available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Ronald C. Chen on pp. 211–212 of this issue

Cardiovascular Mortality Following Short-term Androgen Deprivation in Clinically Localized Prostate Cancer: An Analysis of RTOG 94-08

Justin C. Voog[a], *Rebecca Paulus*[b], *William U. Shipley*[c], *Matthew R. Smith*[c], *David G. McGowan*[d], *Christopher U. Jones*[e], *Jean-Paul Bahary*[f], *Kenneth L. Zeitzer*[g], *Luis Souhami*[h], *Mark H. Leibenhaut*[e], *Marvin Rotman*[i], *Siraj M. Husain*[j], *Elizabeth Gore*[k], *Adam Raben*[l], *Susan Chafe*[d], *Howard M. Sandler*[m], *Jason A. Efstathiou*[c,*]

[a] *Harvard Radiation Oncology Program, Boston, MA, USA;* [b] *NRG Oncology Statistics and Data Management Center, Philadelphia, PA, USA;* [c] *Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA;* [d] *Cross Cancer Institute, Edmonton, Alberta, Canada;* [e] *Sutter Cancer Centers (Radiological Associates of Sacramento), Sacramento, CA, USA;* [f] *CHUM-Hospital Norte-Dame, Montreal, Quebec, Canada;* [g] *Department of Radiation Oncology, Albert Einstein Medical Center, Philadelphia, PA, USA;* [h] *McGill University, Montreal, Quebec, Canada;* [i] *Brooklyn MB-CCOP/SUNY Downstate, Brooklyn, NY, USA;* [j] *Tom Baker Cancer Center, Calgary, Alberta, Canada;* [k] *Medical College of Wisconsin, Milwaukee, WI, USA;* [l] *Christiana Care Health Services, Inc. CCOP, Newark, DE, USA;* [m] *Cedars-Sinai Medical Center, Los Angeles, CA, USA*

Article info

Article history:
Accepted August 13, 2015

Associate Editor:
Matthew Cooperberg

Keywords:
Prostate cancer
Hormone therapy
Radiation therapy
Cardiovascular mortality
Androgen deprivation therapy
Survival

Abstract

Background: Androgen deprivation therapy (ADT) is associated with coronary heart disease and diabetes in men with prostate cancer (PCa); however, controversy exists regarding ADT and cardiovascular mortality (CVM) with limited data for lower risk disease.
Objective: We conducted a hypothesis-generating retrospective analysis to evaluate the relationship between short-course ADT and CVM in patients with clinically localized PCa enrolled in a phase III trial.
Design, setting, and participants: A total of 1979 men with clinically localized (T1b–2b, prostate-specific antigen [PSA] <20 ng/ml) PCa enrolled in Radiation Therapy Oncology Group (RTOG) 94-08 from 1994 to 2001. Patients were randomized to radiation therapy (RT) with or without short-course ADT (4 mo of gonadotropin-releasing hormone (GnRH) agonist therapy and antiandrogen). Median follow-up was 9.1 yr for survivors.
Outcome measurements and statistical analysis: The Cox proportional hazards model assessed overall survival. The Fine-Gray proportional hazards model assessed disease-specific survival (DSS) and CVM. Covariates included age, race, weight, baseline cardiovascular disease, baseline diabetes, baseline hypertension, Gleason score, T stage, and PSA.
Results and limitations: Short-course ADT improved overall survival and DSS and was not associated with an increased risk of CVM. Overall, 191 cardiovascular-related deaths were observed. At 10 yr, 83 patients (cumulative incidence rate: 10%) receiving RT and ADT versus 95 patients (cumulative incidence rate: 11%) receiving RT alone experienced CVM. The treatment arm was not associated with increased CVM (unadjusted hazard

* Corresponding author. Department of Radiation Oncology, 100 Blossom Street, Cox 3, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA.
Tel. +1 617 726 5866; Fax: +1 617 726 3603.
E-mail address: jefstathiou@partners.org (J.A. Efstathiou).

