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Long-term Impact of Androgen-Deprivation Therapy on Cardiovascular Morbidity after Radiotherapy for Clinically Localized Prostate Cancer

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Abstract

OBJECTIVE—To characterize the impact of androgen-deprivation therapy (ADT) on the incidence of cardiovascular events (CE) in prostate cancer patients treated with radiotherapy (RT).

METHODS—2211 patients with localized prostate cancer were treated with RT from 1988–2008 at our institution. 991 patients (44.8%) received ADT at the time of RT for a median of 6.1 months. Salvage ADT was initiated prior to CE in 365 men (16.5%) at a median of 5.5 years (range, 0.6 to 18.4 years) after RT and continued for a median of 4.3 years. A nomogram was constructed to predict the 10-year risk of CE post-RT.

RESULTS—Patients receiving ADT at the time of RT exhibited significantly higher 10-year incidence of CE (19.6%, 95% CI 17.0–22.6%) than those not receiving ADT (14.3%, 95% CI 12.2%–16.7%, $P = .005$). On multivariate analysis, both ADT at the time of RT ($P = .007$) and the time of salvage ($P = .0004$) were associated with increased CE risk, as were advanced age ($P = .02$), smoking ($P = .0007$), history of diabetes ($P = .0007$), and history of CE before RT ($P < .0001$). A nomogram using patient age, smoking status, history of pre-RT CE, history of diabetes, and ADT use at the time of RT predicted the rate of 10-year CE with a C-index of 0.81 (95% CI, 0.72–0.88).

CONCLUSION—While ADT is often an essential part of prostate-cancer treatment, patients should be counseled regarding increased risks of CE and prophylactic efforts should be considered to mitigate that risk.

Keywords

prostate cancer; androgen-deprivation therapy; radiotherapy; cardiovascular

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INTRODUCTION

Androgen-deprivation therapy (ADT) used in conjunction with radiotherapy (RT) improves disease-specific and overall survival in patients with locally advanced prostate cancer,^{1–3} yet concerns have been raised regarding its potentially harmful effects on cardiovascular health. Prospective studies have shown that ADT increases fat mass and serum lipid levels, while also promoting insulin resistance,⁴ and several population-based observational studies have suggested that such metabolic changes may translate into an increased risk for cardiac mortality.^{5, 6} Despite this evidence, controversy remains regarding the risks posed by ADT, with a recent pooled meta-analysis of randomized trials demonstrating no increased risk of cardiovascular mortality among patients treated with ADT in conjunction with RT,⁷ and other studies suggesting that only subgroups of patients with pre-existing comorbidities may be at risk.^{8, 9}

There remains even less consensus regarding the impact of ADT on non-fatal CEs, which can significantly impact patient quality of life but are often not captured in randomized trials and may not be reliably collected in population-based databases. Furthermore, while the cardiovascular effects of ADT have been studied in the setting of RT, it remains unclear whether these risks persist in the salvage setting after disease recurrence, in which ADT remains the standard first-line therapy.

In this large, retrospective study, we sought to investigate the association between ADT use and cardiovascular morbidity in a well-annotated database of patients with long-term follow-up after RT. We characterize the effects of ADT in both primary or definitive radiotherapy, and the adjuvant or salvage settings, and we construct a nomogram to quantify a patient's risk of cardiovascular morbidity after RT.

MATERIALS AND METHODS

Patient Population

Of 2778 consecutive men treated with external beam RT (EBRT), brachytherapy, or a combination for stages T1–T3 prostate cancer at Memorial Sloan Kettering Cancer Center between 1988 and 2008, 2211 men had adequate follow-up of at least 5 years and were included in this analysis. Patients were staged according to the 2007 American Joint Committee on Cancer staging classification system, and were classified by National Comprehensive Cancer Network (NCCN) risk group. Eligible patients had biopsy-proven adenocarcinoma classified according to the Gleason grading system. Patient and tumor characteristics at the time of RT are listed in Table 1. The median patient age was 68 years (range, 42 to 93 years). 711 (32.2%), 922 (41.7%), and 578 (26.1%) men were classified as having low-, intermediate-, or high-risk prostate cancer, respectively. 345 men (15.6%) had documented histories of a prior cardiovascular event before initiation of RT.

