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Platinum Priority – Prostate Cancer

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Cancer-specific Survival After Metastasis Following Primary Radical Prostatectomy Compared with Radiation Therapy in Prostate Cancer Patients: Results of a Population-based, Propensity Score–Matched Analysis

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Abstract

Background: Data regarding the difference in the clinical course from metastasis to prostate cancer–specific mortality (PCSM) following radical prostatectomy (RP) compared with radiation therapy (RT) are lacking.
Objective: To examine the association between primary treatment modality and prostate cancer–specific survival (PCSS) after metastasis.
Design, setting, and participants: We used the Surveillance Epidemiology and End Results–Medicare linked database from 1994 to 2007 for patients diagnosed with localized prostate cancer (PCa). We used cancer stage and Gleason score to stratify patients into low and intermediate–high risks.
Intervention: Radical prostatectomy or radiation therapy.
Outcome measurements and statistical analysis: Our outcome is time from onset of metastases to PCSM. Propensity score matching and Cox regression were used to analyze the PCSM hazard for the RP group compared with the RT group.
Results and limitations: Our study consisted of 66 492 men diagnosed with PCa, 51 337 men receiving RT, and 15 155 men undergoing RP within 1 yr of cancer diagnosis. During the study period, 2802 men were diagnosed as having metastatic disease. A total of 916 men with metastases were included in the propensity-matched cohort; of these men, 186 died from PCa. During the follow-up, for the low-risk patients, the adjusted PCSS after metastasis was 86.2% and 79.3% in the RP and RT groups, respectively; for the intermediate–high-risk patients, the PCSS after metastasis was 76.3% and 63.3% in the RP and RT groups, respectively. The hazard ratios estimating the risk of PCSM between the RP and RT groups were 0.64 (95% confidence interval [CI], 0.36–1.16) and 0.55 (95% CI, 0.39–0.77) for the low- and intermediate–high-risk groups, respectively. Because of the nature of observational studies, the results may be affected by residual confounders and treatment indication.
Conclusions: Following the development of metastases, men who received primary RP have a longer PCSS than men who received primary RT. Our results may have implications for the timing and nature of local PCa treatment.

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1. Introduction

Since the adoption of prostate-specific antigen (PSA) as a screening tool, more men have received a diagnosis of prostate cancer (PCa) and have undergone treatment earlier than in the pre-PSA era [1]. Given the prolonged natural history of PCa, management requires careful consideration of the severity of the disease, the health of the patient, and the benefits and risks of intervention. Radical prostatectomy (RP) and radiation therapy (RT) are two common interventions for localized PCa [2,3]. However, there is no conclusive evidence that either treatment is superior to the other in terms of cancer control or functional outcome [4]. Although retrospective studies have compared the two treatments in terms of rates of biochemical failure, metastasis-free survival, and PCa-specific survival (PCSS) [5–7], data regarding the difference in the clinical course from metastasis to death following RP compared with RT are lacking.

Mortality [8] and morbidity precipitously increase once metastases develop, but the biologic processes that underlie the development of tumor metastasis and affect the natural history of disease afterward are not well understood. We undertook this study to examine the impact of primary treatment modality on PCSS after metastasis.

2. Methods

2.1. Study population

We used data from the Surveillance Epidemiology and End Results (SEER) database linked to Medicare claims. SEER provides a nearly representative sample of approximately 26% of the US population [9]. Our cohort included PCa patients aged 66–85 yr from 1994 to 2007. Data on patients with incomplete Medicare records during the study follow-up (ie, patients not continuously enrolled in both Medicare Part A and Part B and patients who enrolled in health maintenance organizations) were excluded. The sample was limited to 119 997 men diagnosed with incident localized PCa. We excluded men who were diagnosed as metastatic; who received palliative treatments; who had RP, RT, or androgen-deprivation therapy (ADT) treatment before PCa diagnosis (n = 23 040); who were without cancer grade (n = 3331); or who were without primary treatments (n = 21 889). We further excluded men who received RT with a modality other than brachytherapy, intensity-modulated radiotherapy (IMRT), three-dimensional conformal radiotherapy (3D CRT), or a combination (n = 4589) or who received both RP and RT during the follow-up (n = 656). After exclusion criteria, a total of 66 492 men were included in the study.