http://dx.doi.org/10.1016/j.eururo.2015.08.027

ratio: 1.07; confidence interval, 0.81–1.42; $p = 0.62$). Increased CVM was not observed in patients at low risk of PCa death or at high risk of cardiac-related death.
Conclusions: Data from patients enrolled in RTOG 94-08 support the hypothesis that ADT does not increase CVM risk in men with clinically localized PCa treated with short-course GnRH agonist therapy. These data support ADT use in settings with proven survival benefit.
Patient summary: We investigated the controversial relationship between hormone therapy and cardiovascular mortality in men with prostate cancer (PCa) treated with radiation in a large randomized trial. Our data suggest that hormone therapy does not increase the risk of cardiovascular death in patients with clinically localized PCa and support the use of such therapy in settings with proven survival benefit.

1. Introduction

External-beam radiation therapy (RT) in combination with androgen deprivation therapy (ADT) using gonadotropin-releasing hormone (GnRH) agonist therapy decreases cancer-specific mortality and, in some cases, all-cause mortality for men with intermediate/high-risk or locally advanced prostate cancer (PCa) [1–6]. In part, given this demonstrated survival benefit in intermediate/high-risk disease, GnRH agonist therapy use has increased markedly during the past 2 decades in men with PCa including men with lower stage disease and in older men with significant competing causes of mortality [7–9]. However, caution has been raised regarding ADT use with heightened consideration in those least likely to benefit (ie, lower risk disease with less competing causes of mortality) and those most likely to be harmed (ie, significant comorbidities such as high-risk cardiovascular status) because the risk–benefit ratio is less well defined in these patient populations.

Most but not all population-based analyses have suggested that GnRH agonists are associated with a greater risk of incident coronary artery disease, myocardial infarction, and diabetes (DM) in men with PCa [10–12]. Subsequent reports suggested that men with comorbidities or prior cardiovascular disease (CVD) treated with GnRH agonists may have an increased risk of cardiovascular mortality (CVM) [13,14]. Following these observations, a science advisory consensus statement on GnRH agonist therapy and cardiovascular risk was issued, and a US Food and Drug Administration safety warning addressing the concern of increased risk of myocardial infarction, stroke, sudden cardiac death, and DM was released [15]. However, conflicting results exist regarding the risks of ADT and CVM because a number of analyses from phase III randomized trials and subsequent meta-analysis showed no increased risk of CVM in patients treated with GnRH agonists [16–19]. These studies largely consisted of patients with high-risk and locally advanced disease. As such, significant controversy remains surrounding the potential effects of GnRH agonist therapy on cardiovascular death, especially in men with lower cancer-specific mortality and in men with baseline cardiac risk factors.

Thus to assess the relationship between GnRH agonist therapy and CVM in patients with clinically localized PCa, we conducted an exploratory and unplanned retrospective analysis of data from a large randomized trial, Radiation Therapy Oncology Group (RTOG) 94-08, of men treated by RT with or without short-term ADT [1].

2. Patients and methods

The data used in this hypothesis-generating analysis were derived from RTOG 94-08, a phase III trial designed to compare RT with or without 4 mo of GnRH agonist therapy in men with stage T1b–2b PCa and with prostate-specific antigen (PSA) <20 ng/ml [1]. Following stratification based on PSA level (<4 vs 4–20 ng/ml), tumor grade (well differentiated, moderately differentiated, poorly differentiated), and surgical versus clinical documentation of clinically negative nodal status, patients were randomized to RT plus short-term ADT or RT alone [1].

2.1. Patient eligibility

Patients had histologically confirmed prostate adenocarcinoma, stage T1b–2b and a PSA level ≤20 ng/ml. Pretreatment assessment included digital rectal examination and bone scan. Regional lymph nodes were assessed by surgical sampling, lymphangiography, or pelvic computed tomography. Karnofsky performance score was ≥70. All participating sites were required to have institutional review board approval, and all patients provided written informed consent.

