Testosterone Replacement Therapy in Men with Prostate Cancer: A Time-Varying Analysis

Alan L. Kaplan, MD, Andrew T. Lenis, MD, MS, Adit Shah, BS, Jacob Rajfer, MD, and Jim C. Hu, MD, MPH

Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

DOI: 10.1111/jsm.12768

ABSTRACT

Introduction. The use of testosterone replacement therapy (TRT) in men with prostate cancer is controversial given concerns of androgen-related cancer progression. Although emerging evidence suggests that TRT may be safe in this setting, no study has investigated dose-related effects.

Aim. We used time-varying analysis to determine whether increasing TRT exposure is associated with worse outcomes.

Methods. Using linked Surveillance, Epidemiology, and End Results-Medicare data, we identified 149,354 men diagnosed with prostate cancer from 1991 to 2007. Subjects treated with TRT were stratified by duration of treatment. Weighted propensity score methods were used to adjust for differences between groups. A Cox proportional hazards model was constructed to assess the effect of injectable TRT exposure on outcomes.

Main Outcome Measure. Overall mortality (OM), prostate cancer–specific mortality (PCSM), and use of salvage androgen deprivation therapy (ADT).

Results. Men treated with TRT, regardless of duration, did not experience higher OM or PCSM (all hazard ratio [HR] < 1.0, all $P \leq 0.002$). We found no difference in use of salvage ADT in the ≤30-day and 31–60 day groups compared with no-TRT (HR 1.23 and 1.05, $P = 0.06$ and 0.81, respectively), whereas it was lower for men on long-term TRT (HR 0.70, $P = 0.04$).

Conclusions. TRT following prostate cancer diagnosis and treatment does not increase mortality or the use of salvage ADT. Using time-varying analysis, we demonstrate that longer duration of TRT is not associated with adverse mortality or greater need for ADT. **Kaplan AL, Lenis AT, Shah A, Rajfer J, and Hu JC. Testosterone replacement therapy in men with prostate cancer: A time-varying analysis. J Sex Med 2015;12:374–380.**

Key Words. Testosterone Replacement Therapy; Prostate Cancer; Time-Varying Analysis; Late-Onset Hypogonadism

Introduction

The use of testosterone replacement therapy (TRT) among men with late-onset hypogonadism (LOH) is increasing [1]. TRT has been shown to improve certain cardiovascular risk factors including waist circumference in the obese [2] and hemoglobin A1c in diabetics [3]. Men with LOH treated with TRT experience improved muscle mass, bone mineral density, mood and sexual performance [4–7]. In older men, TRT may ameliorate depressive symptoms and improve health-related quality of life (HRQOL) [8].

The use of TRT in men with a history of prostate cancer is controversial. As prostate cancer is androgen dependent, administering exogenous testosterone was, until recently, considered unsafe. As prostate cancer incidence and LOH are strongly associated with increasing age, the safety profile of TRT in this patient population is particularly relevant. Emerging data indicate TRT may be safe in men with a history of prostate

cancer, although there remain knowledge gaps. In 31 men with localized prostate cancer treated with brachytherapy, only one experienced a transient increase in the prostate specific antigen (PSA) [9]. At 4.5-year follow-up, none had PSA >1.0 ng/dL. In three small series of men treated with radical prostatectomy (RP), none experienced biochemical recurrence with TRT [10–12]. Pastuszak et al. found that even in men with high-risk prostate cancer, TRT was not associated with increased rates of cancer recurrence after RP [13]. Furthermore, active surveillance (AS) is now a recognized expectant management strategy for low risk disease. Morgentaler et al. described 13 men on AS safely treated with TRT without recurrence, but the overall literature on TRT usage in men with untreated prostate cancer is scant [14].

Using linked Surveillance, Epidemiology, and End Results (SEER)-Medicare data, we previously reported that the use of TRT (yes vs. no) in men with a history of prostate cancer was not associated with increased overall mortality (OM), prostate cancer–specific mortality (PCSM), or the use of salvage androgen deprivation therapy (ADT) [15]. The use of salvage ADT was employed as a proxy for clinically significant biochemical recurrence. To further delineate the relationship between TRT in men with a history of prostate cancer and outcomes, we asked whether increased exposure to TRT worsened OM and cancer-related outcomes.

Materials and Methods

Data Source

University of California Institutional Review Board approval was obtained for this study per protocol. We utilized SEER-Medicare data, which currently composes registries from 20 SEER regions and captures nearly 97% of all cancer diagnoses in the United States [16].

Study Cohort

We identified 348,372 men aged 65 years or older with a pathologic diagnosis of prostate cancer from 1991 to 2007. We then excluded 113,844 men who were not enrolled in Medicare Part A and B to obtain a patient cohort with reliable claims submissions. Complete data were available for 169,414 men. To obtain a cohort with sufficient prediagnosis comorbidity data, an additional 20,060 men without 1 year of available data prior to prostate cancer diagnosis were excluded. Our final study cohort consisted of 149,354 men with prostate cancer and complete pre- and postdiagnosis data.

We divided this cohort into men who received TRT following a diagnosis of prostate cancer (1,181) and those who did not (n = 148,173). Physicians Current Procedural Terminology Coding System, 4th edition (CPT-4) was used to identify TRT, including injection based (J0900, J1060, J1070, J2320, J3120, J3130, J3140, J3150) and subcutaneous pellet-based (S0189) formulations. To assess the effect of duration of exposure on outcomes of interest, we stratified TRT (n = 1,181) based on duration of therapy: ≤30 days (n = 652), 31–60 days (n = 166), and >60 days (n = 363). For clarity, we denote these usage groups as short term, intermediate term, and long term, respectively.

Control Variables

Medicare denominator file was used to obtain data on age (65–69, 70–74, >75 years), and SEER registry was used to obtain demographic data, such as race, SEER region, education level and household income, population density, and tumor characteristics. Hawaii and rural Georgia registries were combined given the small number of subjects. Comorbidity data and Medicare-covered preventative testing (e.g., cholesterol testing, influenza vaccination, and colonoscopy) for 1 year prior to prostate cancer diagnosis was obtained from Medicare data. TRT and duration of TRT usage was captured with CPT-4 codes.

Outcomes

Our outcomes of interest included OM, PCSM, and use of salvage androgen deprivation therapy (ADT) among the varying durations of TRT usage.

Analysis

We used weighted propensity score methods to adjust for differences in demographic and tumor data in this nonrandomized study. Rates of events (recorded as events per 100 person years) were due to variation in length of follow up. A Cox proportional hazards model was used to assess the effect of TRT duration on OM, PCSM, and use of salvage ADT. This allowed men to contribute to the TRT group only when on treatment and contribute to the no TRT group when off treatment. Men who received TRT both prior to and after their diagnosis of prostate cancer were included in the current study as we have previously reported no difference in survivorship outcomes in this