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

Robert H. Blackwell,* Alexander M. Kandabarow, Gopal N. Gupta, Matthew M. Harkenrider, Marcus L. Quek and Robert C. Flanigan

From the Departments of Urology (RHB, GNG, MLQ, RCF) and Radiation Oncology (MMH), and the Stritch School of Medicine (AMK), Loyola University Medical Center, Maywood, Illinois

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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* Correspondence: Department of Urology, Loyola University Medical Center, 2160 S. First Ave., Fahey Center, Room 261, Maywood, Illinois 60153 (telephone: 708-216-5100; FAX: 708-216-1699; *e-mail address:* rblackwell@lumcedu).

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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.

Table 1.
Demographics of patients receiving primary RT

	EBRT		BT		EBRT+BT		Overall		
	No. (%)	Median (IQR)	No. (%)	Median (IQR)	No. (%)	Median (IQR)	No. (%)	Median (IQR)	p Value
Age at RT	379	70 (65–75)	225	67 (63–73)	35	70 (63–74)	639	69 (64–74)	0.02
Total mos followup	379	42.9 (15.5–83.6)	225	48.1 (18.2–85.7)	35	61.3 (28.8–93.9)	639	45.7 (16.5–84.7)	0.15
Coronary artery disease	118 (34.7)		50 (27.0)		10 (32.3)		178 (32.0)		0.2
Diabetes mellitus	83 (24.4)		42 (22.7)		6 (19.4)		131 (23.6)		0.77
Hypertension	204 (60.0)		102 (55.1)		15 (48.4)		321 (57.7)		0.31
Obesity (body mass index greater than 30 kg/m^2)	75 (22.1)		39 (21.1)		3 (9.7)		117 (21.0)		0.27
Peripheral vascular disease	67 (19.7)		30 (16.2)		6 (19.4)		103 (18.5)		0.61
Smoking history	42 (12.4)		17 (9.2)		2 (6.5)		61 (11.0)		0.38
Initial PSA (ng/ml):									<0.001
4.00 or Less	32 (9.1)		43 (20.1)		4 (11.4)		79 (13.1)		
4.01–10.00	196 (55.5)		149 (69.6)		18 (51.4)		363 (60.3)		
10.01–19.99	73 (20.7)		20 (9.3)		13 (37.1)		106 (17.6)		
20.00 or Greater	52 (14.7)		2 (0.9)		0 (0.0)		54 (9.0)		
Prostate biopsy Gleason score:									<0.001
2–6	117 (31.6)		186 (83.4)		3 (8.6)		306 (48.7)		
7	155 (41.9)		35 (15.7)		28 (80.0)		218 (34.7)		
8–10	98 (26.5)		2 (0.9)		4 (11.4)		104 (16.6)		
Clinical stage:									<0.001
T1	208 (58.4)		156 (72.6)		17 (50.0)		381 (63.0)		
T2	123 (34.6)		59 (27.4)		15 (44.1)		197 (32.6)		
T3/T4	25 (7.0)		0 (0.0)		2 (5.9)		27 (4.5)		
D'Amico risk class:									<0.001
Low	83 (22.6)		161 (73.9)		0 (0.0)		244 (39.3)		
Intermediate	159 (43.2)		53 (24.3)		30 (85.7)		242 (39.0)		
High	126 (34.2)		3 (34.2)		5 (14.3)		134 (21.6)		

Results

Between 1992 and 2013, 886 patients received RT for prostate cancer at our institution (fig. 1). Median followup was 48.1 months (IQR 18.1–88.2) and median patient age at treatment was 67 years (IQR 62–73).

Pre-RT medical comorbidities were similar among patients in the EBRT, BT and EBRT+BT (primary RT) groups (table 1). Patients in the BT group were younger and had lower risk disease than those in the EBRT and combination therapy groups.

Medical comorbidities were similar between the adjuvant and salvage RT groups. There were no differences in clinical staging or risk between the groups before prostatectomy (table 2). Patients on adjuvant RT had higher disease stage and rates of extracapsular extension and positive surgical margins. Patients on salvage RT had a higher PSA at RT as those on adjuvant therapy, by definition, received RT with an undetectable PSA.