Treatment

1705 men (77.1%) received EBRT, 369 men (16.7%) received brachytherapy, and 137 men (6.2%) underwent combination EBRT and brachytherapy. The radiation techniques used for EBRT¹⁰ and brachytherapy^{11, 12} have been previously described in detail. Briefly, patients

treated with EBRT received a dose of 81 to 86.4 Gy in 1.8-Gy fractions using 15-MV photons. Patients treated before 2002 received primarily three-dimensional conformal RT, while patients treated since that time received intensity-modulated RT. During this time, elective pelvic nodal irradiation was not typically utilized. Patients undergoing brachytherapy received either a low-dose-rate permanent interstitial implant (^{125}I or ^{103}Pd) or high-dose-rate brachytherapy with ^{192}Ir . Combination therapy typically consisted of low- or high-dose-rate brachytherapy followed by EBRT to a dose of 50.4 Gy, as previously described.^{13, 14}

991 men (44.8%) received ADT at the time of RT, including 205 men with low-risk, 390 with intermediate-risk, and 396 with high-risk prostate cancer. The majority of men with low-risk prostate cancer who received ADT did so for the purposes of cytoreduction. Of men with high-risk prostate cancer who did not receive ADT, nearly all were treated prior to 1995, when the benefits of ADT use were not as well established. ADT at the time of RT consisted of a gonadotropin-releasing hormone agonist preceded by the administration of a nonsteroidal antiandrogen (typically bicalutamide, 50 mg daily) by 3–5 days. Bicalutamide was discontinued after 30 days. The gonadotropin-releasing hormone agonist was typically leuprolide, administered as a 7.5 mg depot injection in the first month and 3-month 22.5 mg depot injections thereafter. ADT was continued for a median of 6.1 months (range, 0.9 to 149 months).

Upon recurrence or metastatic progression, salvage ADT (typically leuprolide, 7.5 mg monthly) was initiated at the physician's discretion. Salvage ADT was initiated prior to a CE in 365 men (16.5%) at a median of 5.5 years (range, 0.6 to 18.4 years) after RT, and was continued for a median of 4.3 years (Table 1). The actuarial incidence of patients requiring salvage ADT increased by risk group, with 4.3% of low-risk, 13.9% of intermediate-risk, and 37.7% of high-risk men requiring salvage ADT by 10 years after RT. Among men in the high-risk group, those who did not receive ADT required salvage treatment at a higher rate (48.7% at 10 years) than those who received ADT (32.5% at 10 years).

Follow-Up and Endpoints

Patients were followed for a minimum of 5 years after RT, with a median follow-up of 9.3 years (range, 5.0 to 23.1 years). In general, patients were evaluated every 3 to 6 months for the first 5 years and yearly thereafter. At each visit, comorbidities and interim CEs were recorded. CEs including myocardial infarction (MI), stroke, transient ischemic attack, and coronary revascularization in the form of percutaneous coronary intervention or coronary artery bypass grafting were combined to create a composite endpoint.

Statistical Analysis

Actuarial incidence curves for CE were created using the Kaplan-Meier method and were compared using the log-rank test. Patients were censored when detailed follow-up including medical comorbidity assessment was discontinued. Hazard ratios (HRs) and 95% confidence intervals (CIs) for CE were calculated using a Cox proportional hazards model. Clinical factors considered included age, smoking status, NCCN risk group, RT modality, pre-existing comorbidities including hypertension, hyperlipidemia, diabetes mellitus and prior

CEs, as well as the use of ADT at the time of RT or salvage. Cutpoints for age (median) and smoking status (20 pack-years) were determined a priori. Salvage ADT was analyzed as a time-dependent variable. Multivariate models were constructed for CE to adjust for imbalances in clinical characteristics of the groups compared. Two-sided P values $< .05$ were considered statistically significant. A nomogram was built using all variables that reached significance on multivariate analysis, with the exception of the time-dependent variable salvage ADT. The C-index was calculated according to the method of Liu et al.¹⁵

RESULTS

355 men (16.1%) experienced 431 CEs during the follow-up period. These were most commonly coronary revascularization events ($n=250$), but also included MI ($n=89$), stroke ($n=54$) and transient ischemic attack ($n=38$). The median time from RT to any CE was 5.2 years for revascularization, 5.7 years for MI, 7.6 years for stroke, and 7.8 years for transient ischemic attack. The median time from RT to first CE was 5.6 years (range 0.1 to 20.1 years).

The 10-year incidence of post-RT CE was significantly greater among patients receiving ADT at the time of RT (19.6%, 95% CI 17.0–22.6%) compared with patients treated with RT alone (14.3%, 95% CI 12.2%–16.7%, $P = .005$) (Figure 1). On multivariate analysis (Table 2), the risk of developing a post-treatment CE after definitive RT was significantly associated with ADT at the time of RT (HR, 1.34; 95% CI, 1.09–1.65; $P = .007$). The incidence of post-RT CE was also strongly associated with ADT use in the salvage setting (HR, 1.77; 95% CI, 1.29–2.44; $P = .0004$). Other variables associated with the development of a post-RT CE were advanced age (HR, 1.29; $P = .02$), smoking status (>20 vs. 0–20 pack-years; HR, 1.42; $P = .0007$), history of diabetes mellitus (HR, 1.69; $P = .0007$), and history of CE before initiation of RT (HR, 2.15; $P < .0001$).