2.2. Treatment

Details of RT technique, doses, and fields, and follow-up were previously described [1]. Patients assigned to short-term ADT received flutamide 250 mg three times a day and either monthly 3.6 mg goserelin subcutaneously or 7.5 mg leuprolide intramuscularly for 4 mo.

2.3. End points

Cause of death was investigator defined and reported on follow-up case report forms by each institution. All corresponding end-point times were measured from date of randomization until death or last follow-up. Death due to any cause was an event for overall survival (OS). Death due to PCa was an event for disease-specific survival (DSS). An event for CVM was death from coronary artery disease, cardiac arrest, cardiovascular arrhythmia, myocardial infarction, congestive heart failure, or sudden

cardiac death. For DSS and CVM, deaths due to other reasons were considered as competing risk. Patients still alive were censored at the date of last follow-up.

2.4. Cardiovascular risk group analyses

Patients denoted as higher risk for cardiac mortality were ≥70 yr of age and had a history of CVD or DM. The presence of CVD or DM was noted at the time of registration. Patients with unknown CVD or DM status were excluded from analyses including this risk group ($n = 7$).

2.5. Prostate cancer risk group analyses

Patients were grouped as low risk (Gleason score [GS] ≤6, PSA ≤10, clinical stage T2a or lower), intermediate risk (GS 7 or GS ≤6 with either PSA 10–20 or clinical T2b), or high risk (GS: 8–10). Patients with unknown GS were excluded from analyses of this risk group ($n = 46$).

2.6. Statistics

The purpose of this analysis was to generate a hypothesis regarding the relationship between ADT and CVM. For OS, the Cox proportional hazards model was used. For DSS and CVM, the Fine-Gray proportional hazards model was used [20]. Age and PSA were treated as continuous variables in all analyses. All p values are two sided; p values <0.05 were considered significant. Analyses assessing interaction of prostate cancer risk group and treatment arm were restricted to patients with data for all covariates tested ($n = 1933$).

3. Results

3.1. Pretreatment characteristics

Between 1994 and 2001, a total of 1979 eligible patients were enrolled in the trial. Overall, 987 patients were assigned to RT and short-course ADT; 992 patients were assigned to RT alone. Median age was 71 yr. Median follow-up was 9.1 yr for patients alive at the last data collection (range: 0.1–14.1 yr). Pretreatment characteristics including GS, PSA, and T stage were balanced between treatment arms (Table 1). Approximately 90% of patients analyzed were classified with low- or intermediate-risk PCa (approximately 35% low risk and 55% intermediate risk). The presence of traditional cardiovascular risk factors including DM and hypertension (HTN) were similar between arms, although patients in the RT and ADT arm had a slightly higher rate of baseline CVD compared with RT alone (34% vs 30%) (Table 1).

Table 1 – Pretreatment characteristics

Characteristic	RT and ADT ($n = 987$)		RT alone ($n = 992$)	
	n	%	*n*	%
Age, yr				
Mean (SD)	69.6 (6.2)		70.0 (6.1)	
Median	70		71	
Baseline CVD				
No	642	65	690	69.6
Yes	335	33.9	297	29.9
Unknown	10	1.0	5	0.5
Baseline DM				
No	819	83	807	81.4
Yes	157	15.9	180	18.1
Unknown	11	1.1	5	0.5
Baseline HTN				
No	535	54.2	550	55.4
Yes	445	45.1	437	44.1
Unknown	7	0.7	5	0.5
Race				
Nonwhite	242	24.5	236	23.8
White	745	75.5	756	76.2
Gleason score				
2–6	623	63.1	592	59.7
7	252	25.5	286	28.8
8–10	93	9.4	87	8.8
Missing	19	1.9	27	2.7
T stage				
T1	488	49.4	476	48.0
T2	499	50.6	516	52.0
PSA				
Mean (SD)	8.8 (4.4)		8.9 (4.3)	
Median	7.9		8.1	
<4	109	11.0	100	10.1
≥4	878	89.0	892	89.9
Prostate risk group	($n = 968$)		($n = 965$)	
Low	351	36.3	334	34.6
Intermediate	524	54.1	544	56.4
High	93	9.6	87	9.0
Cardiovascular risk group	($n = 984$)		($n = 988$)	
No	764	77.6	771	78.0
Aged ≥70 yr and either CVD or DM	220	22.4	217	22.0

ADT = androgen-deprivation therapy; CVD = cardiovascular disease; DM = diabetes mellitus; HTN = hypertension; PSA = prostate-specific antigen; RT = radiation therapy; SD = standard deviation.