Hematuria

The 5 and 10-year actuarial risks (95% CI) of hematuria in patients who had received RT were 23% (19–27) and 42% (36–48), respectively (fig. 2). Median time from the completion of RT to hematuria was 36 months (IQR 16–64). Overall microscopic hematuria developed in 87 patients (9.8%) and gross hematuria developed in 137 (15.4%). Microscopic hematuria was evident sooner than gross hematuria at a median of 25 vs 39 months, respectively (p=0.02). Evaluation with cystoscopy and upper tract imaging was performed in 83.5% and 77.5% of patients with hematuria, respectively. For the 171 patients with isolated hematuria (without a concurrent/subsequent diagnosis of bladder cancer or stricture disease) the studies performed included cystoscopy (169, mean 1 per patient, range 0 to 5), computerized tomography (131, median 1, range 0 to 4), renal/bladder ultrasound (62, mean 0, range 0 to 3) and excretory urography (15, mean 0, range 0 to 1) during the course of followup. Evaluation was refused or not performed for medical reasons in 9% of these patients. On stepwise Cox regression a history of smoking significantly increased the risk of hematuria after RT (HR 2.575 [1.7–3.9], p <0.001, table 3).

Urethral Stricture Disease

The 5 and 10-year actuarial risks (95% CI) of urethral stricture in patients who had received RT were 7% (5–9) and 12% (8–16), respectively (fig. 2). Median time from

Table 2.
Characteristics of patients on RT after prostatectomy

	Adjuvant RT		Salvage RT		Overall		
	No. (%)	Median (IQR)	No. (%)	Median (IQR)	No. (%)	Median (IQR)	p Value
Age at RT		60 (54–65)		63 (59–68)		63 (58–68)	0.33
Total mos followup		53 (19–83)		53 (22–97)		53 (21–95)	0.88
Coronary artery disease	6 (14.3)		32 (18.0)		38 (17.3)		0.57
Diabetes mellitus	5 (11.9)		37 (20.8)		42 (19.1)		0.19
Hypertension	23 (54.8)		83 (46.6)		106 (48.2)		0.34
Obesity (body mass index greater than 30 kg/m^2)	11 (26.2)		55 (30.9)		66 (30.0)		0.55
Peripheral vascular disease	3 (7.1)		16 (9.0)		19 (8.6)		0.7
Smoking history	5 (11.9)		10 (5.6)		15 (6.8)		0.15
Initial PSA (ng/ml):							0.09
4.00 or Less	8 (21.1)		10 (7.5)		18 (10.5)		
4.01–10.00	19 (50.0)		83 (61.9)		102 (59.3)		
10.01–19.99	6 (15.8)		27 (20.1)		33 (19.2)		
20.00 or Greater	5 (13.2)		15 (10.4)		19 (11.0)		
Prostate biopsy Gleason score:							0.38
2–6	14 (34.1)		48 (30.2)		62 (31.0)		
7	13 (31.7)		69 (43.4)		82 (41.0)		
8–10	14 (34.1)		42 (26.4)		56 (28.0)		
Clinical tumor stage:							0.48
T1	17 (54.8)		85 (66.4)		102 (64.2)		
T2	13 (41.9)		40 (31.2)		53 (33.3)		
T3/T4	1 (3.2)		3 (2.3)		4 (2.5)		
D'Amico risk class:							0.27
Low	10 (24.4)		28 (18.5)		38 (19.8)		
Intermediate	14 (34.1)		73 (48.3)		87 (45.3)		
High	17 (41.5)		50 (33.1)		67 (34.9)		
Prostatectomy technique:							0.08
Retropubic	33 (70.2)		164 (82.0)		197 (79.8)		
Robotic	14 (29.8)		30 (15.0)		44 (17.8)		
Perineal	–		5 (2.5)		5 (2.0)		
Suprapubic	–		1 (0.5)		1 (0.4)		
Pathological Gleason score:							0.34
2–6	9 (20.5)		45 (24.7)		54 (23.9)		
7	21 (47.7)		98 (53.8)		119 (52.7)		
8–10	14 (31.8)		39 (21.4)		53 (23.5)		
Pathological tumor stage:							<0.001
T1	–		–		–		
T2	11 (25.0)		104 (54.5)		115 (48.9)		
T3/T4	33 (75.0)		87 (45.5)		120 (51.1)		
Pathological nodal stage:							0.13
N0	40 (93.0)		179 (97.8)		219 (96.9)		
N1	3 (7.0)		3 (1.6)		6 (2.7)		
N2	–		1 (0.5)		1 (0.4)		
Pathological extracapsular extension	27 (57.5)		79 (39.3)		106 (42.7)		0.02
Pathological pos margin	35 (74.5)		98 (48.8)		133 (53.6)		0.001
Pathological seminal vesical invasion	10 (21.3)		23 (11.4)		33 (13.3)		0.07
Pathological perineural invasion	37 (90.2)		124 (80.5)		161 (82.6)		0.14
Mos from surgery to RT		6 (4.6–6.8)		27.6 (10.8–60.0)		19.5 (6.9–48.8)	<0.001
Failure PSA (ng/ml)		–		0.35 (0.17–0.60)		0.27 (0.10–0.50)	<0.001

