
Urethrectomy Following Cystectomy for Bladder Cancer in Men: Practice Patterns and Impact on Survival

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Purpose: The benefit of urethrectomy in patients with bladder cancer who are undergoing cystectomy is controversial. We describe the frequency of urethrectomy by bladder cancer stage and identify clinical characteristics that predict urethrectomy. We also investigated whether urethrectomy offers any additional independent survival benefit.

Materials and Methods: A total of 2,401 men who underwent radical cystoprostatectomy between 1991 and 2002 were identified in the Surveillance, Epidemiology and End Results-Medicare database. A multivariate logistic regression model was used to analyze factors driving urethrectomy. We then analyzed the records of 195 men who underwent urethrectomy to find predictors of that procedure as salvage for urethral recurrence vs concurrently with cystoprostatectomy or as a staged procedure. Using multivariate Cox regression analysis we analyzed whether urethrectomy had an independent effect on disease specific survival.

Results: The only significant predictor of urethrectomy was stage. Patients at a teaching hospital were more likely to undergo salvage urethrectomy for recurrence vs immediate urethrectomy compared to those at urban nonteaching hospitals. Patient age, race, number of comorbidities and tumor stage were significant independent predictors of survival. Survival in men who underwent urethrectomy concurrently with cystoprostatectomy was higher than in those who did not undergo urethrectomy but not statistically significant (HR = 0.775, 95% CI 0.592–1.014, p = 0.0632).

Conclusions: Disease stage is related to urethrectomy performance. Age, race, stage and comorbidities were independent predictors of overall survival in patients with bladder cancer undergoing cystectomy. Urethrectomy did not confer a significant independent survival benefit.

Key Words: urethra; bladder; carcinoma, transitional cell; neoplasm recurrence, local; urethrectomy

The reported incidence of urethral recurrence after radical cystoprostatectomy for bladder TCC is 4% to 17%^{1,2} with 1 large review suggesting a 10.1% recurrence rate.³ Complete urethrectomy is the treatment of choice for urethral recurrence since it has been shown to be superior to local transurethral resection.³ Because of the poor prognosis following urethral recurrence, prophylactic urethrectomy is also performed in patients at high risk for recurrence. This is most often advocated in patients with TCC of the prostatic urethra or tumor invading the prostatic stroma.⁴ Tumor multiplicity, papillary pattern, CIS, tumor at the bladder neck, prostatic urethral mucosal involvement and prostatic stromal invasion confer a risk of urethral recurrence in an additive manner.⁵ More contemporary data suggest that prostate urethral involvement may be the only important pathological predictor of subsequent urethral recurrence.⁶ The poor prognosis of urethral recurrence can be

related to the high prevalence of metastatic disease in these patients. In a study of 1,054 patients who underwent radical cystectomy urethral recurrence was documented in 47 and 36 had died at a median followup of 26 months, including 25 of metastatic disease.⁷

However, the overall independent benefit of performing urethrectomy concurrently with cystectomy or for subsequent isolated recurrence is not clear. For study purposes the reappearance of metachronous urothelial cancer in the unresected urethra has been considered recurrent urothelial cancer, although it could also be construed as a second primary tumor. In addition, to our knowledge there are no published reports of the prevailing practice pertaining to urethrectomy in the United States. We examined the frequency of urethrectomy in a sample population from the United States using the SEER data set to identify factors that predict the performance and timing of urethrectomy. We also investigated whether urethrectomy offers any independent survival benefit.

METHODS

The SEER-Medicare linked database⁸ was used for these analyses. The SEER program captures data on all cancers diagnosed in a representative sample of 26% of the American population from various designated sites and metropol-

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itan areas. Data from the SEER program can be linked to administrative claims data from Medicare obtained through the Centers for Medicare and Medicaid Services, which provide information on comorbidity, longitudinal care, chemotherapy, surveillance and other variables that are not available in the SEER data set. We identified men who underwent radical cystoprostatectomy for urothelial carcinoma between 1991 and 2002. These men were divided into 3 groups, including those who underwent concurrent or staged urethrectomy, defined as having a claim for urethrectomy within 6 weeks of cystectomy, those who underwent delayed urethrectomy, defined as having a claim for urethrectomy later than 6 weeks after cystectomy, and those who underwent radical cystectomy without a claim for urethrectomy. Clinicopathological characteristics, including age, grade, AJCC stage (3rd edition⁹) and race were compared using chi-square analysis. Age was treated as a categorical variable by compressing the data into the 3 age ranges 30 to 69, 70 to 79 and 80 to 99 years.