3.2. Cardiovascular mortality

There was a total of 763 deaths with 191 deaths (25%) attributed to cardiovascular causes. Ninety-two patients treated with ADT and RT died of cardiovascular causes during follow-up compared with 99 patients treated with RT alone.

3.3. Univariate analysis

In univariate analysis, patients receiving RT alone had a greater risk of all-cause mortality (hazard ratio [HR]:1.17; 95% confidence interval [CI], 0.81–1.42; $p = 0.03$) and death due to PCa (HR: 1.87; $p = 0.001$). Figure 1 depicts OS, DSS, and CVM based on treatment arm.

There was no increase in CVM in patients treated with ADT. At 10 yr, 83 men (cumulative incidence rate: 10%) on the RT and ADT arm and 95 men (cumulative incidence rate: 11%) on the RT-alone arm experienced CVM. This is a difference of 1.0% (95% CI, −2.0 to 3.9). The relatively narrow CI and its inclusion of 0 suggest there is no meaningful difference in the 10-yr rate of CVM. The corresponding unadjusted HR was 1.07 and did not meet statistical significance (95% CI, 0.81–1.42; $p = 0.62$) (Table 2).

CVM was significantly associated with traditional cardiac risk factors including age (HR: 1.05; $p = 0.0003$), baseline CVD (HR: 2.14; $p < 0.0001$), and baseline DM (HR: 1.93; $p < 0.0001$). Baseline HTN did not reach conventional levels of statistical significance (HR: 1.33; $p = 0.054$) (Table 2). There was no interactive effect between any

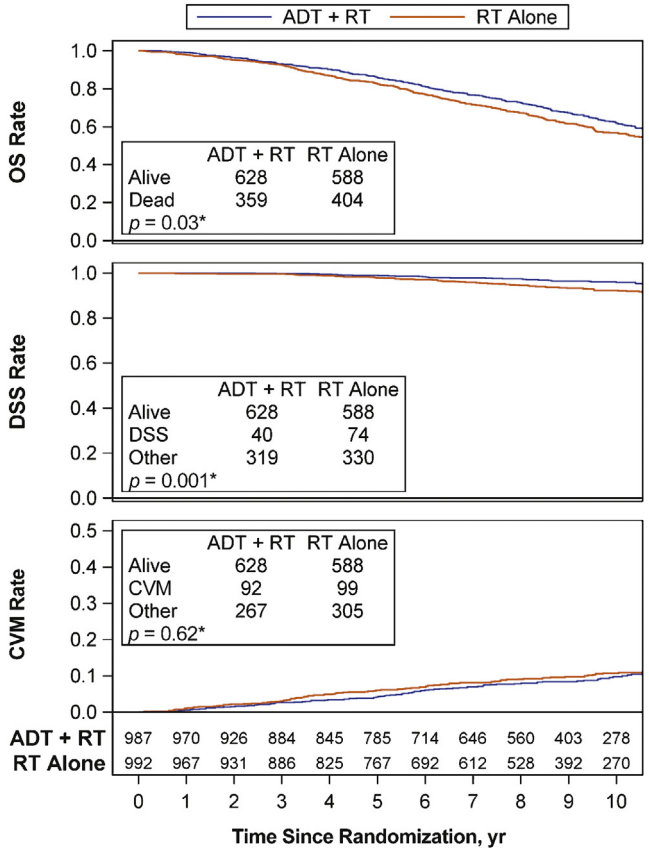

Fig. 1 – Overall survival (OS) of patients treated with short-course androgen deprivation therapy (ADT) and radiation therapy (RT) versus RT alone, disease-specific survival (DSS) of patients treated with short-course ADT and RT versus RT alone, and cardiovascular mortality (CVM) of patients treated with short-course ADT and RT versus RT alone.
ADT = androgen deprivation therapy; CVM = cardiovascular mortality; DSS = disease-specific survival; OS = overall survival; RT = radiation therapy.
*** The *p* value for DSS and CVM are from the Gray-Fine test; OS is from the log-rank test.**

individual cardiac risk factor and treatment arm with respect to CVM.