2.2. Outcome variables

The primary outcome was PCSS after metastases. We created an algorithm [10] to identify metastasis in men diagnosed with PCa from Medicare claims. A diagnosis of metastases had to meet the following conditions: (1) at least two claims with International Classification of Diseases, Ninth Revision (ICD-9), codes 198.5 (bone and bone marrow), 197.0 (lung), 197.7 (liver), or 198.3 (brain and spinal cord) and (2) two Medicare claims separated by 30 d to minimize false positives. We defined the date of metastasis as the earliest occurrence of one of the previously mentioned claims patterns at any time during follow-up. The occurrence of PCa- specific mortality (PCSM) was determined from SEER cause-of-death data through December 31, 2007.

2.3. Study covariates

The study population was divided into the following age cohorts: 66–69, 70–74, 75–79, and ≥80 yr at diagnosis. Clinical stage (extent of disease in SEER) was categorized into T1 or T2 using the American Joint Committee on Cancer classification system [11]. The SEER registry described cancer stage as *well differentiated, moderately differentiated*, and *poorly differentiated* based on a Gleason score of 2–4, 5–7, and 8–10, respectively, before 2003. Starting in 2003, Gleason 7 was reclassified from *moderately differentiated* to *poorly differentiated*. The Charlson score was derived from Medicare claims during the year prior to PCa diagnosis using a validated algorithm [12]. Participation of state buy-in was included in the study as a proxy for poverty. Because of the lack of PSA data before 2004, PSA was not used to classify risk levels. Patients with well-differentiated or moderately differentiated tumor and cancer stage ≤T2a were categorized as low risk. Patients who did not have low-risk cancer were grouped in the intermediate–high-risk category.

We searched for Medicare claim records of computed tomography, magnetic resonance imaging, and radionuclide bone scanning [13] from the last date of primary treatments to metastasis. We also abstracted records of chemotherapy and ADT from 180 d after primary treatments to metastasis and after.

2.4. Statistical methods

To compare the differences in proportions of baseline characteristics between RT and RP, χ^2 tests were used. The cumulative incidence of PCSM, treating other causes of death as a competing risk, was computed to estimate the PCSS [14]. The median follow-up time was computed using Kaplan-Meier methods [15].

We adopted the propensity score–matching method [16] to balance observed covariates between RT and RP. Propensity scores reflect the probability that a patient received RT or RP based on his baseline characteristics. We defined the logit of predicted probability of treatment as a propensity score using the following baseline characteristics: age, race, year of diagnosis, SEER region, state buy-in, comorbidity, and cancer grade/stage. Subjects receiving RT were matched on a one-to-one basis with subjects receiving RP. Matching was performed based on nearest-neighbor matching, and RP and RT patients were matched within their respective risk groups.

With time from metastasis to PCSM as the response variable, the Cox regression method was used to analyze hazard ratios (HRs) and 95% confidence intervals (CIs) for PCSM for RP compared with RT. Finally, we performed a sensitivity analysis to measure the potential influence that an unmeasured confounder might have on the HR estimates.

Descriptive analysis and propensity score matching were performed using SAS statistical software v.9.2 (SAS Institute, Cary, NC, USA). Cox regressions were carried out using R v.2.13, (R Foundation for Statistical Computing, Vienna, Austria). Sensitivity analyses were conducted using Microsoft Excel. Statistical significance was set at 0.05, and all tests were two-tailed.

3. Results

3.1. Baseline characteristics of men at diagnosis

Among a total of 66 492 men, 51 337 men receiving RT and 15 155 men receiving RP within 1 yr of cancer diagnosis were included in the analysis (Table 1). The median follow-up is 7.3 yr (interquartile range [IQR]: 4.7–9.9) from diagnosis. Among these 66 492 men, 2802 were diagnosed with metastases during the follow-up. Propensity score matching was performed on these men with metastases,