

## URETHRAL TUMOR RECURRENCE FOLLOWING CYSTECTOMY AND URINARY DIVERSION: CLINICAL AND PATHOLOGICAL CHARACTERISTICS IN 768 MALE PATIENTS

JOHN P. STEIN,\* PETER CLARK, GUS MIRANDA, JIE CAI, SUSAN GROSHEN  
AND DONALD G. SKINNER

*From the Departments of Urology and Preventive Medicine, University of Southern California Keck School of Medicine and the Kenneth Norris Comprehensive Cancer Center, Los Angeles, California*

### ABSTRACT

**Purpose:** We evaluated the incidence and risks of urethral recurrence following radical cystectomy and urinary diversion in men with transitional cell carcinoma of the bladder.

**Material and Methods:** Clinical and pathological results were evaluated in 768 consecutive male patients undergoing radical cystectomy with intent to cure for bladder cancer with a median follow-up 13 years, including 397 (51%) who underwent orthotopic urinary diversion with a median followup of 10 years and 371 (49%) who underwent cutaneous urinary diversion with a median followup of 19 years. Demographically and clinically these 2 groups were well matched with the only exception being longer median followup in the cutaneous group ( $p < 0.001$ ). Urethral recurrence was analyzed by univariate and multivariable analysis according to carcinoma in situ, tumor multifocality, pathological characteristics (tumor grade, stage and subgroup), the presence and extent of prostate tumor involvement (superficial vs stromal invasion) and the form of urinary diversion (cutaneous vs orthotopic).

**Results:** A total of 45 patients (6%) had urethral recurrence at a median of 2 years (range 0.2 to 13.6), including 16 (4%) with an orthotopic and 29 (8%) with a cutaneous form of urinary diversion. Carcinoma in situ and tumor multifocality were not significantly associated with an increased risk of urethral recurrence ( $p = 0.07$  and  $0.06$ , respectively). The presence of any (superficial and/or stromal invasion) prostatic tumor involvement was identified in 129 patients (17%). Prostate tumor involvement was associated with a significantly increased risk of urethral recurrence ( $p = 0.01$ ). The estimated 5-year chance of urethral recurrence was 5% without any prostate involvement, increasing to 12% and 18% with superficial and invasive prostate involvement, respectively. Patients undergoing orthotopic diversion demonstrated a significantly lower risk of urethral recurrence compared with those undergoing cutaneous urinary diversion ( $p = 0.02$ ). Patients without any prostate tumor involvement and orthotopic diversion (lowest risk group) demonstrated an estimated 4% year chance of urethral recurrence compared with a 24% chance in those with invasive prostate involvement undergoing cutaneous diversion (highest risk group). On multivariate analysis any prostate involvement (superficial and/or invasive) and urinary diversion form remained independent and significant predictors of urethral recurrence ( $p = 0.035$  and  $0.01$ , respectively).

**Conclusions:** At long-term followup urethral tumor recurrence occurs in approximately 7% of men following cystectomy for bladder transitional cell carcinoma. Involvement of the prostate with tumor and the form of urinary diversion were significant and independent risk factors for urethral tumor recurrence. Patients undergoing orthotopic diversion have a lower incidence of urethral recurrence compared with those undergoing cutaneous diversion. Although prostate tumor involvement is a risk factor for urethral recurrence, it should not preclude orthotopic diversion, provided that intraoperative frozen section analysis of the urethral margin is without evidence of tumor.

**KEY WORDS:** bladder; bladder neoplasms; carcinoma, transitional cell; urethra; urethral neoplasms

The advent of orthotopic lower urinary tract reconstruction has arguably improved quality of life in patients following cystectomy for bladder cancer.<sup>1–3</sup> Only those who explicitly desire cutaneous urinary diversion have significantly compromised renal function or those found to have a positive margin at the proximal urethra on intraoperative frozen

section are specifically excluded from orthotopic reconstruction.

Since the initial application of orthotopic diversion, increasing enthusiasm to preserve the urethra following cystectomy has been seen. The historical incidence of urethral recurrence in the retained urethra following cystectomy for bladder cancer is 6% to 10%.<sup>4,5</sup> Specific clinical and pathological risk factors that may provide risk assessment for urethral recurrence are multifocal tumors, carcinoma in situ (CIS), tumor involvement of the prostate, particularly invasion of the prostatic stroma, and the form of urinary diversion (orthotopic or cutaneous) performed.<sup>4–10</sup>

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Study received ethics committee and institutional review board approval.

\* Correspondence: Department of Urology, University of Southern California, Norris Comprehensive Cancer Center, MS #74, 1441 Eastlake Ave., Suite 7416, Los Angeles, California 90089 (telephone: 323-865-3709; FAX: 323-865-0120).

Because orthotopic diversion has evolved into a more common and standard form of diversion, coupled with longer followup in these patients, it becomes imperative from a cancer perspective to evaluate the outcomes of and risk factors for tumor recurrence of the retained urethra. We evaluated our experience with the incidence of and associated risk factors for urethral recurrence in male patients undergoing radical cystectomy.

#### MATERIALS AND METHODS

**Patients.** An established ethics committee and institutional review board approved, comprehensive computerized bladder cancer/cystectomy database was used to report outcomes in all patients who underwent cystectomy and urinary diversion for bladder transitional cell carcinoma (TCC). The records and clinical outcomes of 1,054 consecutive patients previously reported on during a 26-year period were reviewed.<sup>11</sup> A total of 768 men were included in the final study analysis. Excluded from study were 210 women (20%) and 76 men (9%) who underwent prophylactic urethrectomy at surgery or shortly thereafter (within 3 months postoperatively) because of concerns found on final pathological evaluation of the cystectomy specimen.