the completion of RT to stricture was 38 months (IQR 15–63). Stricture location was bladder neck (22), prostatic urethra (4), membranous urethra (4), bulbar urethra (23) and penile urethra (5). On stepwise Cox regression obesity (HR 2.5 [1.3–4.8], p=0.005) was associated with the development of stricture disease, as were EBRT+BT (HR 3.8 [1.5–10.0], p=0.006) and adjuvant RT (HR 3.1 [1.3–7.8], p=0.015) compared with primary EBRT (table 3).

Bladder Cancer

The 5 and 10-year actuarial risks (95% CI) of BCa developing in patients receiving any form of RT were 2% (1–3) and 5% (3–7), respectively (fig. 2). Median time from the completion of RT to the diagnosis of BCa was 57 months (IQR 24–76). Bladder cancer developed in 19 patients, of whom 7 (36.8%) presented with muscle invasive or metastatic disease. BCa histology was urothelial in all cases.

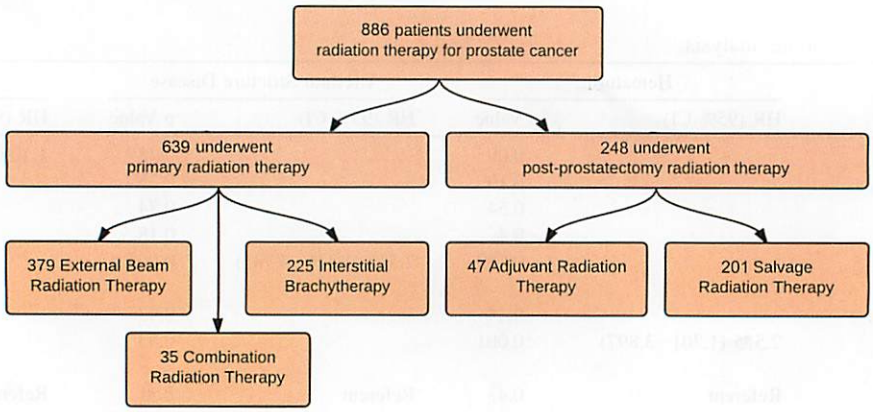
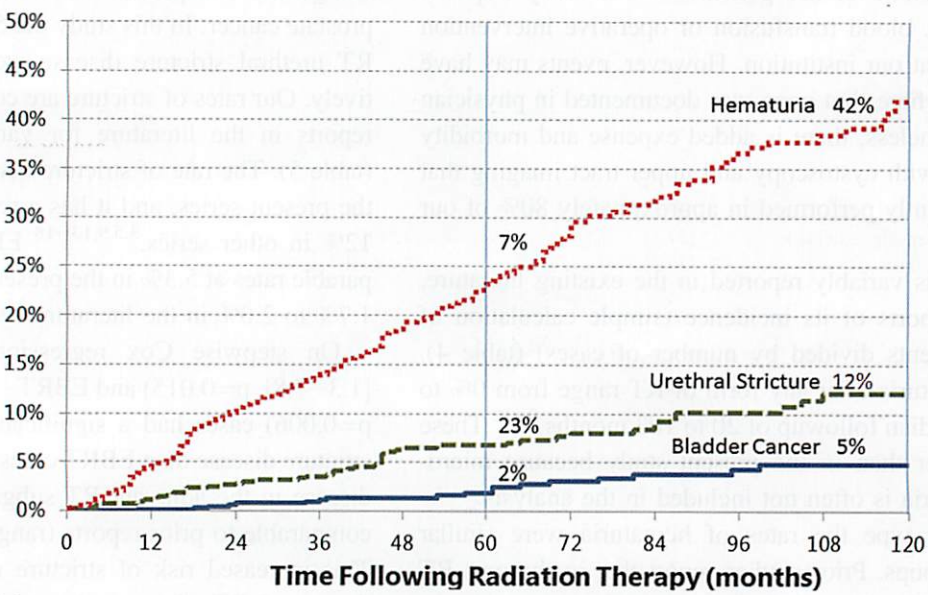