To better quantify the contribution of ADT to a patient's risk of CE, a nomogram was constructed based on pre-RT comorbidities and ADT use. This nomogram, which incorporates information on ADT use at the time of RT, patient age, smoking status, history of diabetes mellitus, and history of pre-RT CE, can be used to predict a patient's 10-year risk of CE (Figure 2). The C-index of the nomogram was calculated to be 0.81 (95% CI, 0.72–0.88).

In an effort to identify a subgroup of patients most susceptible to the cardiovascular effects of ADT, tests for interaction were performed between ADT use at the time of RT and factors reflecting patient comorbidity, which has been reported to be linked to an increased risk of ADT-associated CE in some prior studies.^{8, 9, 16} These tests for interaction did not reach significance for either patient age ($P = .82$) or history of pre-RT CE ($P = .40$).

DISCUSSION

In this study of 2211 men with localized prostate cancer treated with RT, a short course of ADT was associated with a long-term increased risk of cardiovascular morbidity, including coronary artery bypass grafting, percutaneous coronary intervention, MI, stroke and transient ischemic attack. ADT administered for a median of 6.1 months was associated with

a 5.3% absolute increased risk of cardiovascular morbidity at 10 years. This corresponded to a 34% increased relative risk of post-RT CEs. While these findings are consistent with a recent American Heart Association consensus statement that ADT may be associated with an increased incidence of CEs, there have been conflicting data regarding the effect of ADT on cardiovascular risk.⁴ Using a well-annotated database with long-term follow up, this study provides important detailed information regarding the long-term risk of ADT on cardiovascular morbidity when administered at the time of RT or at the time of salvage. Furthermore, we present a clinically useful nomogram that can be employed to estimate the potential additive effect of ADT at the time of RT to a patient's baseline cardiovascular risk.

Post-randomization analyses of Phase III randomized trials have failed to demonstrate an association between the use of ADT and cardiovascular mortality,^{3, 17, 18} yet these post-hoc analyses have been criticized for their relatively low rates of cardiovascular mortality. Furthermore, these studies do not provide data regarding non-fatal CEs. Observational studies have provided valuable insight into the effects of ADT on cardiovascular morbidity, yet they have also yielded conflicting results. In a population-based observational study comprising over 37,000 men from the Veterans Administration patient database, Keating et al. found that ADT use was associated with an increased the risk of MI and stroke.⁶ Additional analyses using the SEER database,¹⁹ Danish Cancer Registry,²⁰ and Swedish PcBaSE²¹ have corroborated this data, yet others have found no clear association between use of gonadotropin-releasing hormone agonists and CE risk.²² Meta-analyses have been conducted to reconcile this data,^{23, 24} but fundamental weaknesses of observational studies limit interpretation. For instance, while observational studies provide large patient cohorts for study, they are particularly susceptible to bias from inconsistent ICD-9 coding and inconsistent or limited patient follow-up. While our study is also retrospective in nature, its lack of reliance on registry data allowed us to capture detailed and accurate information regarding patient comorbidities at the time of RT, including hypertension, hyperlipidemia, diabetes, and smoking status, and to adjust for these in our multivariate model. The extended follow-up of our patient population also provided an opportunity to study the long-term impact of ADT use on non-fatal CEs, which often develop years after treatment.

In addition to investigating the cardiovascular risks associated with ADT use, determining in which settings ADT use may be most harmful is also important. With this goal in mind, we investigated whether the cardiovascular morbidity associated with ADT was also apparent in the salvage setting. To accurately assess its impact on cardiovascular risk, salvage ADT was analyzed as a time-dependent covariate. We demonstrate that the use of salvage ADT for recurrent disease correlates with a significantly increased risk of subsequent CEs. To our knowledge, this is the first report demonstrating an effect of salvage ADT on cardiovascular risk. This data is an important addition to the literature, as it provides evidence that the cardiovascular risk associated with ADT is not limited to its use in the neoadjuvant setting. Furthermore, it suggests that delay of ADT may be indicated when cancer-related outcomes are deemed to be equivalent, and that efforts to mitigate the cardiovascular effects of ADT use remain important in this patient population.

