



Prognostic implications of prostatic urethral involvement in non-muscle-invasive bladder cancer

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Abstract

Purpose Non-muscle-invasive bladder cancer involving the prostatic urethra is associated with pathologic upstaging and shorter survival. We investigated the survival impact of prostatic urethral involvement in non-muscle-invasive patients who are not upstaged at cystectomy.

Methods From 2000 to 2016, 177 male patients underwent cystectomy for high-risk non-muscle-invasive bladder cancer and remained pT1, pTis, or pTa, and N0 on final pathology; 63 (35.6%) patients had prostatic urethral involvement and 114 (64.4%) did not. Prostatic involvement was non-invasive (Ta or Tis) in 56 (88.9%) patients and superficially invasive (T1) in 7 (11.1%) patients. No patient had stromal invasion. Log-rank and Cox regression analyses were used to evaluate survival.

Results Compared to patients without prostatic urethral involvement, patients with involvement were more likely to have received intravesical therapy (84.6% vs. 64.4%, $p < 0.01$), have multifocal tumor (90.8% vs. 51.7%, $p < 0.01$), and have positive urethral margins (7.7% vs. 0%, $p < 0.01$) and ureteral margins (18.5% vs. 5.1%, $p < 0.01$). Log-rank comparison showed inferior recurrence-free, cancer-specific, and overall survival in patients with prostatic involvement ($p = 0.01$, $p = 0.03$, $p < 0.01$). Patients with prostatic urethral involvement were more likely to experience recurrence in the urinary tract ($p < 0.01$). On Cox regression, prostatic urethral involvement was an independent predictor of overall mortality (HR = 2.08, $p < 0.01$).

Conclusions Prostatic urethral involvement is associated with inferior survival in patients who undergo cystectomy for non-muscle-invasive bladder cancer and remain pT1, pTis, or pTa on final pathology. Prostatic urethral involvement is thus an adverse pathologic feature independent of its association with upstaging.

Keywords Bladder cancer · Non-muscle-invasive · Prostatic urethra · Radical cystectomy

Introduction

Bladder cancer is the fourth most common type of cancer in men, with 60,490 estimated male cases in 2017 and 12,240 estimated deaths [1]. Survival is more favorable in patients

with non-muscle-invasive bladder cancer (NMIBC), which is typically treated with transurethral resection of the bladder tumor and intravesical therapy. Many patients also go on to receive radical cystectomy when they are deemed high-risk or Bacillus Calmette–Guerin (BCG) unresponsive [2].

Prostatic urethral involvement (PUI) is a particularly concerning feature of NMIBC because the prostatic urethra is hypothesized to be a sanctuary site where malignant cells have less exposure to intravesical therapy [3–4]. Furthermore, tumor in the prostatic urethra is difficult to accurately stage because it can creep into the prostatic stroma while remaining undetected until the entire prostate is examined after radical cystoprostatectomy (RCP) [5–7]. This progression from < T2 to T4 disease can in part explain the inferior survival observed in NMIBC patients with PUI on transurethral biopsy [5, 6]. However, it is not known if PUI affects survival in NMIBC patients who remain < T2

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on their cystectomy pathology. We hypothesized that PUI is indicative of poor survival in these patients. To test this hypothesis, we compared recurrence-free, cancer-specific, and overall survival in high-risk NMIBC patients with and without PUI on cystectomy pathology to determine if PUI is predictive of shorter survival independent of its association with pathologic upstaging and tumor progression at cystectomy.

Methods

Between January 2000 and August 2016, 950 consecutive men underwent RCP at our institution. From this group, we identified 316 men with cTa, cTis, or cT1 high-grade urothelial carcinoma of the bladder on transurethral resection, of whom 196 were found to be pTa, pTis, or pT1 and N0 on pathologic evaluation of RCP specimen. Of these 196 men, five were excluded from the study for having underwent prior prostatectomy, four were excluded for having received neoadjuvant chemotherapy, four were excluded for having upper tract disease requiring concurrent nephroureterectomy, four were excluded for having variant histology, and two were excluded for having lymphovascular invasion. This resulted in a cohort of 177 patients with non-muscle-invasive urothelial carcinoma, of whom 63 (35.6%) had PUI on RCP specimen and 114 (64.4%) did not. Indication for cystectomy was BCG failure in 123 (69.5%) patients, high-grade T1 disease in 35 (19.8%) patients, and large volume or multifocal tumor unresectable by TURBT in the remaining 19 (10.7%) patients.