On multivariate logistic regression analysis we investigated the effects of the various clinicopathological factors on the probability of a patient undergoing urethrectomy vs radical cystoprostatectomy without urethrectomy. We hypothesized that the primary driver for urethrectomy would be prostatic urethral involvement, which would be captured as stage IV disease (incorporating TNM stage T4 or node positive disease). Covariates that were adjusted for included age, race (white or other), hospital type (rural, urban or teaching), tumor grade, tumor stage and Charlson comorbidity score.¹⁰ In a second multivariate logistic regression model we compared the same characteristics between patients who underwent immediate or staged urethrectomy (within 6 weeks of cystoprostatectomy) and those who underwent a delayed procedure (urethrectomy 6 weeks or later after cystoprostatectomy) to identify predictors of planned urethrectomy. Finally, using a Cox proportional hazards model¹¹ incorporating AJCC stage (3rd edition⁹), grade, age, race, hospital type (urban, rural or teaching), comorbidities and urethrectomy timing (within 6 weeks, after 6 weeks or never) we analyzed whether urethrectomy in those who underwent the procedure had an independent effect on disease specific survival. All statistical analyses were performed using SAS® 9.0 with 2-tailed $p < 0.05$ considered statistically significant.

RESULTS

A total of 2,401 men in the SEER-Medicare linked database underwent radical cystoprostatectomy between 1991 and 2002 with an overall median followup of 29 months (range 0 to 143). Of these men 195 (8.1%) ultimately underwent urethrectomy. Of these procedures 103 (53%) were simultaneous or staged operations performed within 6 weeks of cystoprostatectomy, presumably for positive margins or prophylaxis against a high risk of recurrence. The remaining 92 procedures were deemed to have been performed for observed urethral recurrence at a median of 9 months (range 2 to 79) after cystectomy. On univariate analysis the 3 groups (cystectomy only, urethrectomy within 6 weeks and urethrectomy after 6 weeks) did not differ in age, grade or race. The only significant difference was found in stage, that is a higher percent of stage I disease in the delayed urethrec-

tomy group and a higher percent of stage IV disease in the immediate urethrectomy group ($p < 0.0001$, table 1).

On multivariate analysis age, race, hospital, tumor grade and comorbidities were not significant independent predictors of urethrectomy. However, patients with stages I and IV cancer were significantly less likely to undergo cystectomy alone than those with stage III disease (OR 0.257 and 0.265, respectively, table 2). In men who ultimately underwent urethrectomy the only factor predictive of delayed (more than 6 weeks after cystoprostatectomy) rather than simultaneous or staged urethrectomy was undergoing cystoprostatectomy at a teaching hospital rather than at an urban one (OR = 2.601, 95% CI = 1.189–5.690).

In our Cox proportional hazards model independent predictors of disease specific survival were age, race, comorbidities and tumor stage (table 3). Survival in men who underwent urethrectomy concurrently with cystoprostatectomy was not significantly different than that in those who did not undergo urethrectomy at all (HR 0.775, 95% CI 0.592–1.014). Disease specific survival in men who underwent early or concomitant urethrectomy was no different than in those who underwent delayed urethrectomy (more than 6 weeks after initial cystoprostatectomy).

DISCUSSION

Urethral involvement requiring urethrectomy at or following radical cystectomy is an uncommon event, occurring in 8.1% of our data set, which is similar to the 10.1% in a large review.³ The most common reported indications remain positive surgical margins at the prostatic apex and prostatic stromal invasion. A number of other risk factors have been identified and it was noted that the risk of urethral recurrence more than doubled with each added risk factor. Nevertheless, prophylactic urethrectomy performed for these risk factors resulted in a negative specimen in 17 of 19 cases.⁵

Stage is the most important factor for determining whether urethrectomy is performed because this is also the most significant indication for urethrectomy. The finding of a lower incidence of urethrectomy for stage III cancer is

TABLE 1. Univariate analysis of group clinicopathological characteristics by urethrectomy

	No. Urethrectomy Timing (%)			p Value
	None	Less Than 6 Wks	Greater Than 6 Wks	
Grade:				0.27
1	54 (2.4)	Less than 5	Less than 5	
2	370 (16.8)	18 (17.5)	19 (20.7)	
3	1,212 (54.9)	51 (49.5)	50 (54.3)	
4	442 (20)	21 (20.4)	13 (14.1)	
Unknown	128 (5.8)	12 (11.7)	7 (7.6)	
Stage:				<0.0001
I	846 (38.3)	52 (50.5)	57 (62)	
II	464 (21)	7 (6.8)	14 (15.2)	
III	468 (21.2)	10 (9.7)	6 (6.5)	
IV	428 (19.4)	34 (33)	15 (16.3)	
Age:				0.7922
30–69	700 (31.7)	35 (34)	27 (29.3)	
70–79	1,246 (56.5)	59 (57.3)	56 (60.9)	
80–99	260 (11.8)	9 (8.7)	9 (9.8)	
Race:				0.7786
White	2,009 (91.7)	95 (92.2)	86 (93.5)	
Other	182 (8.3)	8 (7.8)	6 (6.5)	

