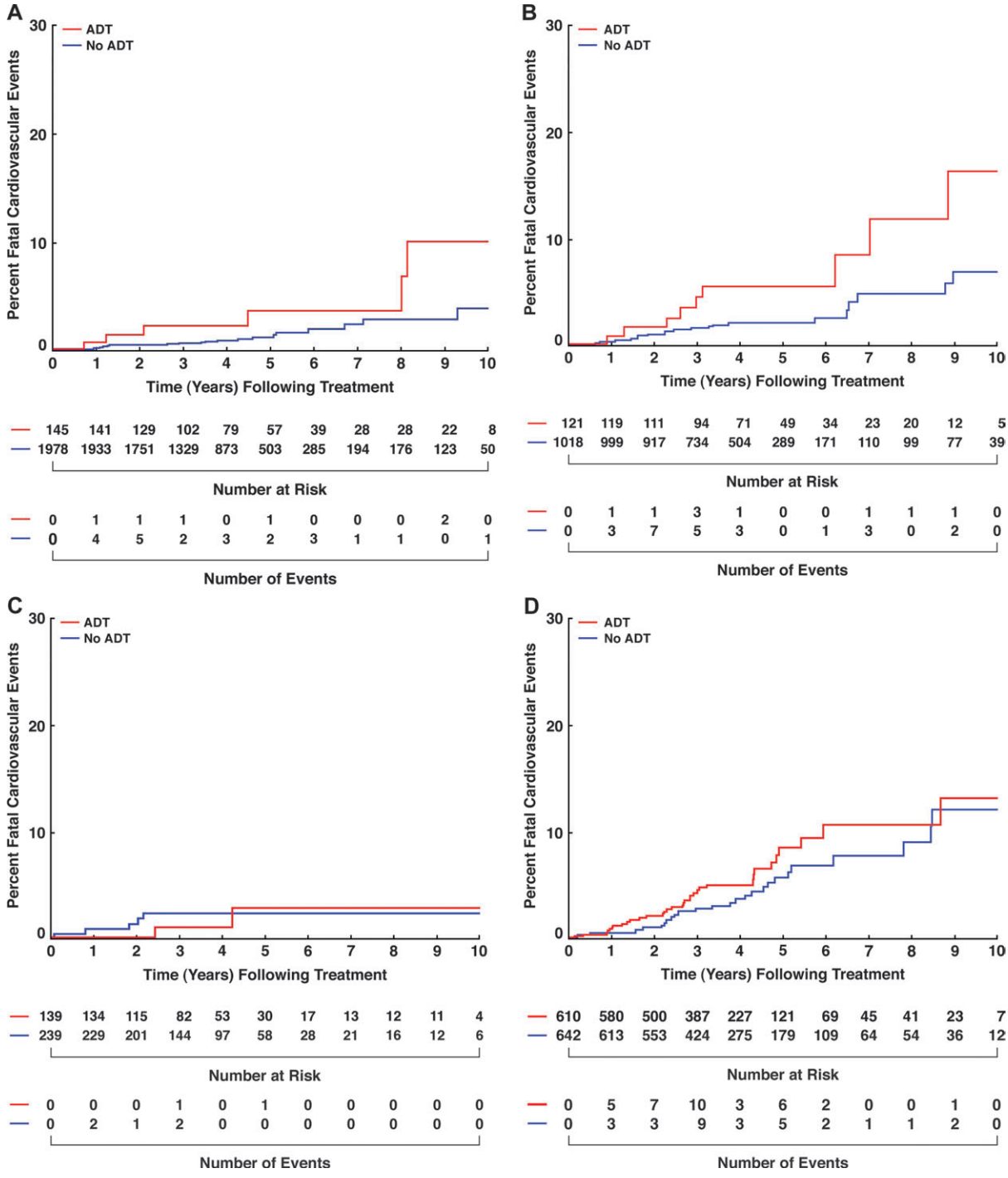

Fig. 1. Cumulative incidence estimates of cardiovascular mortality (i.e., death from cardiovascular causes) stratified by treatment with or without androgen deprivation therapy (ADT). **A**) Patients who underwent radical prostatectomy and were younger than 65 years of age at the time of surgery. The 3-year cumulative incidence estimates of cardiovascular mortality were 2.2% (95% confidence interval [CI] = 0.0% to 4.7%) in patients using ADT and 0.6% (95% CI = 0.2% to 1.0%) in patients not using ADT. The 5-year cumulative incidence estimates of cardiovascular mortality were 3.6% (95% CI = 0.0% to 7.2%) in patients using ADT and 1.2% (95% CI = 0.5% to 1.8%) in patients not using ADT. **B**) Patients who underwent radical prostatectomy and were 65 years of age or older at the time of surgery. The 3-year cumulative incidence estimates of cardiovascular mortality were 4.5% (95% CI = 0.6% to 8.3%) in patients using ADT and 1.6% (95% CI = 0.8% to 2.4%) in patients not using ADT. The 5-year cumulative incidence estimates of cardiovascular mortality were 5.5% (95% CI = 1.2% to 9.8%) in patients using ADT and 2.0% (95% CI = 1.1% to 3.0%) in patients not using ADT. **C**) Patients younger than 65 years of age treated with external beam radiation therapy, brachytherapy, or cryotherapy. The 3-year cumulative incidence estimates of cardiovascular mortality were 1.0% (95% CI = 0.0% to 3.0%) in patients using ADT and 2.3% (95% CI = 0.3% to 4.3%) in patients not using ADT. The 5-year cumulative incidence estimates of cardiovascular mortality were 2.9% (95% CI = 0.0% to 7.0%) in patients using ADT and 2.3% (95% CI = 0.3% to 4.3%) in patients not using ADT. **D**) Patients age 65 years or older treated with external beam radiation therapy, brachytherapy, or cryotherapy. The 3-year cumulative incidence estimates of cardiovascular mortality were 4.2% (95% CI = 2.5% to 6.0%) in patients using ADT and 2.7% (95% CI = 1.4% to 4.1%) in patients not using ADT. The 5-year cumulative incidence estimates of cardiovascular mortality were 8.4% (95% CI = 5.1% to 11.7%) in patients using ADT and 5.7% (95% CI = 3.2% to 8.1%) in patients not using ADT.