Clinicopathologic variables were collected from the Institutional Review Board-approved Cancers of the Urinary Tract Database, which combines patient medical records, patient-completed surveys, the Johns Hopkins Cancer Registry, and the National Death Index. Collected variables included age at cystectomy, race, Charlson comorbidity index, intravesical therapy, type of urinary diversion, presence of PUI, carcinoma in situ (CIS), multifocal tumor, and positive surgical margin on RCP specimen, American Joint Committee on Cancer TNM staging prior to RCP (clinical stage) and at time of RCP (pathologic stage), cause of death, days from diagnosis to cystectomy, and days from cystectomy to cancer recurrence, death, or censoring.

The presence of PUI was determined by review of pathology from RCP specimen. On RCP specimen, PUI was categorized as either non-invasive (Ta or Tis) or superficially invasive (T1). Patients with invasion into the prostatic stroma were excluded from the cohort. Clinical stage was determined by histologic evaluation of transurethral resection (TUR) specimens, physical examination, and imaging via computerized tomography or magnetic resonance. Pathologic stage was determined by

histologic evaluation of RCP specimen. TUR specimens were reviewed for clinical staging but not used for determination of PUI, as only 76 (42.9%) patients underwent prostatic biopsy during TUR. Among the patients who underwent prostatic biopsy, sensitivity and specificity analyses were conducted to determine the accuracy of prostatic biopsy. Patients with PUI on TURBT specimen routinely underwent transurethral resection of prostate (TURP) prior to administration of intravesical therapy. BCG was used in 123 (96.1%) of the 128 patients who received at least one course of intravesical treatment.

After cystectomy, patients were followed at 3–6 month intervals for 3 years and then annually thereafter. Post-cystectomy recurrence and mortality data were collected from these follow-up screening visits as well as from our institutional cancer registry and the national death index. Recurrence was defined as a biopsy-confirmed urothelial carcinoma lesion found anytime after cystectomy. This included recurrence in the urinary tract, lymph nodes, and distant metastasis.

Comparisons of baseline characteristics between PUI and non-PUI patients were made using Wilcoxon–Mann–Whitney test for continuous variables and Chi-squared test for categorical variables. Time from diagnosis to cystectomy was analyzed as a categorical variable with stratification at 2 years, based on prior research showing increased risk of mortality at >2 years after initial BCG therapy [8]. Kaplan–Meier curves with log-rank test were created to compare recurrence-free, cancer-specific, and overall survival between PUI and non-PUI patients. Multivariate logistic and Cox regression were used to identify independent predictors of prostatic urethral involvement and overall mortality. The multivariate regression models were created using the stepwise selection process, with a *p* value < 0.10 required for entry into the model. Statistical significance was defined as a two-tailed α of 0.05. All analyses were performed using SAS Studio 3.6 (Cary, NC).

Results

In a cohort of 177 patients who underwent cystectomy for high-risk NMIBC and remained pTa, pTis, or pT1 and N0 at cystectomy, there were 63 PUI patients and 114 non-PUI patients. On final pathology, PUI was non-invasive (Ta or Tis) in 56 (88.9%) patients and superficially invasive (T1) in 7 (11.1%) patients. Non-invasive PUI consisted of CIS in 49 of 56 (86.0%) patients and high-grade Ta in 7 (14.0%) patients. Of the 63 patients with PUI, 6 (9.5%) patients had tumor isolated in the prostatic urethra and 57 (90.5%) patients had additional tumor in the bladder. Prostatic urethral biopsy slides were available for review for 76 patients

Table 1 Sensitivity and specificity of transurethral biopsy prior to cystectomy

	Radical cystectomy		Total
	PUI	No PUI	
Biopsy			
PUI	26	7	33
No PUI	12	31	43
Total	38	38	76
	Sensitivity:	Specificity:	
	68.4%	81.6%	

in the cohort: 38 with PUI on final pathology and 38 without PUI. Sensitivity of biopsy in these patients was 68.4% and specificity was 81.6% (Table 1).

