Published in final edited form as:

J Urol. 2008 November ; 180(5): 1933–1937. doi:10.1016/j.juro.2008.07.039.

Urethrectomy following cystectomy for bladder cancer in men: Practice patterns and impact on survival

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Abstract

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

Methods—2401 men who underwent radical cystoprostatectomy between 1991 and 2002 were identified in the SEER-Medicare database. A multivariate logistic regression model was used to analyze factors driving the performance of urethrectomy. We then analyzed men who received urethrectomy ($n = 195$) to find predictors of receiving it as salvage for urethral recurrence vs. concurrently with cystoprostatectomy or as a staged procedure. Using a multivariate Cox regression analysis, we analyzed if performance of urethrectomy had an independent effect on disease specific survival.

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

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

Introduction

The reported incidence of urethral recurrence after radical cystoprostatectomy for transitional cell carcinoma (TCC) of the bladder varies from 4 to 17%^{1,2}, with one large review suggesting a 10.1% recurrence rate³. Complete urethrectomy is the treatment of choice for urethral recurrence, having been shown to be superior to local transurethral resection³. Because of the poor prognosis following urethral recurrence, prophylactic urethrectomy is also used for patients at high risk of recurrence. This is most often advocated for patients with TCC of the prostatic urethra or tumor invading the prostatic stroma⁴. Tumor multiplicity, papillary pattern, CIS, tumor at the bladder neck, prostatic urethral mucosal involvement, and prostatic stromal invasion each confer risk for urethral recurrence in an additive manner⁵. More contemporary data suggest that prostate urethral involvement maybe the only important pathologic predictor of subsequent urethral recurrence⁶. The poor prognosis of urethral recurrence can be related to the high prevalence of metastatic disease in these patients. In one study of 1054 patients who underwent radical cystectomy, urethral recurrence was documented in 47. 36 had died at a median follow up of 26 months, including 25 of metastatic disease⁷. However, the overall independent benefit of performing urethrectomy either concurrently with cystectomy or for subsequent isolated recurrence is not clear. For purposes of this study reappearance of a metachronous urothelial cancer in the unresected urethra was considered a “recurrence” of the urothelial cancer though it could also be construed as a “second primary” tumor. In addition, to our knowledge, there are no published reports on 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 for performance and timing of a urethrectomy. We also sought to investigate if urethrectomy offers any independent survival benefit.

Methods

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

In a multivariate logistic regression analysis, we investigated the effects of the various clinicopathologic factors on the probability of a patient receiving a urethrectomy vs. a 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 (Caucasian or other), hospital type (rural, urban, or teaching), tumor grade, tumor stage, and Charlson comorbidity score¹⁰.

In a second multivariate logistic regression model, we compared the same characteristics between patients who had an immediate or staged urethrectomy (within 6 weeks of cystoprostatectomy) and those patients who had a delayed (urethrectomy 6 weeks or later after cystoprostatectomy) procedure to identify predictors of receiving planned urethrectomy.

Finally, using a Cox proportional hazards model¹¹ incorporating stage (AJCC 3rd ed.), grade, age, race, type of hospital (urban, rural or teaching), comorbidities, and the timing of urethrectomy (within 6 weeks, after 6 weeks, or never), we analyzed if performance of urethrectomy (in those who did undergo the procedure) had an independent effect on disease specific survival. All statistical analyses were performed using SAS 9.0 (SAS Institute, Gary NC) and a two tailed p value of <0.05 was considered statistically significant.

Results

2401 men underwent radical cystoprostatectomy between 1991 and 2002 in the SEER Medicare linked database, with an overall median follow up of 29 months (range 0–143). Of these men, 195 (8.1%) ultimately underwent urethrectomy. 103 (53%) of these were simultaneous or staged procedures performed within 6 weeks of cystoprostatectomy, presumably for positive margins, or prophylaxis against a high risk of recurrence. The remaining 92 were deemed to have been performed for observed urethral recurrence after a median interval of 9 months (range 2–79) post cystectomy. On univariate analysis, the three 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, with the delayed urethrectomy group having a higher percentage of Stage I disease and the immediate urethrectomy having a higher percentage of Stage IV disease ($p < 0.0001$) (Table 1).

In the multivariable analysis, age, race, hospital, tumor grade and comorbidities were not significant independent predictors of performance of urethrectomy. However, both Stage I and Stage IV cancers were significantly less likely to undergo cystectomy alone than Stage III (OR = 0.257, 0.265 for stage I and IV, respectively) (Table 2).

Among those men who ultimately received a urethrectomy, the only factor predictive of receiving a delayed (>6 weeks post cystoprostatectomy) rather than simultaneous or staged urethrectomy was undergoing the cystoprostatectomy at a teaching hospital rather than an urban one (OR = 2.601, 95% CI = [1.189, 5.690]).

In our Cox proportional hazards model, independent predictors of disease-specific survival included age, race, comorbidities, and tumor stage (Table 3). The survival of men who underwent urethrectomy concurrently with cystoprostatectomy was not significantly different from those who did not undergo urethrectomy at all (hazard ratio = 0.775, CI 0.592 – 1.014). The disease specific survival in men who received early or concomitant urethrectomy was no different compared to those who underwent a delayed urethrectomy >6 weeks after the initial cystoprostatectomy.

Discussion

Urethral involvement requiring urethrectomy at the time of or following radical cystectomy is an uncommon event, occurring in 8.1% of our dataset, which is similar to the 10.1% found in a large review³. 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 cases⁵.

