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BLADDER CANCER RISK FOLLOWING PRIMARY AND ADJUVANT EXTERNAL BEAM RADIATION FOR PROSTATE CANCER

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ABSTRACT

Purpose: Increased rates of secondary bladder malignancies have been reported after external beam radiation therapy (EBRT) for gynecological malignancies with relative risks of 2 to 4. This study was designed to determine if there was an increase in bladder cancer after EBRT for prostate cancer.

Materials and Methods: We retrospectively reviewed the Mayo Clinic Cancer Registry for patients who received EBRT for prostate cancer (1980 to 1998). Patients diagnosed with bladder cancer were identified. Comparative incidence rates were obtained from the national Surveillance, Epidemiology and End Results database. Subset analysis included patients treated with adjuvant radiation and those residing locally. Medical histories of patients with bladder cancer were reviewed.

Results: A total of 1,743 patients received EBRT for prostate cancer at our institution. In more than 12,353 man-years of followup no increase in bladder cancer risk was encountered. Subset analysis of men who received adjuvant radiation demonstrated that the relative risk of bladder cancer was increased but was not statistically significant. When the analysis was restricted to patients residing in the local area, the number of patients in whom subsequent bladder cancer developed was similar to Surveillance, Epidemiology and End Results rates. However, in the adjuvant radiation subset there was a statistically significant increase in subsequent bladder cancer. Patients in whom bladder cancer develops after EBRT often present with low grade disease but many have recurrence and progression.

Conclusions: This retrospective review suggests there is not evidence of increased risk of bladder cancer after radiation therapy, assuming unbiased followup and complete ascertainment of cases. The natural history of bladder cancer in this population does not seem to be altered by a history of radiation.

KEY WORDS: radiotherapy, adjuvant; prostatic neoplasms; carcinoma, transitional cell; bladder neoplasms

Studies of atomic bomb survivors link ionizing radiation with increased malignancy risk. However, the risks of second malignancies associated with therapeutic radiation therapy are unclear. Several studies of patients with cervical cancer treated with radiation have noted a 2 to 4 times higher incidence of subsequent bladder cancer than expected in a nonirradiated population.[1–3] The risk was noted to increase with increasing followup time and in women treated younger than 55 years.[1,2] Whether external beam radiation for prostate cancer (CaP) leads to an increased risk of bladder cancer has been disputed in the literature.[4–8] For urologists this is a clinically relevant question since we are commonly asked to evaluate patients with recurrent hematuria after pelvic radiation. How aggressively we pursue diagnostic testing needs to be modified according to the risk of malignancy.

Studies in the literature evaluating the risk of a radiation induced second malignancy use 1 of 2 approaches. Single institution studies follow a group of patients and observe the frequency of second malignancies in comparison with an external standard.[5,9,10] Such research is usually limited by small numbers of cases (poor statistical power), selection bias (referral patterns) and uncertainty regarding the accuracy of the comparative standard. Multi-institutional tumor registry cohorts have the advantage of large numbers of patients (statistical power) but often lack reliable information on second malignancies, patient comorbidities and risk factors.[6–8]

Previous studies have addressed bladder cancer diagnosed concurrently or after CaP diagnosis (regardless of CaP treatment) and have found an increase in concurrent cases greater than the number expected, often associated with a decrease in subsequent cases.[9,10] Such trends have been partially attributed to diagnostic or staging bias, which refers to the detection of cancer found in the course of evaluation for another malignancy.

To our knowledge there is not a study in the literature addressing secondary bladder malignancies after adjuvant radiation in particular. Since benefits of adjuvant radiation after radical retropubic prostatectomy (RRP) for margin positivity or poor prognostic factors have been disputed in the literature,[11,12] it is imperative to determine if there are antecedent health risks that accompany such external beam radiation therapy (EBRT). After removal of the prostate, the bladder is mobilized distally and reanastomosed to the urethral stump. Postoperatively the radiation port includes the prostatic fossa, an area now occupied by the bladder. Theoretically the bladder receives more radiation than in primary CaP therapy.

For those patients in whom bladder cancer does develop after EBRT, there are few data available regarding their natural history. We explore whether presentation, stage, grade and clinical course are similar to that of sporadic bladder cancers. In addition, we determine if the distribution

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in time of bladder cancer following CaP treated with EBRT differs from that of a nonirradiated population. As medical care improves, patients live longer, and more young patients may choose radiation for treatment of primary localized CaP, it is prudent to understand the long-term risks of primary and adjuvant radiation in this population.

METHODS

The Mayo Clinic Cancer Registry was retrospectively reviewed for patients who received EBRT for CaP at this institution between 1980 and 1998. The registry is maintained by a dedicated staff that abstracts information from the current electronic medical record and annually follows patients (via questionnaires and telephone calls) who receive care elsewhere. Date of diagnosis, EBRT and age were recorded as well as diagnosis of bladder cancer and date of last contact or death. Patients noted to have been diagnosed with bladder cancer before CaP were excluded from analysis. Patients diagnosed with concurrent or subsequent bladder cancer were identified and their medical histories reviewed.

