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Bladder Cancer

Risk Assessment of Prostatic Pathology in Patients Undergoing Radical Cystoprostatectomy

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Abstract

Objectives: To determine the incidence and location of prostate adenocarcinoma (PCa) and prostatic urothelial carcinoma (PUC) for patients undergoing radical cystoprostatectomy (RCP) for bladder cancer and to ascertain what preoperative information may be useful in predicting PUC or PCa in patients who may be candidates for prostate-sparing cystectomy.
Methods: Between 2001 and 2004, 235 consecutive patients underwent RCP and had whole-mount sections of the prostate. We reviewed our prospective radical cystectomy database for preoperative clinicopathological information associated with each patient. The bladder and whole-mount prostate sections were re-reviewed to determine the location and depth of the bladder tumor as well as the presence of any associated PCa and PUC.
Results: We identified 113 of 235 (48%) and 77 of 235 (33%) men with PCa and PUC, respectively. Among patients with PCa, 33 (29%) had Gleason score of ≥ 7, 25 (22%) had PCa tumor volume > 0.5 cc, and 15 (13%) had extracapsular extension. On multivariable analysis, only increasing age was significantly associated with PCa (odds ratio = 1.3, $p = 0.046$). Of the 77 with PUC, 28 (36%) had in situ disease only, while 49 (64%) had prostatic stromal invasion. Bladder tumor location in the trigone/bladder neck ($p < 0.001$) and bladder carcinoma in situ ($p < 0.001$) was strongly associated with PUC in the final specimen. Overall, 158 (67%) had either PCa or PUC in the prostate.
Conclusions: PCa and/or PUC is present in a majority of RCP specimens. Current preoperative staging and tumor characteristics are not adequate for determining who can safely be selected for prostate-sparing cystectomy.

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1. Introduction

Radical cystoprostatectomy (RCP) is the gold standard of treatment for men with invasive bladder urothelial carcinoma (UC). The operation has undergone significant refinement since its initial description with the current application of nerve-sparing techniques [1,2], extended pelvic lymphadenectomy [3,4], and orthotopic bladder substitution. While technical advances have led to improvements in functional outcome, RCP is associated with alterations in quality of life for many. More recently, some have suggested that prostate-sparing cystectomy (PSC) may be appropriate in selected men to improve postoperative sexual and urinary function [5–8]. Reports of PSC series note improved sexual function compared with standard RCP, although long-term oncological efficacy remains to be proven. Prostate adenocarcinoma (PCa) and prostatic urothelial carcinoma (PUC) are widely reported as incidental findings in RCP specimens [9–11]. Therefore, candidates for PSC must be selected carefully to minimize the risk of leaving significant PCa or PUC because both may have profound effects on the oncological outcome.

In this study, we sought to identify the incidence and location of PUC and PCa in whole-mount prostates taken from cystoprostatectomy specimens. This information would be necessary to identify variables predictive of PUC and PCa involvement, which may serve to aid in the appropriate selection of patients for PSC techniques.

2. Methods

Following institutional review board approval, we identified 235 consecutive men who underwent RCP for bladder UC at our institution from January 2001 to July 2004, and had the entire prostate submitted and processed for histopathological examination using whole-mount techniques. We reviewed our prospectively collected institutional bladder cancer database and extracted the following characteristics for all study patients: age, race, date of diagnosis, transurethral bladder tumor resection (TURBT) pathological data, staging preoperative imaging, examination under anesthesia (EUA) findings, and final pathological stage. The composite clinical stage was determined by taking the highest stage from EUA, computed tomography/magnetic resonance imaging, and TURBT pathological findings. For patients who received neoadjuvant chemotherapy, we used the prechemotherapy clinical stage. Similarly, in those whose last TURBT was for restaging, the initial clinical stage was assigned. Transurethral prostate biopsies were taken according to the surgeon's discretion, and the RCP specimen was considered to also have PUC when it was identified on TURBT. For the purpose of describing bladder tumor location, we divided the bladder into two anatomical areas: (1) proximal (away from the prostate) to the trigone and (2) the trigone and bladder neck. We assigned bladder location on the basis of the distal most extent of the tumor.

All of the bladder and prostate slides were re-reviewed by two genitourinary pathologists (H.A.A., S.O.); the results were recorded for location and pathological characteristics of each bladder tumor. The entire prostate was submitted and processed with 5-mm whole-mount step sections. The presence of PCa and PUC was defined as prostatic UC in situ (PUCIS) and/or prostatic stromal invasion. Stromal invasion was defined as UC invading through the basement membrane of the prostatic/periurethral ducts and/or directly involving the surrounding stroma, while PUCIS was defined as UC confined to the prostatic urothelium or prostatic/periurethral ducts. PUC occurred by either Pagetoid transurethral spread or direct extension as previously described by Donat and colleagues [12]. The latter was defined as transmural invasion through the bladder neck or through the extravesical soft tissue into the prostatic stroma. We defined clinically significant PCa features as any of the following: PCa tumor volume > 0.5 cc, Gleason score ≥ 7, extracapsular extension, seminal vesicle invasion, and/or a positive surgical margin for PCa [13].