It is also critical to determine which patients may be at the highest risk of the detrimental cardiovascular effects of ADT. Several studies have suggested that the risk of ADT-

associated CEs is highest in patients with pre-existing comorbidities. In an analysis of randomized trial data, D'Amico et al. reported increased risk of cardiac death after ADT among patients with moderate to severe comorbidity.⁸ Publications from Nanda et al. and Ziehr et al. demonstrated that, in a cohort of 5077 men with clinically localized prostate cancer, ADT use increased all-cause mortality⁹ and cardiac-specific mortality¹⁶ only among patients with a prior history of congestive heart failure or acute MI. The authors of these studies reasonably conclude that, in patients with an already compromised cardiovascular status, ADT may precipitate cardiovascular mortality.

In contrast, we were unable to identify a subgroup of patients at increased cardiovascular risk from ADT. Tests for interaction between ADT use and pre-RT CE or age were non-significant. Several potential explanations may exist. First, our study assessed risk of non-fatal CEs rather than cardiovascular mortality. It stands to reason that the effects of ADT on cardiovascular mortality, a less common event, may be more pronounced in patients with pre-existing cardiovascular disease. Non-fatal CEs, on the other hand, may be more readily induced by ADT use in patients with mild or subclinical cardiovascular disease. In addition, the long follow-up of our study likely allowed for the manifestation of more ADT-induced CEs in patients without pre-existing cardiovascular disease. Such patients would be expected to have a longer latency to the occurrence of an incident CE, which would only become apparent with long follow-up.

Although we found no evidence to support a difference in the relative risk of ADT among patients with and without comorbidities, the increase in absolute risk posed by ADT is still greatest in patients with a history of cardiovascular disease. This reflects the fact that, in patients with a higher baseline risk, the same relative risk increase is magnified. To better quantify the relative contribution of ADT to a patient's risk, we constructed a nomogram to predict 10-year risk of CE as a function of pre-RT comorbidities and ADT use at the time of RT. Using this nomogram, the addition of ADT to treatment of an elderly patient without other risk factors would increase the 10-year risk of CE from approximately 12% to 16%. In a similar patient with a history of pre-RT CE and diabetes mellitus, ADT would increase this risk from approximately 36% to 46%, indicating a larger change in absolute risk. This emphasizes the need to consider patient comorbidities when making clinical decisions regarding ADT use. While this nomogram should not substitute for other established calculators of cardiovascular risk, such as the American College of Cardiology Atherosclerotic Cardiovascular Disease (ASCVD) Risk Score²⁵ or the Framingham Risk Score,²⁶ this nomogram is an additional tool that provides important information regarding the relative effect of ADT use on a patient's cardiovascular risk. In patients with an elevated cardiovascular risk, guidelines from the American Heart Association (AHA) suggest initiation of secondary preventive measures that may include statin therapy, antihypertensive medications, low-dose aspirin, glucose-lowering therapies in patients with DM, and smoking cessation.

In our clinical practice, we counsel all patients regarding the possible increased risks of CEs. We routinely recommend long-course ADT in the setting of high-risk prostate cancer based on studies demonstrating a clear survival benefit.^{27, 28} While our data demonstrate a 5.3% absolute increase in cardiovascular events, the benefits of ADT use clearly outweigh the

risks in high-risk patients, as nearly 95 out of 100 men will not experience cardiovascular morbidity as a result of ADT. For low-risk prostate cancer, we advocate ADT only when prostate volume reduction is required, either to reduce pubic arch interference during brachytherapy or to reduce the morbidity from EBRT. In such cases, EBRT may require less volume reduction than brachytherapy. Alternative management strategies such as surgery or active surveillance may be also considered to avoid the toxicity associated with ADT. If only minimal volume reduction is required, use of oral antiandrogens alone could potentially reduce toxicity. Outside of these considerations, we believe that ADT should be avoided for low-risk patients. For intermediate-risk prostate cancer, it is our practice to consider the use of short-term ADT, particularly in the setting of high- to intermediate-risk disease.²⁹ In men receiving combination brachytherapy and EBRT, we believe that in many cases ADT can be omitted to reduce cardiovascular risk, as the effects of dose escalation likely diminish any benefit of ADT.^{30, 31} The role of short-term ADT in the setting of dose-escalated RT for low- to intermediate-risk prostate cancer is currently being studied by RTOG 0815.

