

Undiagnosed prostatic malignancy at the time of radical cystoprostatectomy after prior prostatic radiation therapy

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Abstract

Purpose: We determined the prevalence of prostatic malignancy in patients undergoing radical cystoprostatectomy (RC) for urothelial carcinoma (UC) with a history of radiation therapy (XRT) treatment for prostatic adenocarcinoma (PCa).

Materials and Methods: Fifty-three men who underwent a RC for UC that were previously treated for PCa with XRT were retrospectively identified. Pathology reports were reviewed to assess for residual PCa or prostatic UC at the time of surgery.

Results: Thirteen (25%) patients had residual PCa, 16 (30%) had prostatic UC, and 8 (15%) had both. Sixteen (30%) patients had no evidence of prostatic disease. Patients with PCa had median tumor volume of 2.2 cc (interquartile range: 1.2–2.5 cc) and one-third had high-risk features (Gleason score >8 or pT3-T4 disease). Sixteen of 24 patients (67%) with prostatic UC had a stromal invasion, 5 (21%) had a ductal invasion, and 3 (13%) had carcinoma *in situ*. Tumors at bladder neck or trigone during transurethral resection were predictive of prostatic UC (odds ratio: 4.32, 95% confidence interval: 1.2–15.5, $P = 0.025$).

Conclusions: Despite prior XRT for PCa, less than one-third of patients had no prostatic disease at the time of RC. Routine prostatic sampling should be considered in these patients especially if considering the orthotopic diversion.

Key Words: Pathology, prostate cancer, radiation, radical cystectomy, urothelial carcinoma

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Received: 20.04.2015, Accepted: 30.06.2015

INTRODUCTION

Radical cystoprostatectomy (RC) with bilateral pelvic lymph node dissection is currently the preferred treatment for high-risk bladder cancer (BC) such as muscle-invasive bladder cancer (MIBC), persistent carcinoma *in situ* (CIS), or refractory high-grade non-MIBC.^[1] The prevalence of prostatic disease at the time of RC, however, is highly variable and often difficult to

predict. Routine prostatic sampling to more accurately determine clinical stage prior to RC is controversial but important to consider, especially in patients that are candidates for orthotopic urinary diversion. Prior prostatic radiation therapy (XRT), however, may affect the prevalence of prostatic malignancy at the time of RC. Rates of residual prostatic disease in this setting are relatively unknown, and whether routine sampling

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How to cite this article: Sharma P, Zargar-Shoshtari K, Spiess PE, Sexton WJ, Poch MA. Undiagnosed prostatic malignancy at the time of radical cystoprostatectomy after prior prostatic radiation therapy. *Urol Ann* 2016;8:151-6.

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/0974-7796.163797

of the prostate is necessary for appropriate clinical staging in this patient population is a topic of discussion.

The purpose of this study was to determine the degree of prostatic malignancy in the RC specimens of urothelial carcinoma (UC) patients who were previously treated with XRT for prostatic adenocarcinoma (PCa). By assessing the amount of tumor in these patients, we hoped to determine if routine preoperative sampling of the prostate is necessary for adequate staging prior to RC. Traditional risk factors associated with prostatic UC were also analyzed to determine if any were predictors of prostatic extension in this patient population.

MATERIALS AND METHODS

Data source

After Institutional Review Board approval, we retrospectively analyzed the charts of 767 patients treated with RC for high-risk BC at our institution from 2003 to 2013. We identified 64 patients who had undergone pelvic XRT for PCa prior to their BC diagnosis with an appropriate treatment response. Patients with non-UC histology, a prior prostatectomy, and known prostatic UC were excluded, leaving 53 patients in our study population with clinical Tis, T1, or T2 UC. No patient had clinical evidence of prostatic disease on either digital rectal examination (DRE) or cystoscopy. We noted the method of pelvic XRT used as well as any prior use of androgen deprivation therapy (ADT). Due to the time interval between diagnoses and the fact that most patients received treatment at an outside facility, pre-XRT Gleason scores and pre-/post-XRT prostate specific antigen (PSA) levels were not available.