Stage is the most important factor in determining whether a urethrectomy is performed, as this is also the most significant indication for urethrectomy. The finding of a lower incidence of urethrectomy in Stage III cancer is 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 urethrectomy¹². However, the SEER data base uses the 1988 3rd edition of the AJCC guidelines^{9,13}. Under that staging system, invasion of the prostate is considered Stage IV cancer. While this explains the relatively low incidence of urethrectomy in Stage III urothelial cancer, it does not account for the strikingly high incidence in Stage I cancer. This is not a result of small numbers, as 109 of 195 urethrectomies were performed for Stage I disease. It is possible that those individuals had pan-urothelial disease or multifocal CIS which may have prompted the urethrectomy. The stage grouping used in the SEER dataset includes Ta, T1 and CIS under Stage I¹³, not allowing us to further address this issue. In contrast, the immediate urethrectomy group had a higher proportion of Stage IV disease, which is consistent with these patients having urethrectomy for prostatic involvement or positive margins at the time of surgery.

The lower likelihood of concurrent urethrectomies at teaching hospitals may be related to the increasing use of orthotopic continent diversions, which preclude a urethrectomy. A previous study showed that treatment at academic medical centers and NCI-designated cancer centers was independently associated with receiving continent reconstruction¹⁴. However, another possible explanation is that these hospitals perform a higher proportion of urethrectomies for recurrence due to a high rate of referral to academic centers for that procedure after cystectomy 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 diversions preclude 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. Subsequent recurrences were then treated with urethrectomy, with no evidence of local recurrence or metastasis¹⁶.

In our retrospective dataset, the timing of urethrectomy did not appear to impact survival. This however, 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 earlier¹⁷. Moreover, a previous study suggests that there is no difference in either surgical morbidity or survival between immediate and staged urethrectomy¹⁸. The true independent benefit of a urethrectomy can perhaps be best identified by comparing the survival of a group of men who had urethrectomy for isolated local recurrence in the urethra to another group who had a similar disease recurrence with or without distant metastases but did not undergo urethrectomy. The current population based datasets do not provide such information nor can it be discerned from the current staging system making this analysis impossible to perform using this data source.

The limitations of our study include the lack of data regarding adjuvant chemotherapy. We were unable to stratify stage I disease according to the presence of CIS which may have been an important driver of urethrectomy. We also do not have data regarding prostatic urethral margin status at the time of cystectomy which may have determined the need for concurrent or staged urethrectomy. Interpretation of our survival data may be confounded by selection bias. We are also unable to assess the presence of new metastatic disease that occurred along

with localized urethral disease in patients who underwent delayed urethrectomy but made the assumption that these patients would not have undergone the urethrectomy if there was evidence of systemic disease at the same time. It is interesting to note that in spite of undergoing delayed urethrectomy, these patients' survival was no different from those who did not undergo urethrectomy. It is expected that the patients who only underwent cystectomy included those who had no involvement or subsequent recurrence in the urethra as well as those who had a urethral recurrence along with metastatic disease elsewhere that developed during follow-up. Due to the retrospective nature of these data, the survival effect of urethrectomy must be interpreted cautiously because of the possibility for selection bias that a multivariate model cannot account for. One such selection or ascertainment bias could arise from the fact that some patients may develop urethral recurrence several years following cystectomy and the follow up in this study may not be long enough to capture these patients. Even in these studies demonstrating the likelihood of urethral recurrence long after cystectomy, such patients constitute a minority with 42% of the recurrences occurring within 1 year of cystectomy⁷. In those patients who died with urethral recurrence, most of the deaths were from metastatic disease. However, these data are still valuable in that they provide information regarding 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 transitional cell carcinoma. Primary tumor stage (I or IV) is the strongest factor driving the performance of urethrectomy, with delayed urethrectomy significantly more likely to be performed for Stage I disease. Performance of urethrectomy either around the time of cystoprostatectomy or >6 weeks following cystoprostatectomy does not appear to yield a significant independent survival advantage. These data may have implications in selecting patients for orthotopic continent urinary diversions

Acknowledgements

Supported by National Institute of Health T32 Grant DK07790-01 (JLN)

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Table 1
A univariate analysis comparing clinicopathological characteristics of groups by urethrectomy.

		Urethrectomy Timing		p-value
	None	<6 weeks	>6 weeks	
Grade				0.27
1	54 (2.4%)	<5	<5	
2	370 (16.8%)	18 (17.5%)	19 (20.7%)	
3	1212 (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	1246 (56.5%)	59 (57.3%)	56 (60.9%)	
80–99	260 (11.8%)	9 (8.7%)	9 (9.8%)	
Race				0.7786
Caucasian	2009 (91.7%)	95 (92.2%)	86 (93.5%)	
other	182 (8.3%)	8 (7.8%)	6 (6.5%)	

Table 2

The logistic regression analysis demonstrating that only stage predicted performance of a urethrectomy. The odds ratio represents the relative probability of having a cystectomy alone; i.e., the odds of NOT having a urethrectomy.

Variable	Odds Ratio		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
Comorbidity *				
0 or 1	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

* Charlson score⁹

Table 3

Cox proportional hazards analysis demonstrating that age, race, comorbidities, and stage increased risk of disease-specific death.

Variable	Hazard Ratio		95% CI	p-value
Urethrectomy				
within 6 weeks	0.775	0.592	1.014	0.0632
after 6 weeks	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
Comorbidity *				
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

* Charlson score⁹