Age, gender and race adjusted bladder cancer incidence rates were obtained from the national Surveillance, Epidemiology and End Results (SEER) database. Although some of our patients had bladder tumors in the 1980s, the incidence has changed minimally for this population during the last 15 years so 1996 to 2000 SEER rates were used for all calculations. SEER incidence rates are published by age intervals. Time from EBRT to either bladder cancer diagnosis, time of last followup or death was calculated for each patient, producing person-years of followup for each individual. The number of person-years of followup was calculated for each age interval and then multiplied by the published age specific rate. Then the products were summed to produce the expected number of bladder malignancies for that population. This analysis controls for the fact that risk of bladder cancer changes dynamically with age.

The observed number of cases was obtained in 2 ways to allow easy comparison with other studies in the literature. True subsequent (diagnosed more than 30 days after CaP treatment) observed cases were classified as Post RT, while Concur/Post also included those patients with concurrent diagnoses of bladder cancer and CaP. Although our overall goal was to determine if EBRT contributes additional risk of bladder cancer, which would obviously only be noted in cases after radiation, it was imperative to detect the baseline bladder cancer rate accurately for comparison with that of the general population. The Concur/Post group included concurrently diagnosed cancers to correct for staging bias.

The expected number of cases was compared with the observed number in our irradiated population. The ratio of observed-to-expected cases gives an estimated relative risk of bladder cancer developing in our radiated cohort compared with the general population. We calculated 95% CI around this relative risk using Byar's limits, assuming a Poisson distribution.

Subset analysis focused on patients treated with adjuvant radiation after RRP. The analysis was identical to that previously described but observed cases did not include concurrently diagnosed malignancies (none found in this cohort). Finally the entire analysis including the adjuvant subset was repeated using only patients from 5 local counties identified by current zip code. This was done in an attempt to isolate those patients most likely to have accurate followup, thus minimizing referral bias.

RESULTS

The database contained 1,749 patients who had CaP treated at Mayo with external beam radiation between 1980 and 1998. Of the patients 6 had a prior diagnosis of transitional cell carcinoma (TCC) and were excluded from analysis, leaving 1,743 patients in the cohort. A total of 12,353 person-years of followup were accrued. The median year of radiation was 1992, mean age at radiation was 70.5 years (range 38 to 91) and 50.2% of patients were dead at last followup. Average followup was 7.1 years after radiation (range 0.01 to 19.45). There were 24 cases of bladder cancer that occurred after radiation for CaP (Post RT group) and 6 patients were diagnosed with tumors concurrently, leaving 30 patients in the Concur/Post group. Table 1 shows the breakdown of observed and expected cases by time since radiation for the Post RT and Concur/Post groups. There was no statistically significant increase in subsequent bladder cancer risk among patients with a history of EBRT compared to those in the national SEER database. When the subset of 184 patients who received adjuvant radiation for CaP was analyzed separately (table 2), the relative risk (95% CI) was increased at 2.345 (0.943, 4.824) but did not reach statistical significance.

When the analysis was restricted to patients living in our local area, 574 were identified who had EBRT for CaP. Subsequent bladder cancer developed in 8 patients after radiation treatment for CaP (Local Post RT) and 2 were diagnosed with tumors concurrently, leaving 10 patients in Local Concur/Post group. Bladder cancer was expected to develop in 10 patients based on SEER. Table 3 shows the breakdown of observed and expected cases by time since radiation for the Local Post RT and Local Concur/Post groups. The relative risk (RR, 95% CI) in Local Post RT group was 0.83 (0.36, 1.63) while the RR in Local Concur/Post group was 1.03 (0.50, 1.9). There was no statistically significant increase in subsequent bladder cancer risk among local patients with a history of EBRT compared to those in the national SEER database. The subset of 43 local patients who received adjuvant radiation for CaP had 364 person-years of followup. There were 3 cases of bladder cancer compared with 0.599 expected. The estimated relative risk (95% CI) for this group was 5.01(1.04, 14.61) and was statistically significant ($p = 0.046$). Additionally, there was no correlation between age at radiation and risk of subsequent bladder cancer.

The medical history of the patients in whom bladder cancer developed was evaluated, and time since radiation, followup since second cancer diagnosis, cell type, grade, stage, recur-

TABLE 1. *Observed and expected cases of bladder cancer*

Yrs	Person-Yrs	Observed Cases		Expected Cases	RR (95% CI)
		Post RT	Concur/Post		
0–1	1,679	1	7	3.428	0.292 (0.007, 1.619) (Post RT) 2.042 (0.821, 4.207) (Concur/Post)
1–4	5,731	12	12	13.207	0.909 (0.469, 1.586)
5–9	3,939	7	7	10.534	0.665 (0.267, 1.367)
10–19	1,004	4	4	2.920	1.370 (0.373, 3.507)
Totals	12,353	24	30	30.089	0.798 (0.511, 1.187) (Post RT) 0.997 (0.671, 1.41) (Concur/Post)

All results apply to Post RT group (subsequent bladder cancer only) and Concur/Post group (concurrent plus subsequent bladder cancer) unless otherwise noted.