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PROSTATIC URETHRAL BIOPSY HAS LIMITED UTILITY IN COUNSELING PATIENTS REGARDING FINAL URETHRAL MARGIN STATUS DURING ORTHOTOPIC NEOBLADDER RECONSTRUCTION

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Abstract

Purpose—To determine the value of preoperative transurethral (TUR) prostatic urethral biopsy in predicting final distal urethral margin status at radical cystectomy.

Materials and Methods—Out of 1006 patients undergoing radical cystectomy at our institution between 1990 and 2004, 252 were male patients who underwent ileal neobladder and form the basis of this report. Variable collected include pathology of prostatic urethral biopsies, final pathology of the prostate, frozen section of the distal urethra, final urethral margins, and survival data.

Results—Median age of patients was 61. Of 252 patients, 245 had data regarding pre-operative TUR prostatic urethral biopsy and/or frozen section of urethra at time of surgery: 127 patients had TUR of the prostatic urethra alone, 68 had urethral frozen section alone, 50 had both. The incidence of positive distal urethral margin (on final pathology) was 1.1% (3/252) and urethral recurrence was 0.7% (2/252). The correlation between TUR findings and frozen section margins was only 68%; 16 patients with positive TUR findings had negative frozen section margins. The negative predictive value of TUR biopsy with respect to final margins was 99.4% and that of frozen section was 100%.

Conclusion—While patients with no tumor on TUR biopsy of the prostatic urethra have a high likelihood of negative urethral margins on final pathologic evaluation, optimal negative predictive value is obtained with frozen sections. Furthermore, a positive TUR prostatic urethral biopsy does not correlate with final margin and should not exclude patients from consideration for an orthotopic diversion.

Keywords

bladder cancer; cystectomy; neobladder; prostatic urethral biopsy; counsel

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INTRODUCTION

Radical cystectomy with pelvic lymph node dissection (PLND) is the gold standard for treatment of muscle-invasive urothelial carcinoma (UC) of the bladder. Ileal neobladder has gained increasing popularity as a form of urinary diversion in patients undergoing radical cystectomy for UC, in part due to reports showing equivocal oncologic efficacy with potentially improved quality of life in selected patients compared with ileal conduit diversions.[1–5]

Several groups have recently reported pelvic recurrence rates following radical cystectomy and orthotopic diversion ranging from 10 to 15% with 0.5% to 5% of these recurrences occurring in the urethra.[6–10] It is estimated that between 0.5% to 18% of patients with invasive TCC of the bladder will develop urethral recurrences following radical cystectomy.[7, 11–13] Risk factors that have been associated with increased urethral recurrence include multifocal disease, carcinoma in situ (CIS), tumor located at the bladder neck, a positive transurethral (TUR) prostatic urethral biopsies, prostatic stromal invasion, positive urethral margin on frozen section, and non-orthotopic urinary diversion.[14] Although it is generally accepted that patients with high risk for urethral recurrence should not be advised to undergo an ileal neobladder, some authors still advocate an ileal neobladder as long as negative margins of urethral frozen section are obtained.[7] Reports on the value of prostatic urethral biopsy are conflicting: some authors recommend TUR biopsy of the prostatic urethra to counsel patients on the feasibility of orthotopic urinary diversion while others rely on findings at frozen section examination of the urethral margin during radical cystectomy. Here we sought to determine the value of preoperative transurethral (TUR) prostatic urethral biopsy in predicting final distal urethral margin status at radical cystectomy and to correlate this with findings on intra-operative frozen section of the urethra.