Multivariable logistic regression models were fit to determine the impact of clinical preoperative variables on the presence of PUC or PCa. Instances of missing data were excluded from analysis, and only two-tailed p values are reported. All statistical calculations were performed with STATA (College Station, TX, USA).

3. Results

All 235 patients included in our analysis had the prostates processed in whole-mount sections following radical cystoprostatectomy. The preoperative characteristics of the cohort are listed in Table 1. Pathological examination revealed PUC in 77 (33%) and PCa in 113 (48%) patients. Overall, 158 (67%) patients had either PUC or PCa in the whole-mount prostate sections.

The median age of the 77 patients with PUC was 68 (interquartile range [IQR]: 62, 74). Of these, 49 (64%) had stromal invasion, while the remaining 28 (36%) had PUCIS of the urethra and/or the periurethral/peripheral prostatic ducts only. Coexisting PUCIS and stromal invasion were found in 40 of 49 (82%), indicating Pagetoid transurethral spread. Three (4%) and 17 (22%) patients with PUC had clinical TIS and T1 disease involving the bladder, respectively, while the remaining 57 (74%) had muscle-invasive tumors (Table 2). The PUC involved prostatic apex in 17 (7%) patients; however, none was exclusively confined to the apex. On multivariable analysis of preoperative characteristics (Table 3), CIS in the bladder (odds ratio [OR] = 6.3, $p < 0.001$) and trigone/bladder neck involvement

Table 1 – Patient characteristics

		Freq	%
N		235	
Age, yr, median (IQR)		69	(61, 75)
PCa history		12	5
Preop BCG		46	20
Neoadjuvant chemo		33	14
Abnormal DRE		46	21
Race	White	192	92
	Black	6	3
	White Hispanic	6	3
	Asian	2	1
	Asian Indian	1	0.5
	Pacific Islander	1	0.5
	Black Hispanic	1	0.5
CIS in bladder		137	69
Multifocal bladder tumor		99	42
Clinical stage	TIS	9	4
	T1	40	17
	T2	127	54
	T3	39	17
	T4	20	8
Pattern	HGUC	219	93
	LGUC	4	2
	CIS only	10	4
	Adenocarcinoma	1	0.4
	Sarcomatoid carcinoma	1	0.4
Location	Proximal to trigone	162	69
	Trigone and bladder neck	73	31

Freq, frequency; IQR, interquartile range; PCa, prostate cancer; BCG, bacillus Calmette-Guérin; chemo, chemotherapy; DRE, digital rectal examination; CIS, carcinoma in situ; HGUC, high-grade urothelial carcinoma; LGUC, low-grade urothelial carcinoma.

Table 2 – Clinicopathological characteristics of urothelial carcinoma in the prostate

		Freq	%
N		77	
Age, median (IQR)		68	(62, 74)
CIS in bladder		69	91
Multifocal bladder tumor		44	57
Bladder clinical stage	TIS	3	4
	T1	17	22
	T2	34	44
	T3	12	16
	T4	11	14
Bladder tumor location	Proximal to trigone	40	52
	Trigone and bladder neck	37	48
Depth	Urothelial CIS	28	36
	UC invasive into prostatic stroma	49	64
Direct extension		8	10

Freq, frequency; IQR, interquartile range; CIS, carcinoma in situ; UC, urothelial carcinoma.

(OR = 3.5, $p = 0.001$) were significantly associated with PUC after RCP. Nevertheless, 40 of 77 (52%) patients with PUC had disease proximal to the trigone on the last TURBT, and 7 of 77 (9%) had no CIS in the bladder. Of the entire cohort, 51 (22%) had a bladder tumor proximal to the trigone and no associated CIS. PUC was identified in 3 of 51 (6%) of those patients, and 2 of 3 had prostatic stromal invasion. Interestingly, neither multifocal bladder lesions (OR = 1.4, $p = 0.3$) nor clinical stage T4 (OR = 2.0, $p = 0.26$) was significantly associated with pathological evidence of PUC. Neither neoadjuvant chemotherapy nor restaging TURBT was associated with PUC on univariate analysis and was not included in the multivariable model.