Assessment of prostate pathology

Pathology reports from the RC specimens were used to determine which patients had no prostatic malignancy versus those that harbored adenocarcinoma or UC at the time of RC. For patients with PCa, we recorded the Gleason score, margin status, pathological tumor (pT) stage and calculated the tumor volume. Tumor volume measurements were accomplished by estimating the volume of the entire prostate using the standard ellipsoid formula: $\text{Width} \times \text{height} \times \text{length} \times \pi/6$ (dimensions were obtained from the pathologist's measurement of the specimen). This volume was then multiplied by the percentage of the prostate that was involved with adenocarcinoma (based on the pathologist's assessment). For patients with prostatic UC, we noted the depth of invasion (CIS vs. ductal invasion vs. stromal invasion) and any associated seminal vesicle (SV) extension. Noncontiguous prostatic stromal involvement arising from within the urethra (i.e. subepithelial stromal invasion) was also distinguished from tumor extending transmurally through the bladder wall and into the stroma of the prostate (pT4a).

Study variables

The demographic and clinical characteristics were recorded for our study population, including age, body mass index (in kg/m^2), preoperative creatinine (Cr [in mg/dl]), smoking history, American Society of Anesthesiologists (ASA) Physical Status classification score, use of neoadjuvant chemotherapy, clinical tumor (cT) stage, presence of CIS or multifocal tumors on transurethral resection (TUR), and bladder tumor location at the time of TUR. Preoperative Cr levels were drawn 2–4 weeks prior to RC, and ASA score was determined by the anesthesiologist on the morning of surgery. For bladder tumor location, we differentiated bladder neck (BN) or trigonal involvement from all other areas in the bladder (dome, lateral, anterior, posterior wall) due to the theoretical higher risk of prostatic invasion. The presence of CIS, multifocal tumors, bladder tumor location, and cT stage were based on operative reports and pathology from any TUR (at our institution or at an outside hospital) that occurred before RC. The most aggressive pathology was recorded, and any patient with a history of BN or trigonal involvement (even in cases with multifocal tumors) was grouped into this category.

Statistical analysis

Clinicodemographic variables were compared between patients with and without prostatic UC. Continuous variables were reported as medians and interquartile ranges (IQRs), and categorical variables were reported as frequency counts and percentages. We used the Mann–Whitney U-test to determine any differences in medians between the two groups and the Fisher's exact test for proportions. Logistic regression was performed to evaluate the association of these variables with prostatic UC. All factors that were found to be strong predictors on univariable analysis ($P < 0.2$) were included on the final multivariable model.

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) Software Package version 21.0 (IBM Corporation, Armonk, NY, USA). All tests were two-sided with a $P < 0.05$ considered as statistically significant.

RESULTS

Demographic and clinical characteristics

Median age of our study cohort was 76.8 years (IQR: 74.3–81.0) [Table 1]. The median time between PCa and UC diagnosis was 6 years (IQR: 3–10.3) although the date of PCa treatment was not known in five patients. The majority of patients (49%) were previously treated with brachytherapy for their PCa while 32% received external-beam XRT, and 19% had both.

The majority of patients (83%) underwent RC for MIBC, and 19% received chemotherapy prior to surgery. Sixty-two percent of patients had bladder tumors at the BN or trigone diagnosed on TUR, and 23% had CIS.

Prostate pathology

On review of the prostatic portion of RC specimens, 25% of patients had residual adenocarcinoma, 30% had UC, and 15% had both [Table 2]. Less than one-third of patients (30%) had no evidence of tumor within the prostate at the time of surgery.

Median tumor volume for those patients with PCa was 2.2 cc (IQR: 1.2–2.5 cc), and only 10% had a tumor volume <0.5 cc. Twenty-nine percent of patients with PCa had a Gleason score >8, and 33% had pT3-T4 disease. The positive margin rate associated with PCa was 29%.

Of those patients with prostatic UC, 67% had a stromal invasion, 21% had a ductal invasion, and 13% had CIS. Direct extension of tumor into the prostate (pT4a) was responsible for most cases of stromal invasion (88%) while 13% arose from within the urethra. Fifty-seven percent of patients with pT4a UC had additional SV involvement as well.

Prostatic urothelial carcinoma

Patients with and without prostatic extension of UC had similar demographic and clinical features [Table 3]. There was also no difference between the two groups in either the method of XRT or the usage of ADT in the treatment of their PCa. Patients with prostatic UC, however, were more likely to have tumors at the BN or trigone on TUR ($P = 0.026$).