MATERIALS AND METHODS

An institutional review board approved search was performed of our bladder cancer database. From 1990 to 2004, 1006 patients underwent radical cystectomy at our center and 272 (27%) received an orthotopic neobladder reconstruction. Of these, 252 patients were males and form the basis of this report. Each patient had a preoperative metastatic work-up that included blood tests, a chest x-ray, computerized tomography (CT) of the abdomen and pelvis, and a bone scan. Patients underwent radical cystectomy for standard indications. Patients with cT4b disease despite chemotherapy or with distant metastasis were excluded from the study. Prior to proceeding with an ileal neobladder, patients underwent either preoperative prostatic transurethral (TUR) biopsies, intraoperative urethral frozen section, or both, at discretion of the surgeon. At our institution, we perform TUR biopsy of the prostatic urethra via transurethral resection at 5 and 7 o'clock from the bladder neck to the verumontanum.[15] Our rationale for this biopsy is not merely to study the urethral mucosa, but also to identify any prostatic stromal involvement (cT4a) in patients whom we deem to be high risk using clinical judgment and are then recommended for neoadjuvant chemotherapy. After surgery, patients were followed with routine blood tests, chest x-rays, CT of the abdomen and pelvis, and bone scans (if indicated) to assess for recurrence of

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disease at predefined intervals. Surveillance of the urethra was performed via history and physical examination, and in select high risk patients, voided urine cytology.

Collected variables included age, clinical stage, lymphovascular invasion, type of urinary diversion, pathology of prostatic urethral biopsies, final pathology of the prostate, frozen section of the distal urethra, final urethral margins, pathological stage, recurrence, site of recurrence, and survival data. Survival was estimated using the Kaplan-Meier method.

RESULTS

General

Median patient age was 61 years (range 53 to 80 years) and median follow-up time was 48 months (range 4 to 161 months). Characteristics of patients are summarized in Table 1. Most patients had ≥ cT2 (63%) lesions; 78 patients (31%) received adjuvant chemotherapy for ≥ pT3 and/or pN+ disease. Pathologic stages were pT0: 26, pTis: 23, pTa: 17, pT1: 31, pT2: 81, pT3: 46, and pT4a: 28. The 5-year disease-specific survival rate was 71.6%.

Urethral Margin, Frozen Section, and TUR findings

A total of 127 patients had TUR of the prostatic urethra alone, 68 had urethral frozen section alone, 50 had both, and 7 had neither; thus a total of 177 patients (70%) had preoperative TUR of the prostatic urethra at 5 and 7 o'clock, and 118 (47%) had urethral frozen sections. As shown in Table 2, twenty-two patients had tumor in the TUR biopsy of the prostatic urethra. Of those, 21 had negative findings on final urethral margins. Notable, one patient had an ileal neobladder despite positive margins on urethral frozen section due to patients' expressed wishes and he subsequently developed recurrence of disease. Overall, 3 patients had positive final urethral margins. Thus the positive predictive value of TUR biopsy of the prostatic urethral was 12.5%. Of the 155 patients with negative TUR finding, one had a positive final urethral margin. No patient with negative frozen section findings had positive final urethral margins. Thus, the negative predictive values of TUR and urethral frozen section with respect to final margins were 99.4% and 100%, respectively. The correlation between TUR findings and frozen section margins among the 50 patients who had both was 68%.

Urethral recurrences occurred in 2 patients out of 252 (0.7%); both had negative TUR of the prostatic urethra, and 1 of whom had negative final urethral margins on the cystectomy specimen. The other patient, as previously mentioned, had positive margins on urethral frozen section and proceeded with an ileal neoabladder due to patients' expressed wishes.

DISCUSSION

We found that while the absence of tumor on TUR biopsy of the prostatic urethra confers a high likelihood of a negative urethral margin on final pathologic evaluation, a positive TUR biopsy correlates poorly with final margin status. The optimal negative predictive value is obtained with urethral frozen sections.

