The role of preoperative prostatic urethral biopsy in clinical decision-making at the time of radical cystectomy

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GAYA JM, MATULAY J, BADALATO GM, HOLDER DD, HRUBY G, MCKIERNAN J. The role of preoperative prostatic urethral biopsy in clinical decision-making at the time of radical cystectomy. *Can J Urol* 2014;21(2):7228-7233.

Introduction: *Involvement of the prostatic urethra by bladder cancer directly impacts prognosis, risk of urethral recurrence, and timing of radical cystectomy (RC); it also affects the type of urinary diversion chosen. Both cold cup biopsies and transurethral (TUR) loop biopsies have been used to evaluate the status of the prostatic urethra. We report our 20 year experience with preoperative and intra-operative prostatic urethral biopsies in order to determine relative efficacy and associated treatment implications.*

Materials and methods: *The Columbia University urologic oncology database was reviewed and yielded 234 men who underwent preoperative endoscopic biopsies of the prostatic urethra before RC between 1990 and 2010. Two techniques were described: 1) cold cup biopsy, and 2) TUR loop biopsy. We evaluated the sensitivity, specificity, and predictive values for these respective techniques relative to the final pathological status of the prostatic urethra (PU) in the RC specimen.*

Results: *Of the 234 urethral biopsies 115 (49.1%) were cold cup and 96 (41.1%) were TUR loop biopsies. In the remaining 9.8% of patients, the technique could not be determined. Eighty-one preoperative biopsies (34.6%) revealed involvement of the urethra. No differences were observed in predictive values, sensitivity, and specificity between the two preoperative techniques. The negative predictive value (NPV) was higher than positive predictive value (PPV) for both preoperative approaches. Thirty-eight patients (16.2%) had a urethral frozen section analysis done intra-operatively. Only 1 patient (3%) had an abnormality on frozen section, being the negative predictive value (NPV) higher than the positive predictive value (PPV) for the test's ability to predict the status of the final urethral margin. Urethrectomy was performed at cystectomy in 52 patients with a positive biopsy; 15 (28.8%) of these patients ultimately had a negative PU on final pathology. Only 2/182 (1%) of the patients with an intact urethra presented with a urethral recurrence with a median follow up of 30.5 months.*

Conclusions: *Preoperative prostatic urethral biopsy does not adequately predict final prostatic urethral status at radical cystectomy. No differences in predictive capacity could be detected with either cold cup biopsy or TUR biopsy. Intra-operative biopsy of the prostatic urethra is predictive of a negative urethral margin. Simultaneous radical urethrectomy should not be performed based up on preoperative prostatic urethral biopsy results alone.*

Key Words: prostatic urethra, transurethral biopsy of urethra, frozen section, radical cystectomy

Introduction

Transurethral resection (TUR) including muscularis propria is necessary to accurately stage urothelial cell carcinoma (UCC) of the bladder. Current American Urological Association guidelines for the treatment of muscle-invasive bladder UCC recommend radical cystoprostatectomy (RC) with extended pelvic lymph node dissection. The type of urinary diversion is in turn contingent on a combination of factors, one of which includes the calculated risk of recurrence within the retained urethra.

Following cystectomy in men, the rate of recurrence in the pendulous urethra ranges from 3.7% to 6% for all diversions, with the estimated frequency of 0.5% to 4% for orthotopic diversions alone.[1-4] Prostatic urethral involvement at any level (urothelium, periurethral ducts, or stroma) is associated with a greater risk of

Accepted for publication January 2014

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urethral recurrence, whether detected on endoscopic biopsy or postoperatively on final pathological specimen.[4-8] The utility of preoperative urethral biopsy for planning urinary diversion is controversial, as it has a reportedly high sensitivity but poor specificity when compared to intra-operative frozen section.[9,10] The high false positive rate may lead to a large number of aborted orthotopic reconstructions and unnecessary urethrectomies in patients undergoing preoperative biopsy for the purposes of planning urinary diversion.[9]

To date, no studies have reported on the relative efficacy of urethral cold cup biopsy versus TUR biopsy of the prostatic urethra for predicting the pathologic urethral status at the time of RC. The increased volume and depth of tissue sampled using TUR should in theory provide better accuracy and greater prognostic information (i.e. prostatic stromal involvement) for the risk of recurrence postoperatively. Accordingly, this study sought to compare preoperative TUR and cold cup urethral biopsy results to the final pathological status following RC in order to determine what role, if any, each should play in preoperative planning of urinary diversion.

Materials and methods

Patient selection and evaluation

The institutional review board-approved Columbia University urologic oncology database was queried for bladder cancer cases involving radical cystectomy following endoscopic prostatic urethral biopsy. From 1990 to 2010, 546 men underwent a radical cystectomy at our center for muscle-invasive disease or high grade non muscle-invasive disease. We excluded patients treated with intravesical (immunotherapy or chemotherapy) between transurethral preoperative biopsy and RC and also the ones who received neoadjuvant chemotherapy since these have the potential to alter the final status of the urethra on final pathology. Two hundred and thirty-four patients met the inclusion criteria and had available clinical and pathologic data. The type of pre-operative biopsy employed (cold cup versus TUR loop) was done at the discretion of the surgeon. In terms of the TUR biopsy, the loop was applied at the 5 and 7 o'clock positions and resection was carried out from the bladder neck to the verumontaum. Surveillance of the urethra was performed using history, physical exam, and cytological analysis of periodic voided urine or the urethral barbotage-wash.