3.4. *Risk group analyses*

Analyses were performed to evaluate the relationship between baseline risk factor groupings and mortality. Patients with a higher risk for CVM (age ≥70 yr and presence of baseline CVD or DM) composed 22% of the study population (Table 1). When accounting for any possible interaction between the cardiovascular risk group and the treatment arm, CVM was not associated with the treatment arm (HR: 1.29; 95% CI, 0.90–1.85; $p = 0.16$).

PCa risk groups were based on GS, PSA, and clinical stage. The risk groups were balanced between treatment arms that included low-risk (approximately 35%), intermediate-risk (approximately 55%), and high-risk (approximately 10%) patients (Table 1). CVM was not associated with the PCa risk group (Table 2). Interaction analyses suggested a relationship between DSS and intermediate-risk patients (Table 3). A subgroup analysis showed a significant association with DSS (HR: 2.49; 95% CI, 1.51–4.11; $p = 0.0004$) in intermediate-risk patients and the treatment arm.

4. Discussion

Using data from a large randomized controlled trial with a long follow-up, we demonstrated that short-course ADT improves OS and DSS and does not appear to increase CVM in patients with clinically localized PCa. Our results are uniquely positioned to address the controversy surrounding ADT use because this study analyzed patients from all risk groups and provides a novel perspective for patients with lower cancer-specific mortality risk. Approximately 90% of the patients analyzed had low- or intermediate-risk disease.

Our findings regarding the lack of association between ADT and CVM are consistent with the observed actuarial 10-yr rates of death due to intercurrent disease previously reported between the treatment arms of RTOG 94-08 (35% RT and ADT vs 37% RT alone; $p = 0.49$) and with prior analyses from large randomized trials that failed to identify increased CVM in patients with locally advanced and high-risk disease [16–18,21,22]. These studies included patients with a significantly higher cancer-specific mortality risk that could mask a small effect in CVM, in contrast to the predominantly low- and intermediate- risk population of this study.

Although our results are encouraging regarding lack of observed CVM in patients treated with short-course ADT, the absence of any observed survival benefit to the addition of hormone therapy in men receiving radiation for low-risk disease does not support routine use of ADT in this patient population. Given that nearly all deaths in this group result from non-PCa causes, the addition of any toxicity from ADT is not warranted.

Based on results from RTOG 94-08, the predicted number of intermediate-risk patients needed to treat with short-course ADT in addition to RT for each death prevented at 8 yr is approximately 17. Consistent with these results, our subgroup analysis demonstrated a significant DSS benefit for the addition of short-course ADT to RT in intermediate-risk patients.

In high-risk and locally advanced disease, the number of patients needed to treat with long-term ADT to prevent one death based on large randomized studies is estimated at three to five. This large treatment effect has set the standard of care for higher risk disease. Although there was no OS or DSS benefit observed in our analyses for patients with high-risk disease based on treatment arm, this was likely due to an inadequate duration of ADT (4 mo instead of the longer term standard of 28–36 mo) and the comparatively small number of high-risk patients included in the trial.