Compared to non-PUI patients, patients with PUI were more likely to have received intravesical therapy (85.7% vs. 64.9%, $p < 0.01$), have multifocal tumor (90.5% vs. 51.8%, $p < 0.01$), have positive urethral margins (7.7 vs. 0.0%, $p < 0.01$) and ureteral margins (19.0% vs. 5.3%, $p < 0.01$) on RCP pathology, and have a recurrence in the urinary tract (23.8% vs. 8.8%, $p < 0.01$). No patients had positive margins outside of urinary tract. Of the five patients with positive urethral margins, three underwent subsequent urethrectomy at our institution, with only one of the three urethrectomy specimens positive for carcinoma. The remaining two patients underwent surveillance with periodic cytology and urethroscopy with no recurrent lesions found. There were no significant differences found for duration of follow-up ($p = 0.72$), age ($p = 0.58$), time to cystectomy ($p = 0.07$), race ($p = 0.66$), Charlson comorbidity index ($p = 0.47$), CIS ($p = 0.05$), clinical T stage ($p = 0.20$), pathologic T stage ($p = 0.27$), urothelial cancer recurrences (0.05), or urothelial cancer-specific deaths (0.07) (Table 2).

Median follow-up for the entire cohort was 56.3 months, with cancer recurrence occurring in 44 (24.9%) patients and death occurring in 64 (36.2%) patients. Recurrence-free survival, cancer-specific survival, and overall survival were inferior in PUI patients compared to non-PUI patients ($p = 0.01$, $p = 0.03$, and $p < 0.01$) (Fig. 1). PUI patients were also more likely to experience recurrence in the urinary tract compared to non-PUI patients ($p < 0.01$), but there was no significant difference in recurrence occurring outside the urinary tract ($p = 0.65$) (Fig. 2). Of the 15 PUI patients who experienced urinary tract recurrence, seven occurred in the urethra, five in the ureter, and three in the renal pelvis; 7 (46.7%) of these 15 urinary tract recurrences were invasive. There were no significant differences in recurrence-free survival ($p = 0.323$) or overall survival ($p = 0.99$) when comparing PUI patients by pathologic T stage (Ta vs. Tis vs. T1).

Multivariate logistic regression using stepwise selection identified prior intravesical therapy (OR = 2.90, $p < 0.02$),

positive urinary tract margin (OR = 4.01, $p = 0.01$), and multifocal tumor (OR = 7.56, $p < 0.01$) as independent predictors of prostatic urethral involvement (Table 3). In multivariate Cox regression, age (HR = 1.03, $p = 0.02$), positive urinary tract margin (HR = 2.01, $p = 0.03$), and PUI (HR = 2.02, $p = 0.01$) were independent predictors of overall mortality, while CIS was predictive of decreased mortality risk (HR = 0.40, $p < 0.01$) (Table 4).

Discussion

Prior studies have shown that PUI in NMIBC is associated with increased risk of mortality. However, PUI in these studies was diagnosed on clinical staging, and a significant number of patients were later found to have T4 disease on pathologic staging [5–7]. This is the first study to show that PUI is associated with increased mortality in NMIBC patients who are not upstaged at cystectomy. We examined the impact of PUI in 177 patients who underwent cystectomy for high-risk NMIBC and remained pTa, pTis, or pT1 at cystectomy. Comparison of Kaplan–Meier curves showed inferior recurrence-free, cancer-specific, and overall survival in patients with PUI. Multivariate Cox regression identified PUI as a predictor of mortality, independent of its associations with CIS, multifocal tumor, and positive urinary tract margins. These findings indicate that PUI is an adverse pathologic feature of NMIBC independent of its association with CIS, positive urinary tract margin, multifocal tumor, and pathologic upstaging.

In addition to having inferior survival, PUI patients were more likely to have positive urethral and ureteral margins compared to non-PUI patients. We hypothesize that the presence of PUI in NMIBC may denote a “pan-urothelial” phenotype, while NMIBC without PUI may denote a localized bladder malignancy. The increased likelihood of PUI patients to recur in the urinary tract further supports this hypothesis and suggests that patients with PUI on cystectomy pathology need to be followed closely for a urinary tract recurrence necessitating operative intervention. Future guidelines recommending close urinary tract surveillance may improve survival in this population, and genomic profiling of PUI and non-PUI tumors may illicit differences in their tumor biologies. In our practice, patients with PUI undergo urine cytology testing and CT imaging every 3–6 months for the first 2 years after surgery and then annually thereafter. In the patients who do not undergo urethrectomy, urethroscopy is performed every 6–12 months for 3 years. Future prospective trials comparing outcomes between different screening practices may determine the optimal routine.

