Original Study

Oncologic Effect of Cumulative Smoking Exposure in Patients Treated With Salvage Radical Prostatectomy for Radiation-recurrent Prostate Cancer

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Abstract

Smoking is associated with prostate cancer mortality and disease progression after treatment for clinically nonmetastatic prostate cancer with curative intent. We investigated the effect of smoking on biochemical recurrence and metastasis in a retrospective cohort of 214 radiation-recurrent prostate cancer patients who underwent salvage radical prostatectomy. High cumulative smoking exposure was associated with the biologic and clinical aggressiveness of prostate cancer and was an independent predictor of biochemical recurrence after adjusting for established clinicopathologic features. These data support the body of evidence that smoking is detrimental beyond the initial diagnosis of prostate cancer, even when the disease is more advanced.

Introduction: The purpose of the present study was to investigate the association of smoking with biochemical recurrence (BCR) and metastasis in radiation-recurrent prostate cancer (PCa) patients undergoing salvage radical prostatectomy (SRP). **Patients and Methods:** A total of 214 patients treated with SRP for radiation-recurrent PCa in 5 tertiary referral centers were included from January 2007 to December 2015. Kaplan-Meier analyses were used to assess the time to BCR and metastasis. Pre- and postoperative multivariable Cox proportional hazard regression models were fitted. **Results:** Overall, 120 (56.1%), 49 (22.9%), and 45 (21%) patients were never, former, and current smokers, respectively. Low-, medium-, and high-cumulative smoking exposure was registered in 59.8%, 16.4%, and 23.8% of cases, respectively. Patients with high cumulative smoking exposure had a significantly greater rate of a pathologic Gleason score of ≥ 8 ($P = .01$) and extracapsular extension ($P = .004$). Smoking status, cumulative smoking exposure, intensity, and duration were significantly associated with BCR-free survival ($P < .001$ for all). Smoking status, cumulative smoking exposure, and smoking intensity were significantly associated with metastasis-free survival ($P = .03$ for all). High cumulative smoking exposure was independently associated with BCR in both pre- (hazard ratio, 2.23; $P = .001$) and postoperative (hazard ratio, 1.64; $P = .04$) multivariable models adjusted for the effects of established clinicopathologic features. Smoking cessation did not affect either BCR- or metastasis-free survival ($P = .56$ and $P = .40$, respectively). **Conclusion:** High cumulative smoking exposure was associated with the biologic and clinical aggressiveness of PCa in patients treated with SRP

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for radiation-recurrent disease. Smoking is a modifiable risk factor that detrimentally affected the outcomes, even in patients with advanced PCa.

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Introduction

Smoking is a leading environmental risk factor for several genitourinary cancers.[1-4] However, the strength of the association between smoking and prostate cancer (PCa) remains variable.[5-7] PCa patients who smoke have a 24% increased risk of succumbing to their disease.[8] Moreover, smoking has been associated with disease progression after treatment for clinically nonmetastatic PCa with curative intent. For example, smokers have been reported to have a greater rate of locally advanced disease at radical prostatectomy (RP)[9] and a greater rate of biochemical recurrence (BCR) and metastases.[10-12] Similarly, after external beam radiotherapy (EBRT), smoking has been associated with a greater risk of BCR, distant metastasis, PCa death, and long-term genitourinary toxicity.[13,14] Similar to other diseases, the detrimental effect of smoking on the oncologic outcomes after RP seems to be mitigated after $\geq$ 10 years of smoking cessation.[15] These findings rely on data from large cohort studies of patients with mostly low- and intermediate-risk PCa. However, for patients with higher risk PCa, such as those with radiation-recurrent PCa, the differential effect of smoking on the surgical and oncologic outcomes remains unknown.

We hypothesized that heavy, long-term smokers would have more advanced disease and greater recurrence rates than nonsmokers and low-intensity smokers. We tested this hypothesis in a multicenter retrospective observational study of patients treated with salvage RP (SRP) for radiation-recurrent PCa.

Patients and Methods

Patient Selection

Five participating centers provided information for men treated with SRP at their site. The local institutional review boards approved the present study. All institutions shared the agreements before the initiation of the study and provided the necessary clinical data. Before the final analysis, all identified anomalies were resolved through regular communication with all sites, and the database was frozen to produce the final data set. The study cohort included 214 patients with radiation-recurrent PCa treated with SRP from January 2007 to December 2015. The RT modalities included brachytherapy, external beam RT (EBRT), or between distinct RT techniques (EBRT and brachytherapy, EBRT and intensity-modulated RT, or EBRT and 3-dimensional conformal RT). PCa recurrence after RT was defined as an increase of $\geq$ 2 ng/mL greater than the nadir according to the Radiation Therapy Oncology Group–American Society for Radiation Oncology Phoenix criteria.[16] All the patients underwent a pre-SRP biopsy to confirm radiation-recurrent PCa. None of the patients had radiographic evidence of metastatic disease before SRP. Open surgical SRP, including pelvic lymph node dissection, was performed in all the patients.

The preoperative clinical and epidemiologic features of the patients were analyzed. Patients were considered smokers if they had smoked 100 cigarettes during their lifetime. Former smokers were distinguished from current smokers by the report of smoking cessation $\geq$ 1 year before SRP. Smoking intensity and duration were both categorized using 10 cigarettes per day (CPD) groups and 10-year intervals and as $<$ 20 or $\geq$ 20 CPD and $<$ 20 or $\geq$ 20 years. Using the smoking intensity and duration, the cumulative smoking exposure was defined as low ($<$ 20 CPD and $<$ 20 years), medium ($<$ 20 CPD but $\geq$ 20 years or $\geq$ 20 CPD but $<$ 20 years), and high ($\geq$ 20 CPD and $\geq$ 20 years).[17] Smoking cessation duration was categorized as $<$ 10 or $\geq$ 10 years.[2] All prostate specimens were examined by dedicated genitourinary pathologists in each center. The pathologic stage was assigned using the 2007 American Joint Committee on Cancer TNM staging system.

Follow-up Protocol

Follow-up examinations were performed in accordance with institutional protocols. Generally, the patients were followed up quarterly within the first 2 years and semiannually thereafter. The total prostate-specific antigen (tPSA) level and the presence of urinary symptoms were evaluated at each visit. BCR was defined as a tPSA value of $\geq$ 0.2 ng/mL after SRP. No patient had received androgen deprivation therapy before the diagnosis of BCR. Distant metastases were identified using radiologic imaging. The cause of death was determined by the treating physicians, by medical record review corroborated by the death certificate, or by the death certificates alone.[18] In cases for which death certificates were retrieved and reviewed for the cause of death, only men with known recurrence after SRP, who had documented metastatic PCa, and who had PCa listed in the death certificate were considered to have died of PCa. The follow-up duration was calculated from the date of surgery to the date of death or the last follow-up visit.

Statistical Analysis

The normal distribution of data was analyzed for each continuous variable using kurtosis and skewness. The analysis of variance test, Kruskal-Wallis test, and χ^2 test for multiple independent factors were used to compare triplets, as appropriate. The Student unpaired *t* test, Mann-Whitney *U* test, and Pearson χ^2 test were used to compare 2 independent factors. BCR-free and metastases-free survival curves were generated using the Kaplan-Meier method. A