Figure 1.

However, 4 (57%) of those with advanced disease had secondary differentiation into squamous, neuroendocrine or glandular. Eight patients had carcinoma in situ. The remaining cases had low grade cTa and low grade cT1 disease. On stepwise Cox regression age at RT was significantly associated with a 10.5% (1−21) per year increase in the risk of BCa (p=0.03, table 3).

Discussion

Treatment of PCa includes several modalities, and according to an analysis of CaPSURE™ data for primary treatment 49.9% of men elected RP, 11.6% EBRT and 13.0% BT.[1] Patients may also receive RT after prostatectomy, with 45% being candidates for adjuvant RT for nonorgan confined disease (including 11% with positive surgical margins and 5% with seminal vesicle invasion), and 9.7% who experience biochemical recurrence and are candidates for salvage RT.[2] In addition, approximately half of patients treated with RP may be eligible for RT during followup, resulting in nearly 50% of patients with prostate cancer potentially receiving primary or secondary RT. Given the large number of patients who will be offered and will potentially receive RT, it is imperative to know the long-term effects of RT, and understand how to follow this population in a safe, effective and efficient manner.



Number at Risk											
Bladder Cancer	874	721	601	519	438	348	283	229	188	134	94
Urethral Stricture	868	707	585	500	417	330	267	215	175	122	86
Hematuria	853	672	535	443	362	272	211	169	124	90	58

Figure 2. Incidence of urinary event following radiation therapy for prostate cancer.

Table 3.
Stepwise Cox regression multivariate analysis

	Hematuria		Urethral Stricture Disease		Bladder Ca	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age at treatment		0.09		0.48	1.105 (1.009–1.210)	0.032
Coronary artery disease		0.19		0.25		0.82
Diabetes mellitus		0.54		0.74		0.73
Hypertension		0.4		0.18		0.51
Obesity (body mass index greater than 30 kg/m^2)		0.059	2.522 (1.331–4.781)	0.005		0.95
Peripheral vascular disease		0.44		0.43		0.58
Smoking history	2.575 (1.701–3.897)	<0.001		0.53		0.31
Pretreatment Gleason score:						
2–6	Referent	0.43	Referent	0.31	Referent	0.31
7		0.29		0.55		0.23
8–10		0.7		0.32		0.2
Pretreatment clinical tumor stage:						
T1	Referent	0.84	Referent	0.75	Referent	0.58
T2		0.59		0.89		0.68
T3/4		0.76		0.48		0.31
Pretreatment initial PSA (ng/ml):						
Less than 4.00	Referent	0.94	Referent	0.85	Referent	0.7
4.00–9.99		0.59		0.91		0.87
10.00–19.99		0.96		0.44		0.32
20.00 or Greater		0.75		0.63		0.69
Treatment modality:						
EBRT	Referent	0.15	Referent	0.01	Referent	0.75
BT		0.28	0.91 (0.381–2.174)	0.83		0.66
EBRT+BT		0.15	3.818 (1.460–9.989)	0.006		0.32
Adjuvant		0.8	3.131 (1.261–7.776)	0.015		0.57
Salvage		0.045	1.484 (0.561–3.921)	0.43		0.757

Hematuria

Hematuria after RT for PCa is common, with a risk of 42% by 10 years. None of the patients in this study required hospitalization, blood transfusion or operative intervention for hematuria at our institution. However, events may have occurred elsewhere (but none was documented in physician notes). Nevertheless, there is added expense and morbidity to evaluation with cystoscopy and upper tract imaging that were subsequently performed in approximately 80% of our patients.