A total of 113 (48%) patients had PCa in the RCP specimen (Table 4). Eight (7%) had a history of PCa preoperatively, and 2 of 8 had previously received prostate cancer treatment. The median age of patients with PCa was 70 (IQR, 64, 75). Of these patients, 39 (35%), with a median age of 72 (IQR, 66, 76), had clinically significant features. Thirty-three (29%) had Gleason score of ≥ 7, 25 (22%) had PCa tumor volume > 0.5 cc, and 15 (13%) had extra-capsular extension. The PCa involved the peripheral zone in 106 (94%) tumors but was limited to the transitional zone in 7 (6%). PCa was located in the anterior half of the prostate in 70 (61%), and 28 (25%) patients had anterior involvement exclusively. On multivariable analysis only increasing age was associated with PCa (OR = 1.3, $p = 0.046$, Table 5). Preoperative prostate-specific antigen (PSA) was not included in the model because these data were not available for most patients.

Table 3 – Multivariable analysis of factors associated with PUC

		OR	95%CI	p value
Age		1.0	1.0, 1.0	0.8
BCG exposure		1.3	0.6, 3.1	0.5
CIS in bladder		6.2	2.5, 15.6	<0.001
Multifocal bladder tumors		1.4	0.7, 2.8	0.3
Clinical stage[a]	T2	0.7	0.3, 1.6	0.4
	T3	1.0	0.3, 3.1	0.9
	T4	2.0	0.6, 7.0	0.26
Trigone/bladder neck tumor		3.2	1.6, 6.6	0.002

PUC, prostatic urothelial carcinoma; OR, odds ratio; CI, confidence interval; BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ.
[a] Reference: T1/CIS.

Table 4 – Prostate cancer characteristics

		Freq	%
N		113	
Age, years, median (IQR)		70	(64, 75)
History of prostate cancer		8	7
Abnormal DRE		24	24
Gleason score[a]	5	2	2
	6	77	69
	7	30	27
	8	3	3
Extracapsular extension		15	13
Seminal vesical invasion		0	0
Positive margin		3	3
Tumor volume, cc, median (IQR)		0.1	(0.03, 3.2)
Clinically significant features		39	35

Freq, frequency; IQR, interquartile range; DRE, digital rectal examination.
[a] One patient had PCa with radiation changes and did not have Gleason score assigned.

Table 5 – Multivariate analysis of factors associated with prostate cancer

	OR	95%CI	*p* value
Age per 10 yr	1.3	1.0, 1.8	0.046
History of PCa	2.5	0.6, 10.3	0.19
Abnormal DRE	1.2	0.6, 2.4	0.6
Neoadjuvant chemo	1.2	0.5, 2.6	0.7
BCG exposure	0.9	0.4, 1.8	0.8

OR, odds ratio; CI, confidence interval; PCa, prostate cancer; DRE, digital rectal examination; chemo, chemotherapy; BCG, bacillus Calmette-Guérin.

4. Discussion

Our study demonstrates that PUC and PCa are common in RCP specimens, with one or both occurring in approximately 67% of patients. Overall, 33% of our study group demonstrated PUC, which is comparable to the 33–58% reported in previous series [9,11,14]. Stromal invasion of the prostate was the most common pattern of involvement in patients with PUC, accounting for 64% of all cases. Nearly half of patients in this study had pathological evidence of PCa, a third of whom had PCa tumor volume $>$ 0.5, Gleason pattern 4, extracapsular extension, or a surgical margin positive for PCa. This finding is consistent with previous reports of incidental PCa after RCP ranging from 18% to 51% [9,10,15] but is higher than that reported in PSC series, although the median age of our cohort was higher than reported in most PSC series [5–7].

Various selection criteria have been used to identify patients for PSC. Vallencien and colleagues [5] reported that 100 of 165 (61%) cystectectomy patients with a mean age of 64 underwent PSC. In their report, patients were required to have a normal digital rectal examination (DRE) or negative transrectal ultrasound (TRUS) biopsy, a PSA $<$ 4 ng/ml, and free PSA $>$ 15%. This group also included patients with clinical stage T1–3 bladder tumors and did not exclude patients on the basis of tumor location in the bladder. The prostatic urothelium was evaluated for PUC by transurethral resection of the prostate (TURP). Only 3% had pathological evidence of PCa in the TURP chips. The local and distant failure rates from UC were 5% and 31%, respectively, with a median follow up of 38 mo. Botto et al [7] excluded any patient with a clinically staged bladder tumor $>$T2 or a PSA $>$ 8 ng/ml, or PUC or PCa as evaluated by TURP before PSC. Only 42 of 111 (38%) of their eligible patients, with a mean age of 61 yr, met their criteria and had PSC. They reported UC local and distant failures of 2% and 18%, respectively, with a median follow up of 26 mo. Muto and coworkers [6] reported a series of 63 men with a mean age of 49 yr who underwent a modified PSC procedure in which the prostatic transitional zone was resected en bloc with the bladder to avoid urine spillage. Their selection criteria included clinically organ-confined disease located proximal to the trigone, normal DRE, normal TRUS without biopsy, and a negative cold-cup biopsy of the prostatic urethra prior to PSC. They reported that 9.8% of patients died of disease and no patient had local recurrence with a median follow-up of 68 mo. Only 1 (2%) patient had PCa in the resected portion of the prostate. They did not report how many patients did not meet their selection criteria.