From June 1971 through December 1997, 768 male patients with a median age of 66 years (range 27 to 93) who underwent radical cystectomy were analyzed (table 1). Median followup in the entire cohort of 768 patients was 13 years (range 2 to 30). Median followup in 397 patients (51%) undergoing orthotopic diversion was 10 years (range 2 to 15) and it was 19 years (range 2 to 30) in 371 (49%) undergoing a cutaneous form of diversion, that is a conduit or continent cutaneous reservoir. All patients in this study had at least 2 years of followup.

**Followup and clinical presentation.** All patients were followed postoperatively at 4-month intervals for year 1, 6-month intervals for year 2 and annually thereafter, as previously described.<sup>11</sup> Urethral or voided cytology studies were generally performed on an annual basis, although it was modified in patients deemed at higher risk for urethral recurrence or if the clinical scenario indicated. Specific clinical details and outcomes in patients with urethral recurrence have been reported previously, including most commonly symptomatic recurrence (57%) and asymptomatic with abnormal cytology (31%).<sup>12</sup> Notably all patients classified as having urethral recurrence had pathological biopsy and tissue available to confirm the diagnosis.

**Pathological findings.** All bladder tumors were primary TCC. Tumor grading was performed according to the method of Bergkvist et al.<sup>13</sup> Pathological staging was performed ac-

ording to American Joint Committee criteria using the 1997 TMN staging system.<sup>14</sup> All cystectomy specimens were pathologically examined by the same pathological protocol, as described previously.<sup>11</sup> No attempt was made to perform whole mount sections on any bladder or prostate cystectomy tissue.

Pathological stage and subgroups for the cohort included 434 patients (57%) with organ confined, lymph node negative disease, 156 (20%) with extravesical, lymph node negative disease and 178 (23%) with lymph node positive disease (table 2). No differences were observed in pathological stages and/or pathological subgroups when comparing patients undergoing orthotopic vs cutaneous diversion ( $p = 0.54$ , table 2).

Overall 670 of 768 patients (87%) had high grade tumors. CIS was present in 430 patients (56%) and tumor multifocality was observed in 482 (62%). There was no difference in the distribution of high grade tumors, presence of CIS and tumor multifocality when comparing patients undergoing orthotopic vs cutaneous urinary diversion (table 1).

The presence and extent of tumor involvement of the prostate were classified as none—no tumor involvement of the prostatic urethra, prostatic ducts or prostatic stroma, superficial—involving the prostatic urethra or ducts without stromal invasion and invasive—involving the prostatic stroma. Cases of superficial and/or invasive involvement of the prostate were also combined and classified as any prostate tumor involvement.

A total of 639 patients (83%) demonstrated no evidence of tumor involvement of the prostate. Superficial tumor involving the prostatic urethra and/or prostatic ducts without evidence of invasion of the prostatic stroma was found in 78 cases (10%). Invasive tumor involving the prostatic stroma was identified in 51 patients (7%). Overall 129 patients (17%) demonstrated some superficial or invasive evidence of prostate tumor involvement. No difference was observed in the incidence of superficial and invasive prostatic tumor involvement when comparing patients undergoing orthotopic vs cutaneous diversion ( $p = 0.33$ , table 1).

**Form of urinary diversion.** Patients were evaluated and stratified according to the form of urinary diversion. A total of 397 patients (51%) who underwent diversion to the urethra (Kock, Studer or T pouch) were classified as the orthotopic group. The remaining 371 patients (49%) who underwent urinary diversion to the skin (ileal/colon conduit, Kock, right colon reservoir or double T pouch) were classified as the cutaneous group. Comparison of the orthotopic and cutaneous groups demonstrated no significant difference with regard to age, pathological stage, pathological subgroups, tumor grade, CIS, tumor multifocality, or the presence or

TABLE 1. Demographic and pathological characteristics of 768 male patients undergoing radical cystectomy and urinary diversion for bladder TCC

	Total	Diversion		p Value
		Orthotopic	Cutaneous	
No. pts (%)	768 (100)	395 (51)	371 (49)	
Median age (range)	66 (27–93)	66 (36–85)	65 (27–93)	0.60 (Wilcoxon test)
Median yrs followup (range)	13 (2–30)	10 (2–15)	19 (2–30)	<0.001 (Wilcoxon test)
No. urethral recurrences (mean % at 5 yrs $\pm$ SE)	45 (7 $\pm$ 1)	16 (5 $\pm$ 1)	29 (9 $\pm$ 2)	0.018 (log rank test)
No. CIS (%)	430 (56)	221 (56)	209 (56)	0.85 (Pearson chi-square test)
No. multifocal tumors (%)	482 (63)	239 (60)	243 (65)	0.13 (Pearson chi-square test)
No. high grade tumors (%) <sup>13</sup>	670 (87)	343 (87)	327 (88)	0.47 (Pearson chi-square test)
No. pathological subgroups (%):				
Organ confined (includes prostatic ureters + ducts)*	434 (57)	231 (58)	203 (55)	
Extravesical†	156 (20)	75 (19)	81 (22)	
Lymph node pos	178 (23)	91 (23)	87 (23)	0.59 (Pearson chi-square test)
No. prostate involvement (%):				
Superficial (includes prostatic ureters & ducts)	78 (10)	36 (9)	42 (11)	
Invasive (into prostatic stroma)	51 (7)	23 (6)	28 (8)	0.33 (Pearson chi-square test)
None	639 (83)	336 (85)	301 (81)	

\* Lymph node neg P0, Pa, PIS, P1, P2a, P2b.

† Lymph node neg P3, P4.

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