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CLINICAL INVESTIGATION **Prostate**

PROSTATIC IRRADIATION IS NOT ASSOCIATED WITH ANY MEASURABLE INCREASE IN THE RISK OF SUBSEQUENT RECTAL CANCER

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Purpose: To investigate a putative increased risk of rectal cancer subsequent to prostatic radiotherapy.
Methods and Materials: In an analysis of the Surveillance, Epidemiology, and End Results registry, we compared men who had radiotherapy for prostatic carcinoma with those treated surgically and those treated with neither modality. Kaplan-Meier analyses for the time to failure from rectal cancer were performed between age-matched subgroups of the three cohorts. Cox proportional hazards analyses were performed to ascertain what influences might affect the incidence of subsequent rectal cancer.
Results: In all, 33,831 men were irradiated, 167,607 were treated surgically, and 36,335 received neither modality. Rectal cancers developed in 243 (0.7%) of those irradiated (mean age, 70.7 years), 578 (0.3%) of those treated surgically (68.7 years), and 227 (0.8%) of those treated with neither modality (74.2 years). When age effects and the differences between the surgical and untreated cohorts were controlled for, we were unable to demonstrate any significant increased incidence of rectal cancer in men irradiated for prostatic cancer.
Conclusions: An increased frequency of rectal cancer after prostatic irradiation, apparent on crude analysis, could be attributed to age confounding and other unmeasured confounders associated with prostate cancer treatment and rectal cancer risk. **© 2006 Elsevier Inc.**

Prostate carcinoma, Rectal cancer, Radiotherapy, SEER.

INTRODUCTION

Prostate cancer remains a major health concern for adult North American men (1). For the year 2005, the American Cancer Society predicted more than 232,000 new cases and 30,000 deaths in the United States alone (2). Despite the high incidence of prostate cancer, there is no consensus regarding either the indications for treatment (3–5) or treatment modality (6–11). Treatment choice for localized prostatic cancer is usually predicated upon the general fitness of the patient, his life expectancy, the efficacy of the proposed treatment, and its potential toxicities (7–9, 12).

Recently, the prospect of radiation-induced rectal cancers after prostatic radiotherapy has become an issue with respect to follow-up and possibly to treatment choice (13, 14). Such second primary tumors due to radiotherapy are well recognized for various sites (15–29). The typical induction period for radiation-induced solid tumors has been generally regarded to be approximately 10 years or longer (17, 21, 23, 25), and the risk of such tumors is thought to decrease with the age at irradiation (23, 25). Despite the more advanced age of men with prostatic cancer, and thus the relatively short period available for induction of rectal cancer, the question of whether such tumors can follow prostatic radiotherapy has received recent interest. A number of investigators (13, 27, 30) have used the Surveillance, Epidemiology, and End Results (SEER) registry (31) to study this question. Others have relied on local or regional databases for this purpose (26, 32).

One of the earliest SEER investigations claimed an association between prostatic radiotherapy and bladder carcinoma but not with rectal carcinoma (30); other studies have similarly claimed that rectal cancer does not manifest with increased frequency after prostatic cancer or after prostatic irradiation (26, 32). More recent SEER investigations, however, have associated prostatic radiotherapy with an increased risk of subsequent rectal cancer (13, 27). Most notably, Baxter *et al.* (13) reported a hazard ratio for subsequent rectal cancers of 1.7 compared with surgical controls. Their results have been reported widely in the lay press (33, 34) and have led to concerns by patients regarding the choice of radiotherapy as a treatment modality. Because of these concerns, it seemed important to ensure that this perceived increased risk of rectal cancer was appropriate. In the present study, we review the SEER database to deter-

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mine whether Baxter's report of an increased risk of subsequent rectal cancer could be attributed to factors other than the induction of cancer by radiation.

METHODS AND MATERIALS

Study cohorts and data

Population-based data were obtained from the SEER 9 Public-Use registry, released April 2004 and based on the November 2003 submission (31). This study was restricted to men with pathologically confirmed invasive prostatic carcinomas diagnosed from 1973 to 2001, for which prostate carcinoma was listed either as the only primary or as the first of two or more primary cancers.

Three retrospective cohorts were studied: those treated with external-beam radiation without surgery, those treated with cancer-directed surgery without radiotherapy, and those who had neither surgery nor radiotherapy. The first cohort served as an index group to detect rectal cancers that might have been associated with prostatic irradiation; the second and third cohorts served as controls to assess the background incidence of rectal cancer. Cancers of the rectosigmoid colon were excluded from this analysis, because the rectosigmoid colon would not uniformly fall within the usual radiation treatment fields used for prostatic cancer treatment.