On univariable analysis, preoperative Cr and BN/trigonal involvement on TUR were found to be strongly associated with prostatic UC [Table 4]. On multivariable analysis, however, only BN/trigonal involvement on TUR was found to be an independent predictor of prostatic UC (odds ratio: 4.32, 95% confidence interval: 1.2–15.5, $P = 0.025$).

DISCUSSION

This study, to our knowledge, represents the first report looking at the prevalence and features of undiagnosed PCa or prostatic UC in RC patients previously treated with pelvic XRT. Although this represents a unique subgroup of the RC population, the findings are still relevant given the increasing number of older men that are treated for PCa with XRT every year.^[2]

The prevalence of prostatic malignancy in RC patients without prior pelvic XRT is well documented. Revelo *et al.* reported a 41% prevalence of PCa and a 48% prevalence of prostatic UC in 121 consecutive RC specimens.^[3] Forty-four percent

Table 1: Demographic and clinical characteristics

	Total, n=53
Median age, years (IQR)	76.8 (74.3-81.0)
Median BMI, kg/m ² (IQR)	28.1 (25.1-31.5)
Smoking history, n (%)	
Never	5 (9)
Former	43 (81)
Current	5 (9)
Prior XRT for PCa, n (%)	
Brachytherapy	26 (49)
EBRT	17 (32)
Brachytherapy + EBRT	10 (19)
Prior ADT for PCa, n (%)	14 (26)
ASA score, n (%)	
2	14 (26)
3	39 (74)
Median preoperative creatinine, mg/dl (IQR)	1.3 (1.0-1.6)
Neoadjuvant chemotherapy, n (%)	10 (19)
Bladder tumor location on TUR, n (%)	
BN/trigone	33 (62)
Other	20 (38)
Multifocal tumors, n (%)	20 (38)
cT stage, n (%)	
cTis	3 (6)
cTa-T1	6 (11)
cT2	44 (83)
Concurrent CIS, n (%)	12 (23)

ASA: American Society of Anesthesiologists, BMI: Body mass index, BN: Bladder neck, CIS: Carcinoma *in situ*, IQR: Interquartile range, UC: Urothelial carcinoma, EBRT: External-beam radiation therapy, ADT: Androgen deprivation therapy, XRT: Radiation therapy, PCa: Prostatic adenocarcinoma, TUR: Transurethral resection; cT: Clinical tumor

Table 2: Pathological characteristics of prostate specimens

	Total, n=53
Prostate pathology, n (%)	
Adenocarcinoma	13 (25)
UC	16 (30)
Adenocarcinoma + UC	8 (15)
None	16 (30)
Prostatic adenocarcinoma	Total, n=21
Tumor volume, n (%)	
<0.5 cc	2 (10)
0.5-5 cc	16 (76)
>5 cc	3 (14)
Gleason score, n (%)	
6	9 (43)
7	6 (29)
>8	6 (29)
pT stage, n (%)	
pT2	14 (67)
pT3-T4	7 (33)
Positive margins, n (%)	6 (29)
Prostatic UC, n (%)	Total, n=24
CIS	3 (13)
Ductal invasion	5 (21)
Stromal invasion	16 (67)
Direct extension (pT4a)	14 (58)
Intraurethral (noncontiguous)	2 (8)
SV involvement	8 (33)

ADT: Androgen deprivation therapy, CIS: Carcinoma *in situ*, EBRT: External-beam radiation therapy, PCa: Prostatic adenocarcinoma, pT: Pathologic tumor, RC: Radical cystoprostatectomy, SV: Seminal vesicle, UC: Urothelial carcinoma, XRT: Radiation therapy

of patients with PCa had a tumor volume >0.5 cc, 16% had >pT3 disease, and 4% had a Gleason score >8. The positive