Because of the inferior outcomes in patients with PUI, it has been argued that patients with high-grade NMIBC

Table 2 Baseline characteristics of the entire cohort, PUI patients, and non-PUI patients

Variable	All patients	PUI (<i>n</i> = 66)	Non-PUI (<i>n</i> = 118)	<i>p</i> value
Duration of follow-up (months)	56.3 (0.7–187.1)	44.5 (0.7–173.0)	60.7 (1.0–187.1)	0.7170
Age at cystectomy (years)	67.3 (35.8–88.7)	68.1 (42.9–85.1)	66.2 (35.8–88.7)	0.5836
Time to cystectomy				0.0724
≤ 2 years	132 (74.6)	42 (66.7)	90 (78.9)	
> 2 years	45 (25.4)	21 (33.3)	24 (21.1)	
Race				0.6621
White	157 (88.2)	55 (87.3)	102 (89.5)	
Non-white	20 (11.3)	8 (12.7)	12 (10.5)	
Charlson comorbidity index				0.4749
< 3	161 (91.0)	56 (88.9)	105 (92.1)	
≥ 3	16 (9.0)	7 (11.1)	9 (7.9)	
Diversion type				0.1084
Ileal conduit	114 (64.4)	45 (71.4)	69 (60.5)	
Neobladder	58 (32.8)	15 (23.8)	43 (37.7)	
Other	5 (2.8)	3 (4.8)	2 (1.8)	
Intravesical therapy				0.0031
No	52 (28.4)	9 (14.3)	40 (35.1)	
Yes	131 (71.6)	54 (85.7)	74 (64.9)	
CIS				0.0521
No	43 (24.3)	10 (15.9)	33 (28.9)	
Yes	134 (75.7)	53 (84.1)	81 (71.1)	
Multifocal tumor				< 0.0001
No	61 (34.5)	6 (9.5)	55 (48.2)	
Yes	116 (65.5)	57 (90.5)	59 (51.8)	
Positive surgical margin				0.0001
No	155 (87.6)	47 (74.6)	108 (94.7)	
Yes	22 (12.4)	16 (25.4)	6 (5.3)	
Clinical T stage				0.1977
Ta	32 (18.1)	14 (22.2)	18 (15.8)	
Tis	56 (31.6)	23 (36.5)	33 (28.9)	
T1	89 (50.3)	26 (41.3)	63 (55.3)	
Pathologic T stage				0.2655
Ta	27 (15.3)	6 (9.5)	21 (18.4)	
Tis	89 (50.3)	35 (55.6)	54 (47.4)	
T1	61 (34.5)	22 (34.9)	39 (34.2)	
Recurrence				0.0525
No	133 (75.1)	42 (66.7)	91 (79.8)	
Yes	44 (24.9)	21 (33.3)	23 (20.3)	
Urinary tract recurrence				0.0060
No	152 (85.9)	48 (76.2)	104 (91.2)	
Yes	25 (14.1)	15 (23.8)	10 (8.8)	
Urothelial cancer-specific death				0.0722
No	147 (83.1)	48 (76.2)	99 (86.9)	
Yes	30 (16.9)	15 (23.8)	15 (13.1)	

p values are in bold

should undergo transurethral biopsy of the prostatic urethra [9, 10]. In our cohort, the sensitivity of transurethral biopsy in predicting PUI was 68.4% and the specificity was 81.6%. These findings are similar to other studies of

prostatic urethral biopsy accuracy, with reported sensitivities of 63–66% and specificities of 69–89% [11, 12]. Given the significant number of patients with a discrepancy between their biopsy and RCP findings, it is clear

