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Prostate cancer-specific mortality after definitive radiation therapy: Who dies of disease?

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Abstract *Background:* A competing risks analysis was undertaken to identify subgroups at greatest risk of dying from prostate cancer (PC) after definitive external beam radiation therapy (RT) ± androgen deprivation therapy (ADT) in the prostate specific antigen (PSA) era.
Methods: Outcomes of 2675 men with localised PC treated with RT ± ADT from 1987–2007 were analysed. Prostate cancer-specific mortality (PCSM) and non-PCSM rates were calculated after stratifying patients according to National Comprehensive Cancer Network (NCCN) risk-group, RT dose, use of ADT and age at treatment.
Results: Only 0.2% of low-risk men died of PC 10 years after treatment. All of these deaths occurred in patients treated with <72 Gy, and only one patient ⩾70 years old who received ⩾72 Gy died of PC at last follow-up. Likewise, none of the patients with intermediate-risk disease treated with ⩾72 Gy and ADT died of PC at 10 years, and the highest 10-year rate of PCSM was seen in men ⩾70 years old treated with <72 Gy without ADT (5.1%). Among high-risk men <70 years old, treatment with RT dose <72 Gy without ADT yielded similar 10-year rates of PCSM (15.2%) and non-PCSM (18.5%), whereas men treated with ⩾72 Gy and ADT were twice as likely to die from other causes (16.2%) than PC (9.4%). In high-risk men ⩾70 years old, dose-escalation with ADT reduced 10-year PCSM from 14% to 4%, and most deaths were due to other causes.
Conclusion: Low- and intermediate-risk patients treated with definitive RT are unlikely to die of PC. PCSM is higher in men with high-risk disease but may be reduced with dose-escalation and ADT, although patients are still twice as likely to die of other causes.

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1. Introduction

Since the introduction of prostate specific antigen (PSA) screening in the United States, a gradual stage migration has led to earlier presentation and diagnosis of prostate cancer. Following definitive local therapy in the PSA era, a minority of patients will experience a biochemical recurrence, and an even smaller percentage will develop clinical disease progression and die from their disease. Estimates from the Surveillance, Epidemiology and End Results (SEER) database suggest excess mortality rates due to prostate cancer as low as 1% and 5% compared to the general population at 5 and 10 years following diagnosis in the PSA era.[1] In addition, the natural history for many men with prostate cancer is protracted, with some series citing an average of 8 years to the development of distant metastases for patients who develop PSA recurrence after local therapy, and an additional 5 years survival for those patients who ultimately succumb to their disease.[2] In this older patient population with a potentially prolonged disease course, competing causes of mortality are increasingly important.

In this single-institution study looking at patients treated in the PSA era with definitive external beam radiation therapy for localised prostate cancer, we analysed the probability of death from prostate cancer versus other causes using a competing risks model. Patients were stratified by known prognostic factors for disease-specific and all-cause mortality including risk group, radiation dose, treatment with androgen deprivation therapy and age at treatment in order to identify a contemporary cohort of patients at highest risk of dying from prostate cancer and to identify factors predicting for mortality from disease.

2. Materials and methods

2.1. Patient and treatment characteristics

This study was approved by the institutional review board at MD Anderson Cancer Center and waiver of consent was obtained. The cohort analysed in this study was derived from a group of 2838 men with localised prostatic adenocarcinoma who were treated at MD Anderson between 1987 and 2007 with definitive external beam radiation therapy (RT). A total of 2675 patients with pre-treatment PSA < 100 ng/mL, documented T-stage and Gleason score, RT dose $\geqslant 60$ Gy and known or assignable cause of death comprised the final study cohort (Table 1).

Patients were stratified according to risk group as defined by the National Comprehensive Cancer Network (NCCN).[3] Risk groups were defined as follows: Low-risk, stage T1a-T2a and Gleason score $\leqslant 6$ and PSA < 10 ng/mL; high-risk, stage T3-4 or Gleason score $\geqslant 8$ or PSA > 20 ng/mL; intermediate-risk, all others.

2.2. Follow-up and determination of cause of death

Patients were routinely followed every 3–6 months for 2 years, every 6 months during years 3–5 and annually beginning 5 years after treatment with serial digital rectal examinations (DRE) and PSA levels. Cause of death was determined by death certificate as recorded in the National Death Index (NDI) database or by the institutional Tumor Registry that regularly contacts patients about disease and vital status. Prostate cancer-specific survival was defined as death at the time of progressive metastatic disease. Patients who died from other causes or with no documented cause of death and a PSA $\leqslant 1.0$ ng/mL within 1 year of death without metastases were classified as dying from other causes.

2.3. Statistical methods

Due to the relatively low number of patients who died of prostate cancer as compared to other causes, a competing risks analysis using Fine and Gray's proportional sub-hazards regression was performed to generate estimates of the cumulative incidence of prostate cancer-specific mortality (PCSM) in all three risk groups. Follow-up for individual patients was censored at the last date of contact or death. Death from a cause other than prostate cancer was considered a competing risk event and censored at the time of the event in an informative manner. PCSM rates and other cause mortality rates were calculated after stratifying patients by NCCN risk group, age at treatment, dose of RT and treatment with ADT. Differences between patient and treatment characteristics were analysed using the χ^2 test. Using backward elimination, a Cox regression analysis was performed to determine if age at treatment, pre-treatment PSA, Gleason score, T stage, dose RT, treatment with ADT and era of treatment predicted for PCSM, other cause mortality and all-cause mortality. A p-value of 0.05 was considered significant. All statistical analyses were performed using Stata, release 11 (StataCorp, College Station, TX) and SAS, version 9.2 (SAS Institute Inc., Cary, NC), and all tests were two-sided.

3. Results

3.1. Baseline patient and treatment characteristics

The median age was 68.5 years and the median follow-up was 6.4 years (interquartile range, 3.8–10.3 years). A total of 551 men (21%) had low-risk, 1081 men (40%) had intermediate-risk, and 1043 men (39%) had high-risk disease. As shown in Table 1, the median dose delivered to the high-risk group was signif-