Data were retrieved with respect to the follow-up time, the time from diagnosis of the prostate carcinoma to the diagnosis of rectal cancer, the age at diagnosis of prostatic carcinoma, and the attained age (age at observation). These SEER data had no personal identifiers and so were in compliance with Canadian privacy legislation; it was thus not subject to review by the Ottawa Hospital Research Ethics Board.

Statistical methods

Descriptive statistics for each cohort included the number of cases, the mean age at diagnosis, the mean attained age, the follow-up time, and the interval between the diagnoses of prostate cancer and rectal cancer, along with their respective 95% confidence intervals (CIs). In addition, the number and percentage of subsequent rectal cancer cases were tabulated for each cohort. The latency period between the diagnosis of prostate carcinoma and the subsequent rectal cancer was assessed for each affected individual, as was the interval between a point 5 years after the diagnosis of prostate cancer and the diagnosis of rectal cancer (following the convention of Baxter *et al.* [13]). Statistical comparisons between categorical data from the three cohorts were carried out by chi-square analysis. Comparisons between the mean values from continuous variables of the three cohorts were conducted through analysis of variance.

The proportion of prostatic cancer patients who remained free of rectal cancer was analyzed according to the method of Kaplan and Meier and with respect to groups stratified according to 5-year increments of age at diagnosis. Multisample comparisons were conducted here by assigning a score to each survival time with Mantel's procedure (35), and then a chi-square analysis was carried out on the basis of the sums of this score for each group.

Cox proportional hazard analyses were performed on representative populations of prostatic cancer patients, with respect to the interval between the diagnoses of the prostatic and rectal cancers, comparing age at diagnosis, prior prostatic radiotherapy, and the use of cancer-directed surgery as covariates. In these analyses, age was incorporated as a continuous variable and delineated by yearly increments. The use of external-beam radiotherapy was encoded as a binary variable, with 0 representing no treatment and 1 representing treatment. Cancer-directed surgery was similarly encoded as a binary variable. The strengths of the resulting relationships were evaluated with the Wald chi-square test (36). In addition, the hazard ratios and their 95% CIs were estimated for each covariate. The proportional hazard models were additionally corrected for the effects of competing risks, from death by any cause, according to the method described by Lunn and McNeil (37). This method used an augmented Cox regression on the initial covariates as well as the failure type and interaction terms, which was achieved by multiplication of the failure type probability with the original covariates.

Because age at diagnosis and the attained age might have influenced the development of subsequent rectal cancer differently within the three cohorts, we performed a further proportional hazards analysis on the combined data with attained rather than diagnostic age. The attained age was treated as a continuous variable and, in addition, this final model was corrected for the possible effects of competing risks.

We performed additional analyses to test for changes in relative risk over the follow-up period between the three cohorts, as determined by the ratio of the number of cases of rectal cancer per person-year of follow-up. These relative risks were calculated over different portions of the observation period to make the determinations.

RESULTS

The study retrieved a total of 237,773 cases of prostatic carcinoma from all three cohorts. Pertinent details with respect to the three cohorts are summarized in Table 1. Significant differences were evident between the mean ages of individuals from these cohorts. The men treated with cancer-directed surgery tended to be younger; those treated with external-beam radiation were intermediate; and those treated with neither modality were the oldest. Attained age revealed a similar relationship between the three cohorts, and follow-up times were correspondingly longest for the surgical cohort and shortest for those treated with neither modality. The mean interval between the diagnoses of prostatic and rectal cancers was greatest for those treated with radiotherapy and least for those treated with neither modality.

The frequency of subsequent rectal cancer, as determined on this crude overall analysis, differed significantly between the three cohorts. Those treated with prostatic irradiation developed rectal cancer at a rate of more than twice that of the surgical controls, consistent with the increased rate reported by Baxter *et al.* (13). However, the second control cohort, treated with neither surgery nor irradiation, had the highest incidence of rectal cancer of all.

Because the relative differences between the crude incidences of rectal cancer seemed to correspond with the differences corresponding to age at diagnosis of the three groups, we performed a number of analyses to investigate the influence of age at diagnosis. We first stratified the surgically treated cohort into sequential 5-year incremental groups. Figure 1 provides the Kaplan-Meier curves for the development of subsequent rectal cancer within representative subgroups from this stratification. Here we can see that even within the surgical control cohort, the incidence of subsequent rectal cancer was affected by age at diagnosis.