In summary, this large single-institution analysis of patients treated with EBRT and brachytherapy revealed an association between ADT use and an increased risk of cardiovascular morbidity, both among men receiving ADT at the time of RT and those receiving generally longer courses of salvage ADT at the time of recurrence. From this data, a clinically useful nomogram was constructed to help quantify the contribution of ADT at the time of RT to a patient's risk of subsequent cardiovascular morbidity. While ADT is often an essential part of prostate cancer treatment, our study suggests that efforts to mitigate cardiovascular risk are important to consider in all men receiving prostate RT and ADT.

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Figure 1.

Actuarial incidence of cardiovascular events among patients treated with radiotherapy alone vs. radiotherapy with neoadjuvant and concurrent androgen-deprivation therapy (ADT).

Figure 2.
 Nomogram predicting 10-year risk of post-radiotherapy (RT) cardiovascular events (CE).
 ADT, androgen-deprivation therapy; DM, diabetes mellitus.

Table 1

Patient, tumor, and treatment characteristics

Patient characteristics at time of RT	
Age (years)	68 (42–93)
Smoking history	
0–20 pack-years	1194 (54.0%)
>20 pack-years	469 (21.2%)
Unknown	548 (24.8%)
Hypertension	
Yes	959 (43.4%)
No	1252 (56.6%)
Hyperlipidemia	
Yes	612 (27.7%)
No	1599 (82.3%)
Diabetes mellitus	
Yes	203 (9.2%)
No	2008 (90.8%)
Prior cardiovascular event	
Yes	345 (15.6%)
No	1866 (84.4%)
Tumor characteristics	
AJCC T stage	
T1	1049 (47.4%)
T2	937 (42.4%)
T3	225 (10.2%)
Gleason score	
6	1705 (77.1%)
7	369 (16.7%)
8–10	137 (6.2%)
PSA	
4	289 (13.1%)
>4–10	1175 (53.1%)
>10–20	468 (21.2%)
>20	279 (12.6%)
NCCN risk group	
Low	711 (32.2%)
Intermediate	922 (41.7%)
High	578 (26.1%)
Treatment characteristics	
RT modality	
EBRT alone	1705 (77.1%)
Brachytherapy alone	369 (16.7%)

Patient characteristics at time of RT	
EBRT + brachytherapy	137 (6.2%)
ADT at the time of RT	
Yes	991 (44.8%)
No	1220 (55.2%)
Salvage ADT prior to CE	
Yes	365 (16.5%)
No	1846 (83.5%)
Time to salvage ADT (years)	5.5 (0.6 – 18.4)

ADT, androgen-deprivation therapy; AJCC, American Joint Committee on Cancer; EBRT, external beam radiotherapy; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; RT, radiotherapy.

Table 2

Univariate and multivariate Cox regression demonstrating factors associated with cardiovascular-event risk. Variables with *P* values < .05 on univariate analysis were candidates for stepwise multivariate analysis.

	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	<i>P</i> Value	Hazard Ratio (95% CI)	<i>P</i> Value
Age (≥ 68 vs. <68)	1.40 (1.13–1.72)	.002 **	1.29 (1.04–1.59)	0.02 *
Hypertension	1.38 (1.12–1.70)	.002 **		
Hyperlipidemia	1.38 (1.10–1.73)	.005 **		
Diabetes mellitus	1.80 (1.33–2.44)	.0001 ***	1.69 (1.25–2.29)	0.0007 ***
Prior cardiovascular event	2.28 (1.80–2.88)	<.0001 ***	2.15 (1.70–2.73)	< 0.0001 ***
Smoking history				
0–20 pack-years	Reference	N/A	Reference	N/A
>20 pack-years	1.51 (1.17–1.95)	0.002 **	1.42 (1.10–1.84)	0.0007 ***
Unknown	1.33 (1.04–1.71)	0.02 *	1.37 (1.06–1.76)	0.02 *
NCCN risk group				
Low	Reference	N/A		
Intermediate	0.93 (0.72–1.19)	0.56		
High	1.10 (0.84–1.44)	0.47		
RT modality				
EBRT alone	Reference	N/A		
Brachytherapy alone	0.70 (0.50–0.98)	0.04 *		
EBRT + brachytherapy	0.71 (0.42–1.19)	0.20		
ADT at the time of RT	1.35 (1.09–1.66)	0.005 **	1.34 (1.09–1.65)	0.007 **
Salvage ADT	1.74 (1.26–2.39)	0.0007 ***	1.77 (1.29–2.44)	0.0004 ***

ADT, androgen-deprivation therapy; AJCC, American Joint Committee on Cancer; CI, confidence interval; EBRT, external beam radiotherapy; NCCN, National Comprehensive Cancer Network; RT, radiotherapy.

The significance of corresponding *P* values is indicated as follows:

* < .05;

** < .01;

*** < .001.