Original Study

Do Second Primary Cancers Affect the Risk of Biochemical Recurrence in Prostate Cancer Patients Undergoing Radical Prostatectomy? A Propensity Score-Matched Analysis

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Abstract

Although observational studies have reported clinicopathologic data on prostate cancer (PCa) at the time that other primary cancers have been diagnosed, no studies have focused on the prognostic value of the presence of second primary cancers in patients with PCa. In a propensity score-matched analysis, patients with other malignancies had similar biochemical recurrence-free survival rates compared with those without other cancers.

Introduction: The present study evaluated the incidence and prognostic value of second primary cancers in patients with prostate cancer (PCa) who had undergone radical prostatectomy (RP). **Materials and Methods:** From 2003 to 2013, 1915 patients who had undergone RP were included in the present analysis. We calculated the propensity scores of various clinicopathologic factors and matched 298 patients with and without second primary cancers in a 1:1 ratio. To assess the baseline variables, we compared the descriptive statistics between the 2 groups. The post-operative biochemical recurrence (BCR)-free survival rates were calculated using the Kaplan-Meier method. Multivariate Cox regression analysis was performed to identify the independent predictors of BCR after RP. **Results:** Overall, 159 patients with PCa (8.3%) who had undergone RP were diagnosed with second primary cancers. After adjusting the patient characteristics in the propensity score-matched analysis, no variables were significantly different between the 2 groups with 149 with and 149 without other primary cancers. Moreover, the BCR-free survival rates were not significantly associated with the incidence of a second primary malignancy or the time to diagnosis. In the multivariate Cox regression model, serum prostate-specific antigen (hazard ratio [HR], 1.04), extraprostatic extension (HR, 3.29), seminal vesicle invasion (SVI; HR, 2.85), and surgical margin positivity (HR, 4.11) remained as independent predictors for BCR. However, the presence of a second primary malignancy was not predictive for BCR. In patients with a second primary cancer, multivariate analysis identified SVI (HR, 10.38) and positive surgical margin (HR, 3.48) as significant predictors for BCR. **Conclusions:** Our results suggest that the presence of second primary malignancies might not affect BCR in patients with PCa who undergo RP.

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Introduction

Prostate cancer (PCa) is one of the most common malignancies worldwide in older men.[1] Despite its aggressiveness in advanced-stage or high-grade cancer, the early detection of PCa by the widely used serum prostate-specific antigen (PSA) test improves survival rates and life expectancy.[2] In addition, slow growth is a unique feature of PCa; thus, elderly men who have been diagnosed with clinically localized PCa might not experience significant progression to an advanced stage during their lifetime.[3] The risk of

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clinically significant disease development is only 9.5%, and the risk of cancer-specific mortality is only 2.9% in elderly men with PCa.[3]

Because age is significantly associated with the risk of developing cancer, many patients experience second primary cancers before and after diagnosis of PCa.[4] Because cancer can influence the general health of patients, including the immune system, other primary cancers might affect the prognosis after therapy.[5,6] For example, patients with non−small cell lung cancer with a second primary cancer tended to have better overall survival rates than patients without a second primary cancer in a study by Duchateau and Stokkel.[7] Although observational studies have reported clinicopathologic data on PCa at the time that other primary cancers are diagnosed,[8,9] no studies, to our knowledge, have focused on the prognostic value of the presence of other primary cancers in patients with PCa.

In the present study, we examined whether the presence of a second primary cancer influenced biochemical recurrence (BCR) in patients with PCa who had undergone radical prostatectomy (RP). Furthermore, we aimed to identify the independent predictive factors for BCR in patients with PCa with other primary cancers.

