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Long-term Incidence of Hematuria, Urethral Stricture and Bladder Cancer after Radiation Therapy for Prostate Cancer

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Abstract

Introduction: Approximately 25% of patients diagnosed with prostate cancer choose radiation therapy as the primary treatment for this malignancy. Urinary tract toxicity after radiation therapy impacts patients years after treatment of the malignancy. We describe the incidence of hematuria, urethral stricture and bladder cancer after radiation therapy, and measure the effect of the radiation therapy modality in patients with prostate cancer.

Methods: We performed a retrospective review of 886 consecutive patients who received radiation therapy for prostate cancer between 1992 and 2013. Prostate cancer clinical characteristics, radiation therapy treatment modality and events of interest (hematuria, urethral stricture disease and bladder cancer) were recorded. The Kaplan-Meier method was used to estimate the incidence of events of interest and multivariate stepwise Cox regression was performed to analyze associations.

Results: Radiation therapy modalities included external beam radiation therapy (379), brachytherapy (225), combination therapy (35) or post-prostatectomy radiation therapy (adjuvant 47 or salvage 201). Overall the 5 and 10-year risk (95% CI) of hematuria was 23% (19−27) and 42% (36−48), urethral stricture 7% (5−9) and 12% (8−16), and bladder cancer 2% (1−3) and 5% (3−7), respectively. On multivariate regression smoking was associated with hematuria (HR 2.5, $p < 0.001$). Obesity (HR 2.5, $p=0.005$), combination therapy (HR 3.8, $p=0.006$) and adjuvant radiation therapy (HR 3.1, $p=0.015$) were associated with urethral stricture.

Conclusions: Hematuria, urethral stricture and bladder cancer continue to develop several years after radiation therapy for prostate cancer, thereby warranting continued, long-term followup for these conditions.

Abbreviations and Acronyms

BCa = bladder cancer

BT = brachytherapy

EBRT = external beam radiation therapy

EBRT+BT = combination radiation therapy

PCa = prostate cancer

PSA = prostate specific antigen

RP = radical prostatectomy

RT = radiation therapy

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Prostate cancer is the most common malignancy occurring in men in the United States. Current definitive treatment of PCa involves surgical excision (radical prostatectomy) or radiation therapy (external beam radiation therapy and/or brachytherapy), with radiation chosen by approximately 25% of patients as the primary treatment modality.[1] Treatment related toxicity to adjacent normal healthy tissues can occur early or late and is encountered by urologists during the course of followup. In the present study urethral stricture disease, hematuria and bladder cancer after radiation therapy for prostate cancer are reported based on a large, single institution experience.

Methods

After institutional review board approval a retrospective chart review was performed identifying all patients consecutively who underwent radiation therapy for PCa between 1992 and 2013. Using billing data 886 patients were identified who received external beam radiation therapy and/or brachytherapy for the treatment of biopsy confirmed prostate cancer.

Tables 1 and 2 were abstracted from patient demographic information, ICD-9 codes, and comprehensive review of physician notes, laboratory reports (urinalyses, pathology reports etc) and operative reports of patients who received RT. Date of last followup was recorded as the most recent visit with a urologist, radiation oncologist or medical oncologist after RT. Followup was recommended every 6 months for the first 5 years and yearly thereafter, with any alteration at the discretion of the primary treating physician.

Patients were categorized according to treatment modality of EBRT alone, BT alone, EBRT followed by BT, or radical prostatectomy followed by EBRT in the adjuvant or salvage setting. Patients treated with definitive EBRT were prescribed a median dose of 78 Gy in a median of 39 fractions. BT was administered as a low dose rate iodine-125 interstitial implant to a median dose of 145 Gy to the periphery of the prostate. Patients treated with EBRT+BT received an EBRT dose of 45 Gy in 25 fractions followed by low dose rate I-125 implant of 110 Gy to the periphery. Post-prostatectomy RT was provided to patients as adjuvant or salvage RT, with a goal to administer 66.6 Gy fractionated over 37 doses to the prostatic fossa and seminal vesicle remnants, if present. Patients were offered adjuvant RT for adverse pathological features with an undetectable PSA, or salvage RT when PSA failed to reach a nadir after RP or at biochemical recurrence.

The Pearson chi-square test was used to evaluate categorical variables listed in tables 1 and 2 for differences among treatment modality groups, and the independent samples median test was used to compare continuous variables.

Hematuria, urethral stricture disease and bladder cancer were chosen for evaluation after RT given their ability to be objectively demonstrated on physical examination, laboratory studies and/or cystoscopic evaluation, as well as the perception of inconvenience caused to the patient due to the need for invasive procedures, additional imaging and possibly therapeutic procedures.

Patients were considered to have a hematuria event if microscopic or gross hematuria was documented in physician notes or laboratory data, or was documented as the indication for cystoscopy or upper tract imaging. In the event of multiple instances of hematuria, the date of the first event was recorded. Microscopic hematuria was defined as 3 or more red blood cells per high power field. Episodes of hematuria with a clear etiology other than radiation cystitis or bladder cancer, such as urinary tract infection, were excluded from analysis. Patients were considered to have a urethral stricture or bladder neck contracture (hereafter referred to as urethral stricture) if a stricture required any operative intervention (eg dilation, direct visual internal urethrotomy or urethroplasty) after cystoscopic identification. All operative reports after RT were reviewed to ensure the inclusion of all patients with urethral stricture. Bladder cancer was identified by a pathological diagnosis on biopsy.

To compute the Kaplan-Meier complication-free survival functions for hematuria, urethral stricture and BCa, the time between the date of the event and the completion of RT was analyzed. If an event did not occur the patient was considered to be right censored for that event, with time calculated from the last followup visit and the completion of RT.

Stepwise Cox regression was then performed to evaluate the independent effect of the categorical variables and treatment modalities in tables 1 and 2 on these Kaplan-Meier functions. Variables were selected in a forward fashion with $p=0.05$ meeting the standard for inclusion into the model. Variables with $p \geq 0.10$ were deemed insignificant and removed from the model. SPSS® version 20 was used, with all comparisons 2-sided and $p < 0.05$ considered statistically significant.