TABLE 2. Logistic regression of urethrectomy prediction

Variable	OR (95% CI)	p Value
Age	1.005 (0.977–1.034)	0.7249
Race:		
White	1	Referent
Other	1.317 (0.674–2.574)	0.42
Hospital:		
Rural	0.642 (0.345–1.193)	0.1609
Teaching	1.306 (0.891–1.913)	0.1709
Urban	1	Referent
Charlson, comorbidity score: ¹⁰		
0 or 1		Referent
2	1.409 (0.958–2.072)	0.0816
3	0.942 (0.599–1.481)	0.7962
4+	1.399 (0.53–3.692)	0.4975
Grade:		
1 or 2	1.225 (0.791–1.898)	0.3632
3	1	Referent
4	0.951 (0.62–1.46)	0.819
Stage:		
I	0.257 (0.144–0.461)	<0.0001
II	0.796 (0.395–1.605)	0.5232
III	1	Referent
IV	0.265 (0.144–0.487)	<0.0001

Logistic regression demonstrated that only stage predicted urethrectomy and OR represents the relative probability of cystectomy alone, ie the odds of no urethrectomy.

unexpected at first, given that stage III in the modern TNM staging system includes T4a, which is defined as prostatic invasion and is an indication for urethrectomy.¹² However, the SEER database uses the 1988 (3rd edition) AJCC guidelines.^{9,13} Under that staging system prostate invasion is considered stage IV cancer. While this explains the relatively low incidence of urethrectomy for stage III urothelial cancer, it does not account for the strikingly high incidence in cases of stage I cancer. This is not a result of small numbers since 109 of 195 urethrectomies were performed for stage I disease. It is possible that those individuals had panurothelial disease or multifocal CIS, which may have prompted urethrectomy. The stage grouping used in the SEER data set includes Ta, T1 and CIS under stage I,¹³ which does not allow us to address this issue further. In contrast, the immediate urethrectomy group had a higher proportion of stage IV disease, which is consistent with these patients undergoing urethrectomy for prostatic involvement or positive margins at surgery.

The lower likelihood of concurrent urethrectomies at teaching hospitals may be related to the increasing use of orthotopic continent diversion, which precludes urethrectomy. A previous study showed that treatment at academic medical centers and National Cancer Institute designated cancer centers was independently associated with continent reconstruction.¹⁴ However, another possible explanation is that at these hospitals a higher proportion of urethrectomies is performed for recurrence due to a high rate of referral to academic centers for that procedure after cystectomy is done elsewhere. Potential differences in the rigor of monitoring for urethral recurrence through repeated urethral washings could also account for this difference.

Since orthotopic continent urinary diversion precludes urethrectomy, the effect of urethrectomy on survival is an important consideration. While some studies suggest that patients who undergo orthotopic diversions may actually have a lower urethral recurrence rate,^{1,15} the direct independent impact of urethrectomy is unclear. In a recent study superficial urethral recurrence after ileal neobladder

construction was treated primarily with transurethral resection.¹⁶ Subsequent recurrences were then treated with urethrectomy with no evidence of local recurrence or metastasis.

In our retrospective data set the timing of urethrectomy did not appear to impact survival. However, this presumes that all patients who were at high risk for urethral involvement underwent the procedure around the time of cystectomy and those who underwent the procedure later did so for clinically detected isolated urethral recurrence. Other studies have not demonstrated any survival advantage by evaluating patients with urethral washings in an attempt to detect and treat urethral recurrence earlier.¹⁷ Moreover, a previous study suggests that there is no difference in surgical morbidity or survival between immediate and staged urethrectomy.¹⁸ The true independent benefit of urethrectomy can perhaps be best identified by comparing survival in a group of men who underwent urethrectomy for isolated local recurrence in the urethra to survival in another group with similar disease recurrence with or without distant metastasis that did not undergo urethrectomy. The current population based data sets do not provide such information, nor can it be discerned from the current staging system, making this analysis impossible using this data source.

The limitations of our study include the lack of data on adjuvant chemotherapy. We were unable to substratify stage I disease according to CIS, which may have been an important driver of urethrectomy. We also do not have data on prostatic urethral margin status at cystectomy, which may have determined the need for concurrent or staged urethrectomy. The interpretation of our survival data may have been confounded by selection bias. We were also unable to assess new metastatic disease that occurred with localized urethral disease in patients who underwent delayed urethrectomy but we assumed that these patients would not have undergone urethrectomy if there had been evidence of