To address the concern that a subset of patients with baseline comorbidities may have increased risk for treatment-related mortality, our analyses demonstrated that ADT was not associated with CVM even when adjusting for age and preexisting cardiac risk factors including CVD and DM. These results were maintained despite a slight increase

Table 2 – Univariate analyses of cardiovascular mortality

Factor	Patients, *n*	Failure overall, *n*	Number of failures at 10 yr (estimate, %* [95% CI])	Unadjusted HR† (95% CI)	*p* value
Treatment arm					
RT and ADT	987	92	83 (9.8 [7.7–11.8]	RL	
RT	992	99	95 (10.7 (8.7–12.8])	1.07 (0.81–1.42)	0.62
Age, yr, continuous					
	1979	191	178 (10.3 [8.8–11.7])	1.05 (1.02–1.07)	0.0003
Baseline CVD					
No	1332	95	88 (7.7 [6.1–9.3])	RL	
Yes	632	94	89 (15.6 [12.6–18.6])	2.14 (1.62–2.85)	<0.0001
Baseline DM					
No	1626	137	129 (9.1 [7.6–10.6])	RL	
Yes	337	51	46 (14.9 [10.9–19.0])	1.93 (1.40–2.65)	<0.0001
Baseline HTN					
No	1085	91	85 (8.9 [7.1–10.8])	RL	
Yes	882	96	90 (11.6 [9.3–13.9])	1.33 (0.99–1.76)	0.054
Gleason score					
2–6	1215	116	108 (10.3 [8.4–12.1])	RL	
7	538	49	44 (9.1 [6.5–11.8])	0.95 (0.68–1.32)	0.76
8–10	180	18	18 (11.1 [6.1–16.1])	1.04 (0.63–1.71)	0.88
T stage					
T1	964	93	86 (10.2 [8.1–12.3])	RL	
T2	1015	98	92 (10.3 [8.1–12.3])	0.96 (0.73–1.28)	0.81
PSA, ng/ml					
<4	209	20	20 (11.0 [6.3–15.7])	RL	
≥4	1770	171	158 (10.2 [8.6–11.7])	1.02 (0.65–1.63)	0.92
Race					
Nonwhite	478	43	40 (9.5 [6.6–12.3])	RL	
White	1501	148	138 (10.5 [8.8–12.2])	1.06 (0.76–1.49)	0.73
Prostate risk group	(*n* = 968)				
Low	351	71	66 (11.3 [8.8–14.1])	RL	
Intermediate	524	94	86 (9.1 [7.3–11.1])	0.83 (0.61–1.13)	0.23
High	93	18	18 (11.1 [6.8–16.7])	0.95 (0.56–1.60)	0.83

ADT = androgen-deprivation therapy; CI = confidence interval; CVD = cardiovascular disease; DM = diabetes mellitus; HR = hazard ratio; HTN = hypertension; PSA = prostate-specific antigen; RL = referent level; RT = radiation therapy.
* Cumulative incidence estimates; death due to other cause is considered as a competing risk.
† Fine-Gray method; death due to other cause is considered as a competing risk.

in baseline CVD in patients randomized to the ADT and RT arm. However we cannot exclude the possibility of a small treatment effect on CVM or that an unidentified subset of patients (including those with prior CV comorbidity using a validated metric) are at risk for ADT-related harm. Results from RTOG 08-15 will provide clarification on the role for ADT with modern escalated RT doses in patients with intermediate-risk disease and known baseline comorbidities.

Although population-based studies have associated ADT with coronary heart disease, myocardial infarction, stroke,

Table 3 – Treatment arm/prostate cancer risk group interaction analysis (*n* = 1933)

	OS		DSS		CVM	
Factor	HR* (95% CI)	*p* value	HR† (95% CI)	*p* value	HR† (95% CI)	*p* value
Treatment arm						
RT and ADT	RL		RL		RL	
RT	1.07 (0.82–1.39)	0.62	0.64 (0.21–1.95)	0.43	1.13 (0.71–1.79)	0.62
Prostate risk group						
Low	RL		RL		RL	
Intermediate	1.17 (0.093–1.45)	0.18	1.69 (0.75–3.81)	0.23	0.83 (0.53–1.30)	0.42
High	1.48 (1.04–2.12)	0.03	5.32 (2.12–13.33)	0.83	1.34 (0.69–2.60)	0.39
Interaction						
Treatment arm/Intermediate risk	1.15 (0.83–1.58)	0.40	3.89 (1.14–13.21)	0.03	0.99 (0.53–1.83)	0.97
Treatment arm/High risk	0.98 (0.59–1.62)	0.93	2.42 (0.62–9.41)	0.20	0.44 (0.15–1.33)	0.15