Hematuria is variably reported in the existing literature, with crude reports of its incidence (simple calculation of number of events divided by number of cases) (table 4). Rates of hematuria after any form of RT range from 0% to 13.8% at a median followup of 20 to 103 months.[3–12] These rates are lower than in the present study because microscopic hematuria is often not included in the analysis.

By therapy type the rates of hematuria were similar among the groups. Prior studies report that in the post-BT setting (more than 1 week from surgery) hematuria occurs in 0% to 13% of patients[3–5] vs 25% on crude analysis in the present study. EBRT recipients experience hematuria at rates ranging from 4% to 13.8%[6,7,9] vs approximately 24% on crude analysis in the present study.

Urethral Stricture Disease

Urethral stricture disease and bladder neck contractures are recognized complications of RP and RT for localized prostate cancer. In this study the 5 and 10-year rates of post-RT urethral stricture disease were 7% and 12%, respectively. Our rates of stricture are comparable to those of prior reports in the literature for various treatment modalities (table 5). The rate of stricture disease after BT was 5.0% in the present series, and it has a reported incidence of 0% to 12% in other series.[3,5,9,13–18] EBRT recipients have comparable rates at 5.3% in the present study and approximately 1.7% to 2.0% in the literature.[13,18]

On stepwise Cox regression adjuvant RT (HR 3.1 [1.3–7.8], p=0.015) and EBRT+BT (HR 3.818 [1.5–10.0], p=0.006) cases had a significantly higher risk of urethral stricture disease than EBRT cases. The crude rate of stricture disease in the adjuvant RT subgroup was 10.1%, which is comparable to prior reports (range 0% to 17.8%).[10,11,19–21] This increased risk of stricture may be attributable to the timing of RT after prostatectomy, which is significantly earlier in the adjuvant group compared to salvage (median 6 and 37 months, respectively, p <0.001), and may compromise urethrovesical anastomotic healing. In the EBRT+BT subgroup the crude rate of stricture disease was 15.8%,

Table 4.
Hematuria after RT for prostate cancer

References	Mos Followup	No. Cases	No. Events	% Actuarial Event
BT:				
Albert et al[3]	Median 34	201	0	0 (gross only)*
Barker et al[4]	Median 20	215	27	13.0*
Anderson et al[5]	Median 68	263	14	5.3*
EBRT:				
Crook et al[6]	Mean 33	188	26	13.8*
Nguyen et al[7]	Range 24–44	100	13	13.0*
Bekelman et al[8]	Median 30	4,226	30	7.7 (2 yrs)
Hunter et al[9]	Median 103	525	7	4.0*
Adjuvant RT:				
Morris et al[11]	Mean 30	40	0	0*
Bolla et al[10]	Median 60	457	21	4.6*
Salvage RT:				
Morris et al[11]	Mean 32	48	4	8 (microscopic 2, gross 6)*
Post-prostatectomy RT:				
Feng et al[12]	Median 55	959	28	2.8*
Present series	Median 48	886	224	23, 42 (5 + 10 yrs)
Any RT				
BT		221	56	25*
EBRT		380	90	24*
EBRT+BT		38	12	32*
Adjuvant RT		89	21	24*
Salvage RT		160	45	28*

*A crude estimation was defined as a simple estimation of the number of events divided by the total number of cases.