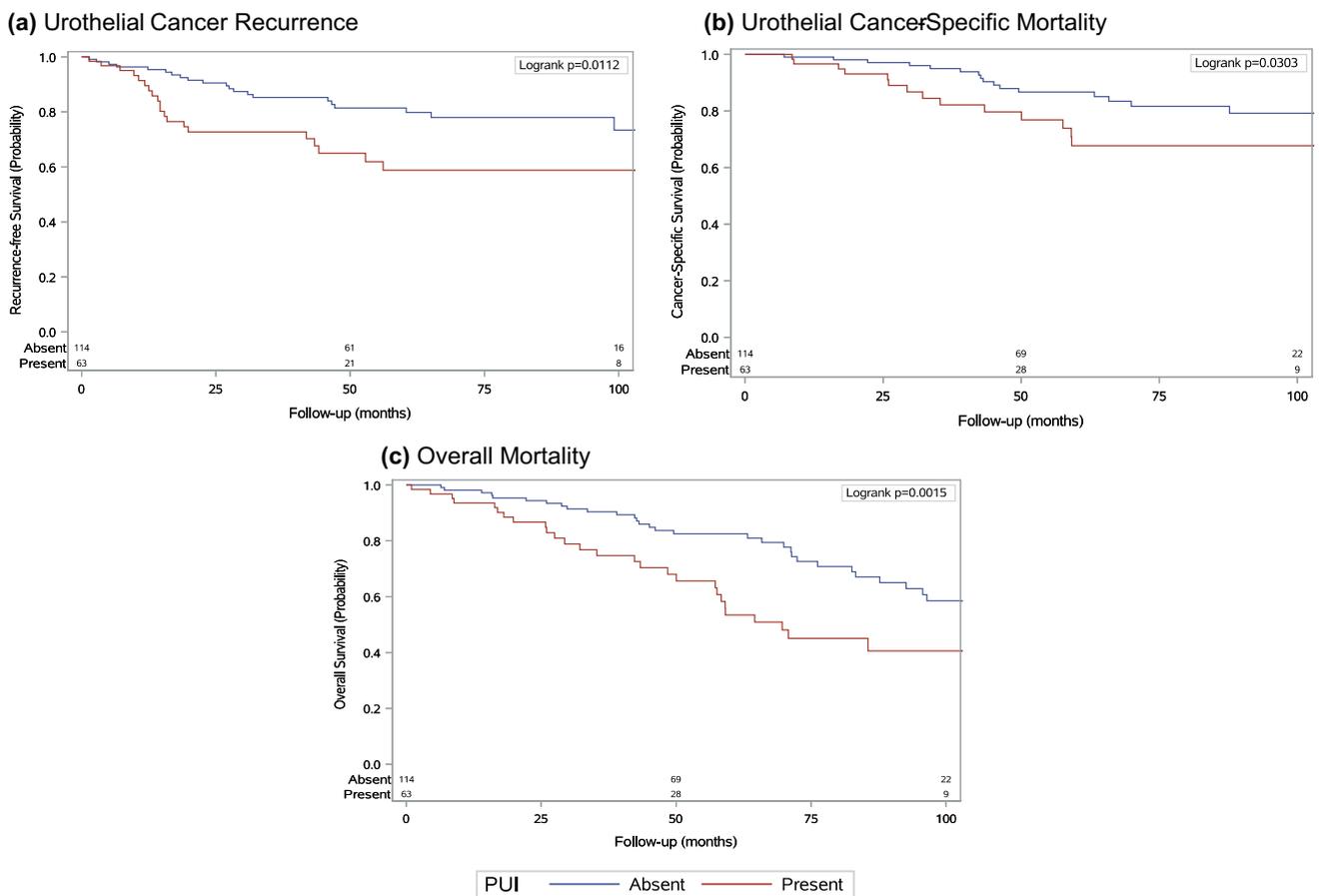


Fig. 1 Kaplan–Meier curves with log-rank test for recurrence-free (a), urothelial cancer-specific (b) and overall survival (c) stratified by presence of prostatic urethral involvement. Number at risk listed at bottom of figure