Materials and Methods

Study Population

We collected data from 3866 patients with PCa diagnosed at Seoul National University Bundang Hospital from May 2003 to March 2013. A total of 1969 patients had undergone RP, and 54 patients were excluded from the analysis for the following reasons: administration of neoadjuvant hormonal therapy, insufficient reduction of serum PSA levels after surgery, immediate postoperative adjuvant treatment, or follow-up data for < 6 months after RP. We finally included 1915 patients as the overall study population for performing a propensity score-matched analysis according to the presence of a second primary cancer. The institutional review board at our hospital approved the present study (B-1404/246-106), and all protocols were in accordance with the principles of the Declaration of Helsinki.[10]

Study Design

We analyzed the following clinicopathologic factors: age, body mass index (BMI), the presence of diabetes mellitus, clinical T stage, serum PSA levels, PSA density (PSAD), total prostate volume (measured by prostate ultrasonography), biopsy Gleason score (GS), percentage of positive biopsy cores, percentage of cancer within the positive biopsy cores, pathologic GS in surgical specimens, extraprostatic extension (EPE), seminal vesicle invasion (SVI), lymph node metastasis, surgical margin positivity, and BCR status. Serum PSA levels were monitored in all patients every 3 to 6 months after surgery. We defined BCR as an increase in serum PSA levels of > 0.2 ng/mL on 2 consecutive measurements.[11]

We determined whether patients with PCa had other primary cancers using the Korean Classification of Disease, 5th edition diagnostic codes. Korean Classification of Disease, 5th edition is a modified classification system based on the International Classification of Diseases, 10th edition, in which 5-digit codes were added to clarify the conditions of patients. After identifying the patients with second primary cancers, we classified the 1915 PCa patients into 2 groups: group 1 included patients in whom no other primary cancers were detected, and group 2 included patients diagnosed with other primary cancers before the PCa diagnosis or before BCR development after surgery.

Statistical Analysis

We compared the study groups using nonparametric statistics, including the χ^2 test for categorical variables and the Mann-Whitney U test for continuous variables. To reduce the selection bias between PCa patients with or without other primary cancers, we used a propensity score-matched analysis. The propensity scores were calculated using multivariate logistic regression for the baseline characteristics, including age, BMI, the presence of diabetes, PSA level, prostate volume, biopsy GS, and pathologic features, including the surgical specimen GS. Finally, we matched 298 patients with and without second primary cancers in a 1:1 ratio. After adjusting for the patient characteristics, we recalculated the descriptive statistics to compare the baseline variables between the 2 groups within the postpropensity score-matched population. Furthermore, the postoperative BCR-free survival rates were calculated using the Kaplan-Meier method within the adjusted population. The log-rank test was used to determine the statistical significance of the differences between the survival curves. Cox regression analysis was performed within the postpropensity score-matched population to identify the independent predictors of BCR after RP. We defined P values $< .05$ as statistically significant.

We used the Statistical Package for Social Sciences software, version 22.0 (IBM Corp., Armonk, NY) and GraphPad Prism, version 5.0 (GraphPad Software Inc., San Diego, CA), for all statistical analyses.

Results

Of the 3866 patients with PCa, 361 (9.3%) had second primary cancers (Table 1). Thirty-six patients (0.9%) were diagnosed with 2 different primary cancers and 1 experienced 3 different additional cancers. Moreover, 159 (8.3%) were diagnosed with second primary malignancies among the 1915 patients with PCa who underwent RP. Numerous types of other primary cancers were noted, with stomach, lung, liver, thyroid, bladder, kidney, and other type of

Table 1 Prevalence of Second Primary Cancers in Overall Prostate Cancer Population and Those Who Had Undergone Radical Prostatectomy (RP)

Cancer Type	Overall Group (n = 3866)	RP Group (n = 1915)
Stomach	70 (1.8)	32 (1.6)
Colon	69 (1.8)	25 (1.3)
Lung	51 (1.3)	18 (0.9)
Liver	15 (0.4)	7 (0.3)
Thyroid	13 (0.3)	10 (0.5)
Bladder	73 (1.9)	24 (1.2)
Kidney	32 (0.8)	17 (0.9)
Other	38 (1.0)	26 (1.3)
Total	361 (9.3)	159 (8.3)

Data presented as n (%).