Table 5.
Urethral stricture after RT for prostate cancer

References	Mos Followup	No. Cases	No. Events	% Actuarial Event
BT:				
Zelefsky et al[13]	Median 24	147	10	12 (5 yrs)
Zelefsky et al[14]	Median 48	248	23	10 (5 yrs)
Ragde et al[15]	Median 69	118	14	12*
Albert et al[3]	Median 34	201	0	0*
Allen et al[16]	Median 46	186	0	0*
Merrick et al[17]	Median 52	1,186	29	3.6 (9 yrs)
Elliott et al (CaPSURE)[18]	Median 32	799	14	2.5*
Anderson et al[5]	Median 68	263	4	1.5*
Hunter et al[9]	Median 103	525	4	3.4*
EBRT:				
Zelefsky et al[13]	Median 36	137	2	2.0 (5 yrs)
Elliott et al (CaPSURE)[18]	Median 32	645	11	1.7*
EBRT+BT:				
Elliott et al (CaPSURE)[18]	Median 32	231	12	5.2*
Adjuvant RT:				
Morris et al[11]	Mean 30	40	2	5*
Van Cangh et al[19]	Mean 24	48	0	0*
Bolla et al[10]	Median 60	457	6	1.4*
Thompson et al[20]	Median 127	213	38	17.8*
Wiegel et al[21]	Median 54	114	2	1.7*
Salvage RT:				
Morris et al[11]	Mean 32	48	3	6*
Post-prostatectomy RT:				
Feng et al[12]	Median 55	959	20	2.1*
Present series	Median 48	886	64	7, 12 (5 + 10 yrs)
Any RT				
BT		221	11	5.0*
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Salvage RT		160	16	10.0*

*A crude estimation was defined as a simple estimation of the number of events divided by the total number of cases.

which is higher than a prior report of 5.2%.[18] This higher incidence may be attributable to the higher radiation dose received with the combined approach vs EBRT alone.

Obese patients are also at increased risk for stricture disease (HR 2.5 [1.3–4.7], p=0.005). Obesity has previously been reported as an independent risk factor for stricture in patients treated with RP alone (HR 2.2 [1.6–3.2], p <0.001).[18] The present study is the first report to our knowledge to demonstrate obesity to be an independent risk factor for stricture disease in patients receiving RT.

Bladder Cancer

The risk of bladder cancer developing after RT for prostate cancer was 2% and 5% at 5 and 10 years after RT, respectively. The incidence of BCa after RT, independent of treatment modality, has been reported in several studies ranging from 0% to 4.9%.[22–29] When comparing the incidence of BCa reported in previous studies to the present stratified by RT modality, EBRT has been associated with a 0.7% to 1.4% incidence[22,24–27] compared with 2.6% (table 6). BT had a 0% to 1.2% incidence[22–24] compared with 1.4%. Interestingly, although in this study combination therapy (EBRT+BT) was not significantly associated with BCa (rate 2.6%), in the literature there does appear to be a trend toward a higher reported incidence at 0.8% to 4.9%.[22–24]

In their classic study Cahan et al described the characteristics of a malignancy secondary to RT, which included a neoplasm with a unique histology from the primary tumor, located in the irradiated region and with a latency of more than 5 years.[30] As such, studies including patients diagnosed with BCa early after treatment of PCa, as in the present study, will estimate the total incidence of BCa, but these cases will not all be attributable to the RT. Studies that include cases diagnosed only after 5 years are more likely to include malignancies secondary to RT, but underestimate the overall incidence of BCa in this population. As such, to our knowledge no standard method to report these cases exists in the literature.

It is noteworthy that in the present series 36.8% (7 of 19) of patients in whom BCa developed presented with muscle invasive or metastatic disease. The time from the completion of RT to the detection of advanced BCa was 69 months, compared with nonmuscle invasive cancer at 37 months (p=not significant).

The long-term effects of RT for PCa remain an area in which further study is needed. Investigating the outcomes

Table 6.
Bladder cancer after RT for prostate cancer

References	Mos Followup	No. Cases	No. Events	% Actuarial Event
BT:				
Moon et al[22]	Median 77	1,285	16	1.2*
Liauw et al[23]	Median 137	125	0	0*
Nieder et al[24]	Median 49	22,889	118	0.5†
EBRT:				
Movsas et al[25]	Mean 47	543	4	0.7‡
Chrouser et al[26]	Median 85	1,560	17	0.1§
Moon et al[22]	Median 77	39,805	568	1.4*
Nieder et al[24]	Median 49	93,059	1,203	1.3†
Zelefsky et al[27]	Median 84	897	12	1.3‖
EBRT+BT:				
Moon et al[22]	Median 77	2,219	25	1.1*
Liauw et al[23]	Median 122	223	11	4.9*
Nieder et al[24]	Median 49	17,956	149	0.8†
BT, + EBRT+BT:				
Zelefsky et al[27]	Median 90	413	4	1.0‖
Any RT:				
Boorjian et al[28]	Mean 49	2,471	33	1.3§
Singh et al[29]	Median 64	123,053	748	0.61*
Post-prostatectomy RT:				
Chrouser et al[26]	Not reported	183	7	3.6§
Boorjian et al[28]	Not reported	232	4	1.7§
Singh et al[29]	Median 94	32,462	401	1.24*
Present series	Median 48	886	19	2, 5 (5 + 10 yrs)
Any RT				
BT		221	3	1.4§
EBRT		380	10	2.6§
EBRT+BT		38	1	2.6§
Adjuvant RT		89	1	1.1§
Salvage RT		160	4	2.5§