TABLE 3. Cox proportional hazards analysis of risk of disease specific death

Variable	HR (95% CI)	p Value
Urethrectomy:		
Within 6 wks	0.775 (0.592–1.014)	0.0632
After 6 wks	0.816 (0.633–1.05)	0.1142
Cystectomy only	1	Referent
Age	1.014 (1.005–1.024)	0.0039
Race:		
White	1	Referent
Other	1.24 (1.016–1.514)	0.0345
Hospital:		
Rural	0.871 (0.684–1.109)	0.2636
Teaching	0.918 (0.809–1.041)	0.1803
Urban	1	Referent
Charlson comorbidity score: ¹⁰		
0 or 1	1	Referent
2	1.08 (0.952–1.226)	0.2315
3	1.312 (1.126–1.528)	0.0005
4+	1.84 (1.384–2.445)	<0.0001
Grade:		
1 or 2	0.909 (0.784–1.054)	0.2066
3	1	Referent
4	1.138 (0.994–1.304)	0.051
Stage:		
I	0.536 (0.458–0.626)	<0.0001
II	0.728 (0.619–0.857)	0.0001
III	1	Referent
IV	1.194 (1.017–1.402)	0.0301

Age, race, comorbidities and stage increased the risk of disease specific death.

systemic disease at the same time. It is interesting to note that, despite delayed urethrectomy, survival in these patients was no different from that in those who did not undergo urethrectomy. It is expected that patients who only underwent cystectomy included those who had no involvement or subsequent recurrence in the urethra as well as those who had urethral recurrence along with metastatic disease at another site during followup.

Due to the retrospective nature of these data the survival effect of urethrectomy must be interpreted cautiously because of the possibility of selection bias that a multivariate model cannot account for. One such selection or ascertainment bias could arise from the fact that some patients may have urethral recurrence several years following cystectomy and followup in this study may not have been long enough to capture these patients. Even in these studies demonstrating the likelihood of urethral recurrence long after cystectomy such patients are a minority with 42% of recurrences developing within 1 year of cystectomy.⁷ Of patients who died with urethral recurrence most deaths were from metastatic disease. However, these data are still valuable, in that they provide information on the prevalence and pattern of use of urethrectomy in patients undergoing cystectomy for bladder cancer as well as the subsequent outcome.

CONCLUSIONS

Urethrectomy is uncommonly performed in concert with cystectomy for lower tract TCC. Primary tumor stage (I or IV) is the strongest factor driving urethrectomy with delayed urethrectomy significantly more likely to be performed for stage I disease. Urethrectomy around the time of cystoprostatectomy or more than 6 weeks following cystoprostatectomy does not appear to yield a significant independent survival advantage. These data may have implications for selecting patients for orthotopic continent urinary diversion.

Abbreviations and Acronyms

AJCC	=	American Joint Committee on Cancer
CIS	=	carcinoma in situ
SEER	=	Surveillance, Epidemiology and End Results
TCC	=	transitional cell carcinoma

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EDITORIAL COMMENT

In this survey of SEER-Medicare data the authors determined that 8.1% of men undergoing radical cystectomy underwent urethrectomy at surgery or as a secondary procedure. Half of the urethrectomies performed within 6 weeks of cystectomy were done for stage I disease, presumably due to the perceived risk of a second urothelial cancer in the retained urethra based on primary tumor features. The authors also did not find an effect of urethrectomy on survival, although the relatively short followup of 29 months may have limited this portion of the analysis as well as the determination of the incidence of urethrectomy performed for subsequent new urethral primary TCC. This series is important, inasmuch as it mirrors current practice reported from centers of excellence. Current indications and guidelines for prophylactic urethrectomy include diffuse CIS involving the prostatic urethra and prostatic stromal invasion, although groups at some centers use only positive frozen section of the apical urethra margin as an indication for urethrectomy.¹

Of the urethrectomies 47% were performed after 6 weeks for a clinical diagnosis of urethral TCC. These cases are usually referred to as recurrence, although they may be considered second primary tumors of the urinary tract, where multifocality with temporal and spatial separation is common. Patients with a retained urethra can be followed with urethral wash cytology with the expectation that in those who are compliant with followup and show urethral TCC the tumor stage is usually Tis or T1 and urethrectomy provides excellent local control (reference 17 in article). A positive urethral wash should prompt biopsies of the urethra and urethrectomy, when indicated. A recent study suggests that patients with CIS of the retained urethra can be successfully treated with intraurethral bacillus Calmette-Guerin.² Survival probability is likely driven more by pathological tumor stage of the radical cystoprostatectomy specimen. While Lin et al suggested that patients requiring urethrectomy who present with symptoms fare similarly to patients who are asymptomatic in whom disease is detected by urethral wash (reference 17 in article), surveillance with urethral wash cytology remains the standard of care.

The current study supports the selective application of prophylactic urethrectomy with close monitoring of the retained urethra. Long-term followup is imperative because the risk of urethra TCC persists with time. This management philosophy fits with a strategy of more liberal use of orthotopic neobladder reconstruction in men with adequate sphincter function who are highly motivated to be free of an external appliance and who accept the risk of incontinence.

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