Table 4. Cox regression analysis for death from any cause in patients in the study cohort*

Variable	No. of patients	No. of all-cause deaths	No. of PC deaths	Unadjusted HR (95% CI)	*P* value†	Adjusted HR (95% CI)‡	*P* value†
Radical prostatectomy group							
Age (continuous), y	3262	114	16	1.08 (1.05 to 1.1)	<.001	1.07 (1.04 to 1.1)	<.001
Pretreatment PSA (continuous), ng/mL	3262	114	16	1.01 (1.002 to 1.03)	.02	1.01 (0.99 to 1.02)	.3
ADT							
No	2996	85	9	1.0 (reference)		1.0 (reference)	
Yes	266	29	7	3.0 (2.0 to 4.6)	<.001	2.2 (1.4 to 3.5)	<.001
Biopsy Gleason score							
≤7	3099	98	11	1.0 (reference)		1.0 (reference)	
≥8	163	16	5	3.3 (2.0 to 5.6)	<.001	2.3 (1.4 to 4.1)	.002
Tumor category§							
T1–2	3221	110	15	1.0 (reference)		1.0 (reference)	
T3–4	41	4	1	1.9 (0.7 to 5.0)	.2	1.2 (0.4 to 3.4)	.7
Heart disease at baseline							
No	2925	97	15	1.0 (reference)		1.0 (reference)	
Yes	337	17	1	1.4 (0.8 to 2.4)	.2	1.1 (0.6 to 1.8)	.8
Diabetes at baseline							
No	3060	99	15	1.0 (reference)		1.0 (reference)	
Yes	202	15	1	2.2 (1.3 to 3.8)	.005	1.9 (1.1 to 3.3)	.03
Hypertension at baseline							
No	2267	74	10	1.0 (reference)			
Yes	995	40	6	1.1 (0.8 to 1.6)	.6	–	–
External beam radiation therapy, brachytherapy, or cryotherapy group							
Age (continuous), y	1630	135	14	1.06 (1.03 to 1.09)	<.001	1.06 (1.03 to 1.09)	<.001
Pretreatment PSA (continuous), ng/mL	1630	135	14	1.01 (0.996 to 1.02)	.3	1.0 (0.99 to 1.02)	.7
ADT							
No	881	73	6	1.0 (reference)		1.0 (reference)	
Yes	749	62	8	1.1 (0.8 to 1.5)	.6	0.9 (0.7 to 1.3)	.7
Biopsy Gleason score							
≤7	1479	115	10	1.0 (reference)		1.0 (reference)	
≥8	151	20	4	1.7 (1.04 to 2.7)	.03	1.6 (0.97 to 2.6)	.07
Tumor category§							
T1–2	1590	126	11	1.0 (reference)		1.0 (reference)	
T3–4	40	9	3	2.1 (1.1 to 4.2)	.03	2.4 (1.2 to 5.2)	.02
Heart disease at baseline							
No	1281	97	10	1.0 (reference)		1.0 (reference)	
Yes	349	38	4	1.2 (0.9 to 1.8)	.3	1.2 (0.8 to 1.7)	.4
Diabetes at baseline							
No	1481	116	12	1.0 (reference)		1.0 (reference)	
Yes	149	19	2	1.7 (1.1 to 2.8)	.03	1.8 (1.1 to 2.9)	.02
Hypertension at baseline							
No	1040	86	11	1.0 (reference)			
Yes	590	49	3	0.9 (0.6 to 1.2)	.4	–	–