Inclusion in each study was variable, depending on the minimum length of time from completion of RT to the diagnosis of bladder cancer. The timing was a minimum of 1 month (§), 2 months (‡), 6 months (†), 1 year (‖) or 5 years (*), depending on the study.

of hematuria and the time from RT to diagnosis may help to elucidate when evaluation is warranted and may lead to a diagnosis for which action is necessary. Larger studies are needed to definitively determine in the post-prostatectomy RT cohort if there is a significantly increased risk of urethral stricture disease with the earlier initiation of RT.

The present study has several limitations. Events of interest that were diagnosed and/or treated elsewhere may not have been captured, thus leading to the underestimation of the incidence of these adverse effects after RT. A prostatectomy only comparator group was not included in the analysis, which would have provided a control group with which to compare these events. In addition, there was no standardized protocol for obtaining urine for analysis so microscopic hematuria may have been underreported. Prior transurethral surgery was not taken into account, which could have contributed to the high rate of urethral stricture disease. Complete quantifiable smoking history (eg pack years) was not available for all patients, nor was occupational exposure, which may have contributed to the incidence of bladder cancer in this cohort.

Conclusions

Clinicians encounter several conditions in patients who have received RT for the treatment of PCa. Hematuria is prominent in this population, with a risk of 42% at 10 years after RT. Similarly, urethral stricture disease is found in 12% of these patients at 10 years. Compared to primary EBRT, adjuvant RT and EBRT+BT are associated with a higher risk of stricture disease. BCa after RT is present in up to 5% of patients at 10-year followup. However, only cases that develop after 5 years after radiation may be secondary to RT. These are large numbers of patients experiencing adverse events and the incidence continues to increase with time. Given the high incidence of these conditions after RT, pre-intervention counseling and subsequent close followup are warranted.

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Editorial Commentary

The authors add to the growing body of literature assessing and quantitating the impact of active treatments for prostate cancer on outcomes beyond cancer control.[1,2] Indeed, given the complexity of decision making with numerous and comparable options, these findings help us better counsel patients regarding treatment.

In this single institution, retrospective review nearly 900 men received some sort of radiotherapy between 1992 and 2013, which included primary and secondary treatments (adjuvant and salvage) with EBRT, brachytherapy and combination therapy assessed. There were significant risks of hematuria, urethral stricture and bladder cancer with steady rates over time. The 10-year risks of these events were 42%, 12% and 5%, respectively.

Limitations of this study include the absence of a comparison group (eg untreated or radical prostatectomy alone) as well as the potential for incomplete capture of data due to local followup of patients treated at this tertiary referral center. In addition, there may be bias in the detection of events depending on the intensity or use of health care by patients, as well as the type of primary provider (urologist, radiation oncologist, medical oncologist) most involved in patient care.

These findings generally corroborate those of other studies. Jarosek et al recently analyzed SEER (Surveillance, Epidemiology and End Results)-Medicare data and found that all treatments for prostate cancer are associated with a significant risk of urinary adverse events, with a 10-year incidence of grade 3-4 events of 27% and 36% in the prostatectomy and prostatectomy + EBRT groups, respectively.[3] In this study the patients were matched with a noncancer control cohort, and also included those undergoing radical prostatectomy and cryotherapy. It should be noted that all patients were 66 years old or older, and neither study addressed other important issues such as bowel and sexual function.

Maxwell Meng
Department of Urology
University of California San Francisco
San Francisco, California

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