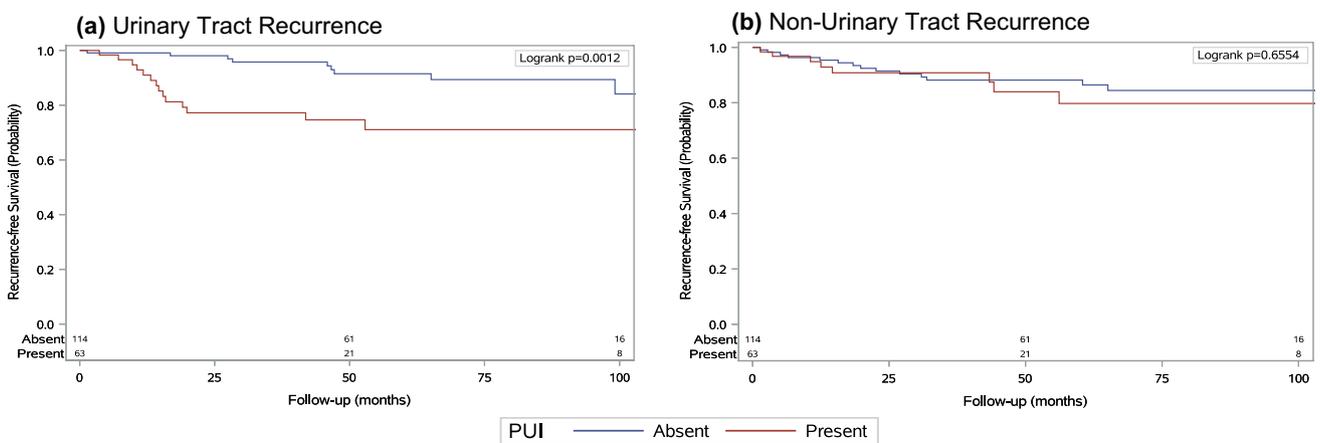


Fig. 2 Kaplan–Meier curves with log-rank test for urinary tract recurrence-free survival (a) and non-urinary tract recurrence-free survival (b) stratified by presence of prostatic urethral involvement. Number at risk listed at bottom of figure

that thorough evaluation of the prostate specimen after RCP is necessary for adequate staging. At our institution, we routinely take frozen sections of the urethral margins

particularly when considering an orthotopic urinary diversion. We have previously demonstrated that frozen urethral sections have reasonable reliability at predicting

Table 3 Multivariate logistic regression using stepwise selection to identify predictors of prostatic urethral involvement

Variable	Predictors of PUI		
	Odds ratio	95% CI	<i>p</i> value
Intravesical therapy			
No	Ref		
Yes	2.90	(1.21–6.95)	0.0167
Positive urinary tract margin			
No	Ref		
Yes	4.01	(1.39–11.58)	0.0103
Multifocal tumor			
No	Ref		
Yes	7.56	(2.94–19.40)	< 0.0001

Table 4 Multivariate Cox regression using stepwise selection for predictors of overall mortality

Variable	Overall mortality		
	Hazard ratio	95% CI	<i>p</i> value
Age at cystectomy			
Years	1.03	(1.00–1.06)	0.0249
CIS			
No	Ref		
Yes	0.40	(0.21–0.75)	0.0041
Multifocal tumor			
No	Ref		
Yes	1.81	(0.93–3.51)	0.0803
Positive urinary tract margin			
No	Ref		
Yes	2.01	(1.06–3.82)	0.0330
PUI			
No	Ref		
Yes	2.02	(1.16–3.53)	0.0133

final urethral pathology, with a negative predictive value of 100% and positive predictive value of 93% [13].

Our study's limitations include its retrospective nature and the fact that all information was collected from a single institution with unique referral and practice patterns. Not all patients underwent pre-cystectomy biopsy of the prostatic urethra, and some patients underwent the procedure at outside institutions with pathology slides sent to our institution for review. Additionally, cystectomy specimens were reviewed by several different pathologists, allowing for potential differences in the manner of identifying tumor in the prostatic urethra. To confirm the validity of our study, further investigation in a prospective and multi-institutional setting is warranted.

Conclusion

Patients with NMIBC involving the prostatic urethra are at increased risk for cancer recurrence and death, even when they remain pTa, pTis, or pT1 on their cystectomy pathology. PUI is thus a high-risk pathologic feature of NMIBC independent of its association with pathologic upstaging at cystectomy. Patients with PUI are more likely to have positive ureteral margins and to experience a post-cystectomy recurrence in the urinary tract. Therefore, these patients may comprise a “pan-urothelial” phenotype and may benefit from close surveillance after cystectomy.

Author contributions AB: project development, data collection, data analysis and manuscript writing/editing; MD: data collection and manuscript writing/editing; MC: data collection and manuscript writing/editing; GJ: data collection and manuscript writing/editing; NS: data collection and manuscript writing/editing; AM: data collection and manuscript writing/editing; TB: project development and manuscript writing/editing; MK: project development, data analysis and manuscript writing/editing.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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