Others have studied risk for PUC in men undergoing RCP. In their series of 70 patients, Kefer et al [16] reported that no patient with a solitary bladder lesion located proximal to the bladder neck and without CIS was found to have associated PUC. In our series, 35 of 235 (15%) patients met these criteria. Nevertheless, 1 of 35 (3%) had PUC, and his disease invaded the prostatic stroma. Nixon and coworkers [17] found that PUC was rare in patients without multifocal disease or CIS in a series of 192 patients. In contrast, of the 45 (19%) of our patients with these characteristics, 4 (9%) exhibited PUC and all had stromal invasion. We found that bladder tumors at or below the trigone ($p = 0.001$) and CIS ($p < 0.001$) in the bladder were associated with PUC. However, about half of patients with PUC had an index lesion proximal to the trigone, and 11% had no evidence of CIS. These findings led us to conclude that tumors situated at or distal to the trigone and/or CIS in the bladder should serve as high-risk criteria for PUC. However, the absence of one or both of these factors is not adequate to identify the entire population of

patients without PUC. Our data suggest that complete TURP would potentially identify and exclude from PSC all patients with PUCIS, which would include at least 80% of patients with stromal invasion because it is associated with PUCIS, but this observation would require prospective validation. Limited biopsies of the prostate urothelium are not adequate to identify PUC because Donat and colleagues [18] reported only a 53% sensitivity of loop biopsy of the prostate in detecting PUC in the final specimen.

Clinical stage did not correlate with PUC in this series. This unanticipated finding may reflect the limitation of abdominal imaging in discerning low-stage extravesical disease and the variability in interpretation of the EUA between clinicians. We found that 20 of 49 (41%) patients with clinical stage T1 or less had PUC, with 10 (21%) of these patients demonstrating stomal invasion. These data underscore the inherent difficulty of accurate preoperative clinical staging of bladder cancer. Other tools such as preoperative nomograms may be helpful in more accurately assessing stage [19]; however, on the basis of this study's findings, clinical stage of the index bladder lesion would not be able to reliably identify patients without PUC.

In published PSC series, candidates tend to be in their early 60s or younger [5,7,8,20], which is considerably younger than the subset of patients with PUC in our cohort who had a median age of 68. However, age was not associated with PUC in our multivariable model, indicating that patients may not have to be excluded from PSC on the basis of age alone.

As expected, PSC series report a low incidence of pathological PCa [5–7,9–11,15,21] because patients who undergo some form of PCa screening tend to be younger in those series and only the transitional zone of the prostate is resected. Some have included preoperative TRUS biopsy screening [5,8] before PSC because most PCa occurs in the peripheral zone. In our series, we found that, while 90% of PCa involved the peripheral zone, 25% were confined exclusively to the anterior half of the prostate. Anterior PCa tumors are difficult to identify with standard TRUS biopsy templates and may require repeat TRUS biopsy for detection [22].

PCa in retained prostatic tissue presents a clinical dilemma because the radiation doses recommended for prostate cancer are above the toxic threshold for bowel, and surgery in this setting would likely compromise functional status [14]. PCa is common in patients with bladder cancer; however, incidentally diagnosed PCa in RCP specimens are typically more indolent than those detected clinically [21], which may explain the low incidence of clinically apparent prostate cancer in the PSC series. Other than increasing age, we did not identify any helpful preoperative data for predicting PCa in this series; however, we did not include preoperative PSA in our model because it was not obtained preoperatively in the majority of patients. This is one of the limitations of a retrospective study and may explain why no predictive factors were identified. Thompson et al [23] recently reported that 19% of placebo-treated patients with PSA $\leq$ 4.0 ng/ml from the Prostate Cancer Prevention Trial had PCa on biopsy, of which 16% had Gleason score 7 or greater. Furthermore, of the patients with PSA $\leq$ 2 ng/ml, 15% had PCa, of whom 11% had Gleason score 7 or higher. Therefore, we feel that all patients considered for PSC should be evaluated for PCa with DRE and TRUS biopsy regardless of PSA. This evaluation should be done in a timely fashion to limit the risk of progression [24].

5. Conclusions

Involvement of the prostate with UC and PCa are both common findings in RCP specimens. Overall, only a third of patients undergoing RCP have no evidence of either PCa or PUC. Our data suggest that tumor involving the trigone and bladder neck or with associated CIS in the bladder should be considered a marker for high risk of PUC, but the absence of these factors does not definitively rule out the presence of PUC.

Conflicts of interest

The authors have nothing to disclose.

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