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

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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

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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