Table 3: Patients with versus without prostatic UC

	No prostatic UC, n=29	Prostatic UC, n=24	P
Median age, years (IQR)	76.7 (74.6-81.0)	78.0 (72.1-81.3)	0.67
Median BMI, kg/m ² (IQR)	28.5 (25.1-31.8)	27.8 (25.3-30.8)	0.51
Prior XRT for PCa, n (%)			0.41
Brachytherapy alone	16 (55)	10 (42)	
EBRT ± brachytherapy	13 (45)	14 (58)	
Prior ADT for PCa, n (%)	9 (31)	5 (21)	0.54
Smoking (current or former), n (%)	26 (90)	22 (92)	>0.99
ASA score, n (%)			
1-2	9 (31)	5 (21)	0.54
>3	20 (69)	19 (79)	
Median pre-op creatinine, mg/dL (IQR)	1.2 (1-1.5)	1.4 (1.1-1.8)	0.25
Neoadjuvant chemotherapy, n (%)	6 (21)	4 (17)	>0.99
Primary tumor location, n (%)			0.026
BN/trigone	14 (48)	19 (79)	
Other	15 (52)	5 (21)	
Multifocal tumors, n (%)	11 (38)	9 (38)	>0.99
cT stage, n (%)			
<cT1	6 (21)	3 (13)	0.49
cT2-T4	23 (79)	21 (87)	
Concurrent CIS, n (%)	8 (28)	4 (17)	0.51

ADT: Androgen deprivation therapy, ASA: American Society of Anesthesiologists, BMI: Body mass index, BN: Bladder neck, CIS: Carcinoma *in situ*, EBRT: External beam radiation therapy, IQR: Interquartile range, PCa: Prostatic adenocarcinoma, UC: Urothelial carcinoma, XRT: Radiation therapy, cT: Clinical tumor

Table 4: Predictors of prostatic UC

	OR	95% CI		P
		Lower	Upper	
Univariate				
Age	0.97	0.90	1.05	0.48
BMI	0.94	0.83	1.07	0.35
Preoperative Cr	2.16	0.75	6.19	0.15
+Smoking Hx	1.27	0.19	8.29	0.80
ASA >3	1.71	0.49	6.03	0.40
+Neoadjuvant chemo	0.77	0.19	3.11	0.71
+BN/trigone	4.07	1.20	13.86	0.025
+Multifocal	0.98	0.32	2.30	0.97
cT2-T4	1.83	0.41	8.24	0.43
+CIS	0.53	0.14	2.02	0.35
+EBRT PCa	1.72	0.58	5.14	0.33
+ADT PCa	0.59	0.17	2.06	0.40
Multivariate				
Preoperative Cr	2.30	0.78	6.80	0.13
+BN/trigone	4.32	1.20	15.53	0.025

ADT: Androgen deprivation therapy, ASA: American Society of Anesthesiologists, BMI: Body mass index, BN: Bladder neck, CI: Confidence interval, CIS: Carcinoma *in situ*, Cr: Creatinine, cT: Clinical tumor, EBRT: External beam radiation therapy, Hx: History, OR: Odds ratio, PCa: Prostatic adenocarcinoma, UC: Urothelial carcinoma

surgical margin rate associated with PCa was 6%. In addition, 22% of patients with prostatic UC had direct stromal invasion through the bladder wall (pT4a).

Barbisan *et al.* also analyzed the prostate sections from 248 RC patients to determine the prevalence and features of undiagnosed PCa or prostatic UC.^[4] Fifty percent of patients

had PCa, and 38% had prostatic UC. Most cases of PCa (81%) were considered clinically insignificant since 95% had a tumor volume <0.5 cc, 87% had a Gleason score <6, 78% were pT2a, and 3.3% had positive surgical margins. Fifteen percent of prostatic UC was associated with stromal invasion, and 6.5% had pT4a disease.

The largest recent series, however, was from Bruins *et al.* who reviewed the records of 1,476 patients who underwent RC.^[5] Thirty-eight percent of patients had PCa, and 21% had prostatic UC. Only 2–4% of patients with PCa had high-risk features (Gleason >8, pT3-T4), and only 10% of patients with prostatic UC had stromal involvement.

Interestingly, our study population had a similar prevalence of prostatic malignancy at the time of RC compared to prior studies in nonirradiated patients. The severity of the prostatic disease, however, was significantly worse. PCa was seen in 40% of patients in our study, and prostatic UC was seen in 45%. Approximately, one-third of patients with PCa, however, had high-risk features with Gleason score >8 or pT3-T4 disease. Median tumor volume was 2.2 cc, and this increased in conjunction with Gleason score and tumor stage. Patients with a Gleason score of 6–7 had an average tumor volume of 1.54 cc, but those with Gleason >8 disease had an average tumor volume of 5.9 cc. Similarly, patients with prostatic UC had an aggressive disease with 67% having a stromal invasion, 58% having pT4a disease, and 33% having SV involvement.