ADT = androgen-deprivation therapy; CI = confidence interval; CVM = cardiovascular mortality; DSS = disease-specific survival; HR = hazard ratio, OS = overall survival; RL = referent level.
* Cumulative incidence estimates; death due to other cause is considered as a competing risk.
† Fine-Gray method; death due to other cause is considered as a competing risk.

and metabolic changes including weight gain, sarcopenia, dyslipidemia, insulin resistance, and DM, the magnitude of effect on CVD has been modest (eg, number needed to harm estimated at 384 for each additional myocardial infarction) [10,11,23–27]. These studies often lack robust risk group stratification and are limited in design to prove cause-and-effect relationships including a causal role for ADT and CVM [28]. It may be that GnRH agonist therapy leads to metabolic changes with mixed effects on predicted cardiovascular risk. For example, ADT may lead to increased low-density lipoprotein cholesterol and decreased insulin sensitivity (increasing risk) but increased high-density lipoprotein cholesterol (decreasing risk) and no effect on blood pressure or C-reactive protein levels [23,27]. As such, any direct metabolic effects may result in a net neutral or insignificant effect on CVM.

Our study has substantial strengths including that it is derived from a large randomized multicenter trial with a control arm of no hormone therapy and long follow-up, and it contains many events to inform our primary analysis. Importantly, the trial includes all PCa risk groups including those with and without DSS or OS advantage to ADT, as well as patients at high risk for cardiac mortality due to existing comorbidities. However, this study did not collect sufficient data to perform analyses regarding comorbidity risk using validated metrics or cancer risk assessment using other multivariable instruments. Although the potential exists for ascertainment bias surrounding cause of death and definition of our primary end point, the recording of cardiac death does appear reliable given the strong association with traditional cardiac risk factors including age, baseline CVD, and DM.

It is reassuring that the observed trial deaths attributed to CVM (approximately 24%) are consistent with cardiac mortality rates (approximately 25%) in the general population during the time period of the study [29]. We further considered that ADT may increase the risk of cerebrovascular disease. However, we observed a limited number of deaths attributed to cerebrovascular disease in this study (10 events in the RT and ADT arms; 14 events in the RT arm) precluding any significant statistical conclusions. Additional information relating to lifestyle factors such as smoking, diet, physical activity, and use of concomitant cardiac medications was not collected in RTOG 94-08.

5. Conclusions

We demonstrated that short-course GnRH agonist therapy is not associated with CVM in patients with clinically localized PCa enrolled on RTOG 94-08. These findings are inclusive of all PCa risk groups and provide important insight into low- and intermediate-risk patients with less competing causes of mortality. The lack of cardiac mortality associated with ADT use extends to patients at low risk for cancer-specific mortality and to patients at high risk for cardiac mortality due to age and the presence of baseline cardiovascular risk factors including CVD and DM. In addition, we demonstrate that OS and DSS are associated with short-course GnRH agonist therapy and RT, principally in intermediate-risk patients. While treatment decisions must always weigh potential risks and benefits, our data support the continued use of ADT in settings with proven survival benefit.

Author contributions: Jason A. Efstathiou had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Efstathiou, Shipley, Smith.
Acquisition of data: Shipley, McGowan, Jones, Bahary, Zeitzer, Souhami, Leibenhaut, Rotman, Husain, Gore, Raben, Chafe, Sandler, Efstathiou.
Analysis and interpretation of data: Voog, Paulus, Smith, Efstathiou.
Drafting of the manuscript: Voog, Paulus, Efstathiou.
Critical revision of the manuscript for important intellectual content: Voog, Paulus, Efstathiou, Smith, Sandler.
Statistical analysis: Paulus.
Obtaining funding: Efstathiou, Smith, Shipley, Sandler.
Administrative, technical, or material support: Efstathiou.
Supervision: Efstathiou.
Other (specify): None.

