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Original article

The characteristics of bladder cancer after radiotherapy for prostate cancer

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Abstract

Objectives: Prostate radiotherapy (RT) has been associated with an increased risk of bladder cancer (CaB). However it is unknown how prior RT affects the stage, grade, and histology of secondary CaB. While irradiated patients have adverse surgical outcomes, how RT affects survival is also unknown. We sought to determine how RT for prostate cancer (CaP) affects the characteristics and outcomes of secondary CaB.

Materials and methods: A retrospective review of 275,200 cases of clinically localized CaP submitted to the Surveillance, Epidemiology, and End Results (SEER) database between 1988 and 2007 was performed. CaP treatment was stratified by radical prostatectomy (RP) alone, RT, or RP + RT. Diagnosis of CaB at least 1 year after CaP, and CaB death were the primary outcomes. The stage, grade, and histology of CaB of patients exposed to RT or RP were compared. A competing risks multivariable survival analysis was performed to determine the effect of RT on CaB-specific mortality.

Results: CaP patients treated with any RT were 1.70 times as likely to develop CaB (95% CI 1.57–1.86, $P < 0.001$) compared with RP alone. CaB in men who had RT were more likely non-urothelial (6.4% vs. 3.8%, $P = 0.004$), trigonal (6.9% vs. 5.4%, $P = 0.012$), and carcinoma in-situ (CIS) (9.2% vs. 7.0%, $P < 0.001$) compared with RP. RT increased CaB-specific mortality (HR = 1.30, $P = 0.02$), which remained significant when adjusted for CaB features (HR = 1.28, $P = 0.05$).

Conclusions: Patients with localized CaP treated with RT have a higher risk of CaB. CaB after RT is more likely to be located at the trigone and contain CIS. Patients with CaB after RT have decreased cancer-specific survival compared with those undergoing RP alone.

Keywords: Prostatic neoplasms; Urinary bladder neoplasms; Radiotherapy; Neoplasms; Second primary

1. Introduction

1.1. Background

Bladder cancer (CaB) is the fourth most common solid malignancy in US men [1]. Cigarette smoking, male sex, white race, and occupational exposures to aromatic amines are known risk factors. Pelvic radiotherapy for prostate cancer (CaP) or other cancers has also been implicated as a risk factor for CaB [2–7].

Second primary cancers (SPC) are a well described complication of radiation exposure, either from therapeutic or environmental sources. Li et al. have found that survivors of the Nagasaki atomic bomb are predisposed to develop radiosensitive solid tumors, including those of the breast, colon, thyroid, lung, and urinary bladder [8]. A study of cervical cancer survivors with 40 years of follow-up showed a significant increase in risk of SPC for patients undergoing radiotherapy, with the largest effect seen to heavily irradiated (>3 Gy) pelvic organs, such as the rectum and urinary bladder [7]. A purported mechanism of secondary cancers is that sublethal doses of radiation to cells cause DNA damage

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and subsequent mutations that may predispose to tumorigenesis. This likely occurs through multiple DNA damage repair pathways, such as p53, which are the subject of laboratory study in prostate and other cell types [9].

While reports have suggested an increased risk of SPC of the bladder after prostatic radiation therapy (RT), less data exist on how these cancers differ with regard to stage, grade, or histology at the time of diagnosis from radiation-naive cancers. Finally, while previously irradiated CaB patients have been shown to have more complications and adverse pathologic outcomes at the time of radical cystectomy [10,11], the association between prior RT and cancer-specific survival is unknown for those who are not eligible for or do not require radical surgery.

1.2. Objectives

The primary goal of this analysis is to determine the association between prior RT and the incidence, stage, grade, histology, and survival of CaB. Secondarily, we examine how the type of RT affects CaB incidence and time to CaB.

2. Materials and methods

2.1. Data

Data for this study are from the Surveillance, Epidemiology, and End Results (SEER) 17 cancer public use database, November 2009 submission, a US population-based registry [12]. The SEER*Stat software, ver. 6.5.2 (Information Management Services, Silver Spring, MD) was used in client-server mode to perform all data queries.

2.2. Variables

Cases of clinically localized prostatic adenocarcinoma were identified using the American Joint Committee on Cancer (AJCC), 7th edition classification of malignant tumors (TNM), which is available in SEER for cases diagnosed in 2004 or later. For cases before 2004, the stages were recoded to this standard utilizing the SEER extent of disease (EOD) classification. Clinically localized CaP was defined as $cT_{1/2}N_0M_0$.

CaP treatment was coded as received radical prostatectomy (RP), radiation following RP (RP + RT), external beam radiotherapy alone (XBRT), external beam and brachytherapy (XBRT + BT), brachytherapy alone (BT), and radiation not otherwise specified (RT NOS). Patients undergoing salvage RP after RT, as well as patients receiving a surgery other than RP before RT, were placed into the category based on the type of RT received.

The time to development of CaB was calculated by subtracting total bladder follow-up time from total prostate follow-up time. While other reports have defined secondary cancer as those occurring at least 5 years after an exposure, this definition is based on secondary sarcomas [13]. Rather than using this definition, we opted for a more inclusive strategy suggested by others: to exclude only synchronous CaB (those diagnosed less than 1 year after CaP, as SEER provides year-level detail for the date of diagnosis) [14]. The analyses were stratified by 5-year follow-up intervals to facilitate a more detailed examination of the effect of follow-up time on CaB risk. CaB grade was stratified to low, intermediate, or high, which correspond to the SEER classification system. CaB histology was stratified into urothelial carcinoma (UC), squamous cell carcinoma (SCC), or other for multivariable analyses.

Age was considered as the age at CaP diagnosis for the CaB incidence analyses, and the age at CaB for the CaB-specific survival analyses. Race was analyzed as a categorical variable (white, black, or other). Region was categorized according to the SEER classification (East, Northern Plains, Pacific Coast/Alaska, or Southwest).

2.3. Statistical analysis

Standardized incidence ratios (SIR) were computed for each CaP treatment modality by comparing observed CaB incidence rates in each group to the male age-specific CaB incidence rates in the SEER for 2003–2007 by 5-year age group and race [black race vs. all other races], adjusted to the US standard population [1]. Incidence rate ratios (IRR) were then calculated with RP as the referent group. The clinicopathologic characteristics of the CaB cases were stratified by radiation exposure and analyzed using Pearson χ^2 tests. Median time to CaB for each RT subtype and RP were compared using the Kruskal-Wallis analysis of variance test.

Cox proportional hazard models were performed to determine the hazard ratios for developing CaB at least 1 year following CaP diagnosis stratified by follow-up time and CaP treatment. Survival analyses were performed using the competing risk regression package (cmprsk) in R, which implements the method of Fine and Gray for proportional subhazards [15]. A multivariable competing risks regression was performed to derive the hazard ratio and 95% confidence interval for radiation on CaB death adjusting for age, and CaB stage and grade.

For all analyses, variables are considered significant predictors if the P value associated with the appropriate test statistic is <0.05. All statistical analyses were performed using R version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).

2.4. Sample

Data for 489,903 cases of clinically localized CaP were reported to the SEER database between 1988 and 2007. As displayed in Supplemental Fig. 1, we excluded 151,951 patients who had no CaP treatment data, as well as 308 patients who received both RT and RP, but where the sequence of treatment was unknown. We examined only CaB cases that were diagnosed at least 1 year following CaP