It is unclear why this cohort of RC patients with prior pelvic XRT had the more severe prostatic disease compared to nonirradiated RC patients reported on in the prior literature. One theory proposed is that pelvic XRT may have a deleterious effect on normal prostatic and urothelial tissues, promoting the development of more aggressive tumors in the future. Further large-scale, prospective studies, however, are necessary to validate any theory regarding the behavior of secondary malignancies in the setting of prior XRT. The majority of patients in our study were also treated with brachytherapy alone for their PCa, which has shown worse long-term oncological outcomes for the intermediate and high-risk disease.^[6,7] In addition, since patients were treated for their PCa at a median of 6 years prior to their UC diagnosis, the dosage and treatment patterns of XRT could reflect older, less effective regimens used at that time.

Prior studies have looked at risk factors for prostatic involvement of UC in patients undergoing RC with prior pelvic XRT. Nixon *et al.* showed that CIS and tumor multifocality were independent predictors of prostatic UC.^[8] Patel *et al.* similarly showed that bladder CIS and trigonal involvement of bladder tumors were independent risk factors for prostatic

UC.^[9] Finally, Mazzucchelli *et al.* showed that multifocal tumors, tumors at the BN or trigone, and history of multiple tumor recurrences were all associated with an increased risk of prostatic UC.^[10] In this study, we found that bladder tumors at the BN or trigone were again strongly associated with prostatic UC in patients with prior pelvic XRT, supporting the use of routine prostatic sampling in this setting.

Routine prostatic sampling of all patients with high-risk UC of the bladder continues to be a source of debate with regards to appropriate clinical staging prior to RC. Currently, neither the National Comprehensive Cancer Network or the European Association of Urology make definitive recommendations regarding prostatic urethral biopsies in these patients as part of the clinical work-up, especially in patients considering the orthotopic urinary diversion.^[11] There is data to suggest that frozen section of the apical prostatic urethral margin at the time of RC is superior to preoperative TUR biopsy in determining the prevalence of prostate UC.^[12,13] A recent study by von Rundstedt *et al.* of 272 patients with UC who underwent RC, however, showed a 100% positive predictive value and 86% negative predictive value of TUR biopsy to detect prostatic UC when taken adjacent to the verumontanum.^[14] The overall rate of prostatic UC was 37.1% in this study, but TUR biopsy missed most prostatic tumors resulting from the transmural invasion of the bladder primary lesion (4 of 15 patients).

There are several limitations to this study. In addition to the smaller sample size and retrospective nature of the analysis, we were unable to obtain pretreatment PSA levels, Gleason scores, or staging information in our study cohort. PSA levels prior to RC were also inconsistently drawn and not readily available. Dosages and duration of XRT were largely unknown because the majority of patients had their PCa treated at outside institutions. As such, we were unable to correlate the severity of prostatic disease with PSA levels before surgery, and we were unable to measure reliably predictors of PCa recurrence in our study population.

While earlier guidelines did not endorse Gleason scoring on post-XRT prostate pathology due to tumor dedifferentiation, a trend toward higher Gleason scores, and histological changes resulting from treatment effect, the topic still remains controversial.^[15,16] Recent multi-institutional studies have included pathologic Gleason scores on salvage prostatectomy specimens post-XRT as predictors of biochemical recurrence, metastasis, and cancer-specific death.^[17,18] As such, we included post-XRT Gleason scores and tumor stage as a frame of reference for tumor severity.

Gleason scoring can also be affected by the usage of prior hormonal therapy, which occurred in 26% of our study group.

Prior ADT has been reported to lead to higher Gleason scores, decreased tumor volume, less capsular penetration, and lower surgical margin involvement.^[19-21] While Gleason scores for PCa may have been overestimated in a small subset of patients in this study, pathologic stage, margin status, and tumor volume may have been underestimated.

CONCLUSION

Undiagnosed prostatic disease in RC patients with a prior history of pelvic XRT for PCa can be equally as prevalent and even more aggressive than in RC patients without prior prostatic XRT. Cognizant use of PSA, DRE, and preoperative prostatic biopsy is necessary to appropriately stage these patients with high-risk BC and provide the most appropriate surgical treatment, especially in patients considering the orthotopic diversion.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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