Financial disclosures: Jason A. Efstathiou certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This project was supported by grants U10CA21661, U10CA180868, U10CA180822, U10CA37422, and U24CA180803 from the National Cancer Institute. Jason A. Efstathiou received support from the Prostate Cancer Foundation Young Investigator Award. Matthew R. Smith received support from the Prostate Cancer Foundation Challenge Award.

References

[1] Jones CU, Hunt D, McGowan DF, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 2011;365:107–18.
[2] D'Amico AV, Chen MH, Renshaw AA, et al. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA 2008;299:289–95.
[3] Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomized trial. Lancet 2002;360:103–6.
[4] Pilepich MV, Caplan R, Byhardt RW, et al. Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85-31. J Clin Oncol 1997;15:1013–21.
[5] Denham JW, Steigler A, Lamb DS, et al. Short-term androgen deprivation and radiotherapy for locally advance prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomized controlled trial. Lancet Oncol 2005;6:841–50.
[6] Hanks GE, Pajak TF, Porter A, 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.
[7] Shahinian VB, Yong-fang K, Freeman JL, et al. Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. Cancer 2005;103:1615–24.

[8] Gilbert SM, Kuo YF, Shahinian VB. Prevalent and incident use of androgen deprivation therapy among men with prostate cancer in the United States. Urol Oncol 2011;29:647–53.
[9] Barry MJ, Delorenzo MA, Walker-Corkery ES, et al. The rising prevalence of androgen deprivation among older American men since the advent of prostate-specific antigen testing: a population-based cohort study. BJU Int 2006;98:973–8.
[10] 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.
[11] Keating NL, O'Malley AJ, Freedland SJ, et al. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst 2010;102:39–46.
[12] D'Amico AV, Denham JW, Crook J, 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.
[13] Saigal CS, Gore JL, Krupski TL, et al. Urologic Diseases in America Project. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007;110:1493–500.
[14] Nanda AN, Chen MH, Braccioforte MH, et al. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. JAMA 2009;302:866–73.
[15] Levine GN, D'Amico AV, Berger P, et al. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. CA Cancer J Clin 2010;60:194–201.
[16] Efstathiou JA, Bae K, Shipley WU, et al. Cardiovascular mortality and duration of androgen deprivation for locally advanced prostate cancer: analysis of RTOG 92-02. Eur Urol 2008;54:816–24.
[17] Roach III M, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results from RTOG 8610. J Clin Oncol 2008;26:585–91.
[18] Efstathiou JA, Bae K, Shipley WU, et al. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. J Clin Oncol 2009;27:92–9.
[19] Nguyen PL, Je Y, Schulz FAB, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer a meta-analysis of randomized trials. JAMA 2011;306:2359–66.
[20] Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. J Am Statist Assoc 1999;94:496–509.
[21] Studer UE, Whelan P, Albrecht W, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006;24:1868–76.
[22] Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 2009;360:2516–27.
[23] Efstathiou JA, Shipley WU, Zietman AL, et al. Hormonal therapies: ADT for prostate cancer: true love or heartbreak? Nat Rev Urol 2009;6:252–3.
[24] Smith MR, Finkelstein JS, McGovern FJ, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 2002;87:599–603.
[25] Braga-Basaria M, Dobs AS, Muller DC, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen deprivation therapy. J Clin Oncol 2006;24:3979–83.
[26] Azoulay L, Yin H, Benayoun S, et al. Androgen-deprivation therapy and the risk of stroke in patients with prostate cancer. Eur Urol 2011;60:1244–50.
[27] Van Hemelrijck M, Garmo H, Holmberg L, et al. Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the Population-Based PCBaSe Sweden. J Clin Oncol 2010;28:3448–56.
[28] Punnen S, Cooperberg M, Sadetsky S, et al. Androgen deprivation therapy and cardiovascular risk. J Clin Oncol 2011;29:3510–6.
[29] CDC WONDER: underlying cause of death 1999–2013. CDC WONDER Web site. http://wonder.cdc.gov.