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The most common treatment for invasive bladder cancer is radical cystectomy and urinary diversion. Ileal neobladder reconstruction provides patients with a more natural mechanism to void without the need for an external collection device and have been shown to be associated with an improved quality of life.[16–18] The incidence of urethral recurrence after radical cystectomy ranges from 0% to 18%, with a recent meta-analysis reporting an incidence of 8.1%.[19] Ileal neobladder reconstruction has been shown to be associated with lower risk of urethral recurrences. Stein el al reported a 5% risk of urethral recurrences with orthotopic neobladder reconstruction compared to 9% with cutaneous diversions; whether these findings are due to the proximity of the ileum in exerting a protective effect on the retained urethra or due to a patient selection bias remains controversial.[8] Although patients with multifocal disease, carcinoma in situ (CIS), or tumor located at the bladder neck are reported to be at increased risk of urethral recurrence, many still desire an ileal neobladder. It has been suggested that a TUR biopsy of the prostatic urethra might allow us to counsel such patients on their risk of positive urethral margin and help select patients for appropriate surgery. Our data suggests that a negative TUR biopsy of the prostatic urethra can be used to counsel those patients as they have a high likelihood (99.4%) of a negative final urethral margin; however the converse is not true, and a positive TUR biopsy of the prostatic urethra does not reliably predict for a positive final urethral margin.

At our institution, we perform TUR biopsy of the prostatic urethra via transurethral resection at 5 and 7 o'clock from the bladder neck to the verumontanum. Our rationale for this biopsy is not merely to study the urethral mucosa, but also to identify any prostatic stromal involvement in patients whom we deem to be high risk using clinical judgment since the presence of stromal invasion (T4a) is an indication for neoadjuvant chemotherapy at our center. It is interesting to note, however, that negative TUR findings do not preclude the presence of prostatic stromal invasion; 3 patients in our series had prostatic stromal invasion on final pathology despite negative TUR findings.

We recommend urethral frozen sections on all our patients that undergo orthotopic reconstruction for bladder cancer. While it is tempting to suggest that our findings support the use of intra-operative frozen section in the decision making process, we hesitate to make such a claim. Since most of the surgeons in our institute would not proceed with a neobladder in the face of a positive frozen section, our series is, by definition, biased towards the negative predictive value of frozen section examination of the urethra. Nonetheless, it is reassuring that none of our patients had a positive final urethral margin after a negative intraoperative urethral margin. We have used the final urethral margin status as a reference standard (or denominator) for our study. However, the 2 patients who developed urethral recurrences in our series, 1 had negative final urethral margins: one was pT2N0 and the other pT2N0 but had TCC in the prostatic ducts. Both received adjuvant chemotherapy; one patient recurred after 3 years and was managed with urethrectomy (pTis) and remains free of disease after 49 months follow-up while the second patient developed a pelvic recurrence after 14 months post cystectomy and succumbed to his disease despite salvage chemotherapy.

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CONCLUSION

While patients with no tumor on TUR biopsy of the prostatic urethra have a high likelihood of negative urethral margins on final pathologic evaluation, optimal negative predictive value is obtained with frozen sections. Furthermore, a positive TUR prostatic urethral biopsy does not correlate with final margin and should not exclude patients from consideration for an orthotopic diversion. Thus, pre-operative TUR biopsy of the prostatic urethra appears to have limited utility in the selection of patients for orthotopic neobladder.

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Key of Definitions

TUR	transurethral resection
UC	urothelial carcinoma
CIS	carcinoma in situ
CT	computerized tomography

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Table 1

Characteristics of patients

	Number of patients (%)	
Number of patients	252	
Median age (years)	61 (range 53 to 80)	
Clinical stage		
≤ cT1	88	(35)
cT2	152	(60)
cT3	12	(5)
Pathologic T-stage		
T0	26	(10)
Tis	23	(9)
Ta	17	(7)
T1	31	(12)
T2	81	(33)
T3	46	(18)
T4a	28	(11)
Pathologic N-stage		
N0	210	(83)
N1	32	(13)
N2	10	(4)
Lymphovascular invasion	54	(21)
Preoperative chemotherapy	49	(19)

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Table 2

Urethral Margin, Frozen Section and TUR findings

		Final Margin Status	
		Positive	**Negative**
TUR Biopsy of Prostatic Urethra			
	Positive	1	21
	Negative *	1	154
	Not done	1	74
Intraoperative Frozen Section of Urethra			
	Positive	1	0
	Negative	0	117
	Not done	2	132

* Both patients who developed urethral recurrence had negative TUR biopsy.