* PC = prostate cancer; HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen; ADT = androgen deprivation therapy.

† Cox regression. All statistical tests were two-sided.

‡ Adjusted for age, PSA, ADT use, biopsy Gleason score, tumor category, heart disease, diabetes, and hypertension.

§ Tumor categories are as described previously (15).

presence of baseline diabetes (adjusted HR = 1.8; 95% CI = 1.1 to 2.9; $P = .02$).

Discussion

After controlling for age and available cardiovascular disease risk factors, we found that treatment with ADT was associated with statistically significantly increased risk of death from cardiovascular causes in patients treated with radical prostatectomy for localized prostate cancer. Patients 65 years or older who were treated with ADT in addition to radical prostatectomy had a 5-year cumulative incidence of cardiovascular death of 5.5%, and those treated with radical prostatectomy alone had a 2.0% incidence of cardiovascular death. An increased risk of cardiovascular death associated with ADT use was also noted in younger patients treated with radical prostatectomy, with 5-year cumulative incidence estimates of cardiovascular death of 3.6% in those treated with ADT and 1.2% in those not treated with ADT. In patients

treated with external beam radiation therapy, brachytherapy, or cryotherapy, the use of ADT was not associated with a statistically significant increase in death from cardiovascular causes.

ADT use has been associated with the development of the metabolic syndrome in patients undergoing treatment for prostate cancer (11). Among the general population, the presence of the metabolic syndrome predisposes patients to premature death from cardiovascular disease (12). Our finding that ADT may increase the risk of death from cardiovascular causes in patients undergoing radical prostatectomy for prostate cancer is consistent with the results of the study by Keating et al. (13) who used the Surveillance, Epidemiology, and End Results Medicare database to investigate the metabolic impact of ADT in 73 196 patients with locoregional prostate cancer. The types of treatment received by these patients were radical prostatectomy in 23%, external beam radiation therapy in 40%, or watchful waiting in 37%. After controlling for patient and tumor characteristics and the type of local treatment, Keating et al. (13) found that patients treated with ADT had a higher risk of diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death than patients not treated with ADT. Among the patients who received ADT, even short-term (1–4 months) use of ADT was associated with an increased risk of developing diabetes and coronary heart disease.

Over the past decade, there has been a dramatic increase in the use of ADT to treat patients with nonmetastatic prostate cancer (22). Although ADT therapy improves survival of patients with high-risk prostate cancer, emerging data also suggest that treatment with ADT might decrease the overall survival of patients with lower risk disease because they may not derive a substantial cancer-specific mortality benefit from ADT use. In a recent randomized trial (23), a long course (28 months) compared with a short course (4 months) of ADT use was associated with improvement in all cancer-control endpoints except overall survival among patients receiving radiation therapy for locally advanced prostate cancer. Although the number of prostate cancer deaths was reduced among patients receiving long-course ADT, this reduction was offset by an increase in the absolute number of deaths from other causes.

D'Amico et al. (24) recently pooled data from three randomized trials comparing various short durations of treatment with ADT among patients undergoing external beam radiation therapy for localized prostate cancer and analyzed the impact of ADT on the timing of a fatal myocardial infarction in these patients. Because serum testosterone levels after a short course of ADT typically recover within 2 years, D'Amico et al. (24) preferentially weighted earlier data when comparing the cumulative incidence estimates of a fatal myocardial infarction and found that patients aged 65 years or older who were randomly assigned to 6 months of ADT had shorter times to a fatal myocardial infarction than patients who were randomly assigned to no ADT. Thus, treatment with ADT for 6 months appeared to hasten the development of a fatal myocardial infarction, although the overall incidence of fatal myocardial infarctions did not differ over time. In this study, among patients aged 65 years or older treated with external beam radiation therapy, brachytherapy, or cryotherapy, we observed a higher cumulative incidence of deaths from cardiovascular causes in those who used ADT than in those who did not use ADT, but the difference in the cumulative incidences did not reach statistical significance. However, the fewer patients and fewer events in the non–radical prostatectomy group limited the power of this analysis to detect a statistically significant increase in the incidence of cardiovascular death related to ADT use. Moreover, the duration of ADT use in the non–radical prostatectomy group of this study varied from 1 to 31 months, with a median duration of 4 months, shorter than the 6 months of ADT use in the previous study of D'Amico et al. (24).

Recent retrospective studies that explored the association between use of ADT and survival among patients treated with brachytherapy have found conflicting results. Beyer et al. (25) reviewed their experience in treating 2378 patients with permanent prostate brachytherapy and found that the 10-year estimate of survival was 20% among patients who used ADT and 44% among patients who did not use ADT. In a multivariable analysis, ADT use was statistically significantly associated with poorer overall survival. In contrast, when Merrick et al. (26) examined the association between use of ADT and survival among 938 patients treated with brachytherapy, ADT use was not associated with poorer survival.

To our knowledge, no other studies have analyzed the association between ADT and death from cardiovascular causes in patients treated specifically with radical prostatectomy. The novel finding in this study is that, in patients who underwent radical prostatectomy, the use of ADT was associated with an increased incidence of death from cardiovascular causes, and this increased risk was apparent in both younger (<65 years) and older (≥65 years) patients. It is unclear why this association between ADT use and death from cardiovascular causes was observed in patients treated with radical prostatectomy and not in the cohort of patients treated with external beam radiation therapy, brachytherapy, or cryotherapy. One plausible explanation is that patients selected for surgery tend to have fewer comorbidities. Such comorbidities might result in competing causes of death that would be experienced by patients selected for nonoperative treatment and thereby may have masked the potential negative impact of ADT on cardiovascular mortality.

Although numerous randomized trials (4–7) have failed to observe an improvement in cancer control with the use of neoadjuvant hormonal therapy in patients undergoing radical prostatectomy, investigators are now exploring the utility of combined neoadjuvant hormonal therapy and systemic cytotoxic chemotherapy as induction therapy before radical prostatectomy in patients with high-risk localized prostate cancer. Thus, studying the possible negative effects of ADT in this population continues to be relevant. Side effects associated with short- and long-term use of ADT can be substantial, and a growing body of literature exists regarding the negative impact that ADT can have on the health and quality of life of patients with prostate cancer. The results of this study and others (13,24) support the view that use of ADT may contribute to death from cardiovascular causes and underscore the importance of careful cardiovascular evaluation and intervention before initiating ADT in patients with localized prostate cancer.

This study has several potential limitations. First, because of the retrospective nature of the study, we could not control for all possible risk factors for cardiovascular death, including hypercholesterolemia, family history of heart disease, and prior smoking history. The possibility of selection bias or bias from omitted confounders must be considered when interpreting the results of this study. Second, this analysis did not take into account any salvage

ADT that patients may have received after initial therapy. Patients who developed metastatic disease or biochemical failure may have received salvage treatment with long-term ADT, which may have confounded the observed risk of cardiovascular death attributed to initial treatment with ADT. However, such patients would likely represent only a small proportion of this study cohort. Third, the study was limited by the relatively short period of follow-up and the few fatal cardiovascular events observed. Finally, the use of death certificates as the sources of cause of death is an important limitation of this type of retrospective study. Investigators have shown that death certificates may not accurately reflect true causes of death and that coronary heart disease may be overrepresented as a cause of death in death certificates (27,28).

In conclusion, it appears that ADT use may be associated with an increased risk of death from cardiovascular causes in patients undergoing radical prostatectomy for localized prostate cancer. Future prospective studies with careful assessment of causes of death are required to confirm the association between ADT use and death from cardiovascular causes.

References

(1) Meng MV, Elkin EP, Latini DM, Duchane J, Carroll PR. Treatment of patients with high risk localized prostate cancer: results from cancer of the prostate strategic urological research endeavor (CaPSURE). J Urol 2005;173:1557–61.

(2) Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337: 295–300.

(3) D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004;292:821–7.

(4) Schulman CC, Debruyne FM, Forster G, Selvaggi FP, Zlotta AR, Witjes WP. 4-year follow-up results of a European prospective randomized study on neoadjuvant hormonal therapy prior to radical prostatectomy in T2-3N0M0 prostate cancer. European Study Group on Neoadjuvant Treatment of Prostate Cancer. Eur Urol 2000;38:706–13.

(5) Soloway MS, Pareek K, Sharifi R, Wajsman Z, McLeod D, Wood DP Jr, et al. Neoadjuvant androgen ablation before radical prostatectomy in cT2bNxMo prostate cancer: 5-year results. J Urol 2002;167:112–6.

(6) Aus G, Abrahamsson PA, Ahlgren G, Hugosson J, Lundberg S, Schain M, et al. Three-month neoadjuvant hormonal therapy before radical prostatectomy: a 7-year follow-up of a randomized controlled trial. BJU Int 2002;90:561–6.

(7) Klotz LH, Goldenberg SL, Jewett MA, Fradet Y, Nam R, Barkin J, et al. Long-term followup of a randomized trial of 0 versus 3 months of neoadjuvant androgen ablation before radical prostatectomy. J Urol 2003;170:791–4.

(8) Konety BR, Eastham JA, Reuter VE, Scardino PT, Donat SM, Dalbagni G, et al. Feasibility of radical prostatectomy after neoadjuvant chemohormonal therapy for patients with high risk or locally advanced prostate cancer: results of a phase I/II study. J Urol 2004; 171:Pt 1:709–13.

(9) Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 2002;87:599–603.

(10) Lee H, McGovern K, Finkelstein JS, Smith MR. Changes in bone mineral density and body composition during initial and long-term gonadotropin-releasing hormone agonist treatment for prostate carcinoma. Cancer 2005;104:1633–7.

(11) Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol 2006;24:3979–83.

(12) Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709–16.

(13) Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448–56.

(14) Lubeck DP, Litwin MS, Henning JM, Stier DM, Mazonson P, Fisk R, et al. The CaPSURE database: a methodology for clinical practice and research in prostate cancer. CaPSURE Research Panel. Cancer of the Prostate Strategic Urologic Research Endeavor. Urology 1996; 48:773–7.

(15) Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, et al., editors. American Joint Committee on Cancer: manual for staging cancer. 6th ed. New York: Springer; 2002.

(16) Gaynor JJ, Feuer EJ, Tan CC, Wu DH, Little CR, Straus DJ, et al. On the use of cause-specific failure and conditional failure probabilities: examples from clinical oncology data. J Am Stat Assoc 1993;88:400–9.

(17) Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

(18) Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. 2nd ed. New York: Springer; 2003.

(19) Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005;352:1977–84.

(20) Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988;16:1141–54.

(21) D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969–74.

(22) Shahinian VB, Kuo YF, Freeman JL, Orihuela E, Goodwin JS. Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. Cancer 2005;103:1615–24.

(23) Hanks GE, Pajak TF, Porter A, Grignon D, Brereton H, Venkatesan V, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. J Clin Oncol 2003;21:3972–8.

(24) D'Amico AV, Denham JW, Crook J, Chen MH, Goldhaber SZ, Lamb DS, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol 2007;25:2420–5.

(25) Beyer DC, McKeough T, Thomas T. Impact of short course hormonal therapy on overall and cancer specific survival after permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys 2005;61:1299–305.

(26) Merrick GS, Butler WM, Wallner KE, Galbreath RW, Allen ZA, Adamovich E. Androgen-deprivation therapy does not impact cause-specific or overall survival after permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys 2006;65:669–77.

(27) Lloyd-Jones DM, Martin DO, Larson MG, Levy D. Accuracy of death certificates for coding coronary heart disease as the cause of death. Ann Intern Med 1998;129:1020–6.

(28) Smith Sehdev AE, Hutchins GM. Problems with proper completion and accuracy of the cause-of-death statement. Arch Intern Med 2001; 161:277–84.

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