We evaluated demographic information, clinical and pathologic stage, the presence of high risk features (high grade disease, carcinoma in situ, lymphovascular invasion), the pre and postoperative assessment of urethral status, and the type of diversion performed. At same time, all operative reports were retrospectively reviewed to classify the endoscopic biopsy technique employed. In the cases were urethral frozen section was performed urethral status was analyzed and compared with final pathological urethral status in RC specimen. The subset receiving urethrectomy at the time of RC was further analyzed to determine whether the rates of pendulous urethral recurrence varied based on final status of the prostatic urethra.

Statistical analysis

In order to examine the ability of each of the biopsy technique to predict the final urethral status at the time of radical cystectomy; sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were determined for the endoscopic preoperative biopsies (cold cup and TUR) combined and separately as well as the intra-operative frozen sections. All analysis was performed using STATA 11.0 software.

Results

The overall cohort

A total of 234/546 (42.8%) of men undergoing RC during the study period were identified who had undergone preoperative endoscopic biopsy with information on urethral status before and after RC. Clinical and demographic characteristics of the cohort are shown in Table 1. The majority of patients were Caucasian (81.2%); the median age of this population was 68 years (mean 66.9 +/- 11.0) and patients were followed for a median of 34 months after endoscopic biopsy of the prostatic urethra. The preponderance of patients were clinical stage T2 (107/234, 45.7%) and underwent surgery involving construction of an ileal conduit (148/234, 63.2%). In terms of high risk features, the majority of patients had high grade disease (81.2%) and associated CIS (76.9%), while lymphovascular invasion was seen in 33.3% of patients.

Urethral biopsy technique

A total of 115/234 patients (49.1%) had an endoscopic cold cup urethral biopsy and 96/234 (41.1%) had a preoperative TUR of the urethra; the balance of the patients did not have a technique specified/discernable in the operative report (23/234, 9.8%), Table 2. For each of these approaches, the urothelium was the preeminent layer sampled (206/234, 88.8%); while a minority of patients had a deeper layer represented, with 7.8% (20/234) of specimens

TABLE 1. **Clinical and pathologic characteristics of the cohort**

Variable	Number (%)
Total	234
Race	
Caucasian	190 (81.2)
African American	10 (4.3)
Hispanic	13 (5.5)
Other	21 (9.0)
Clinical stage	
cTx	2 (0.9)
cTis	19 (8.1)
cTa	21 (9)
cT1	68 (29)
cT2	107 (45.7)
cT3	7 (3)
cT4	10 (4.3)
Pathological T stage	
pT0	14 (5.9)
pTa	15 (6.4)
pTis	42 (17.9)
pT1	36 (15.4)
pT2	29 (12.4)
pT3	65 (28)
pT4	33 (14)
Pathological N stage	
N0	169 (72.2)
N+	65 (27.8)
Positive margin	16 (6.8)
High grade	190 (81.2)
Lymphovascular invasion	78 (33.3)
Concomitant CIS	180 (76.9)
Conduit type	
Ileal conduit	148 (63.2)
Mainz I	1 (0.4)
Indiana pouch	13 (5.6)
Studer neobladder	68 (29.1)
Unknown	4 (1.7)
Chemotherapy	
Neoadjuvant	22 (9.4)
Adjuvant	37 (15.8)

containing periurethral ducts, and 3.4% (8/234) having stromal tissue. Comparing the two techniques, the TUR technique achieved a higher proportion of periurethral tissue sampling, with 10.8% versus 6.1% of samples containing periurethral ducts, and 4.3% versus 1.4% samples containing stroma.

TABLE 2. **Urethral and transurethral findings**

Variable	Number (%)
Biopsy technique	
Cold cup biopsy (CC)	115/234 (49.1)
Transurethral urethra	96/234 (41.1)
Unknown	23/234 (9.8)
Urethral layer sampled	
Urothelium	206/234 (88.8)
Periurethral/prostatic ducts	20/234 (7.8)
Stroma	8/234 (3.4)
Endoscopic biopsy of prostatic urethra	
Positive	81/234 (34.6)
Pathologic status of prostatic urethra	
Positive	62/234 (26.4)

Correlations with pathological urethral status

The median time interval between preoperative urethral biopsy and RC was 26 days (mean 51 days). A total of 81/234 specimens (34.6%) were positive on endoscopic biopsy (cold cup and TUR combined) of the prostatic urethra, while only 62/234 (26.4%) were positive at final pathological review, Table 2. A total of 12 patients (7.7%) with a negative preoperative urethral biopsy had urethral involvement on final pathology. This group represents 19.7% (12/61) of final pathologically positive specimens. Conversely, 31/81 (38.2%) of the patients with a positive urethral biopsy of any kind were negative at the time of cystectomy. Table 3 estimates the relative positive predictive value (PPV) and negative predictive value (NPV) based on urethral sampling technique: cold cup biopsy versus TUR. Notably, the sensitivity and specificity of preoperative urethral biopsy in correlation with final pathological prostatic urethral status was estimated at 80.6% and 81.9%, respectively.

TABLE 3. **Accuracy of prostatic urethral biopsy to predict final urethral status in at radical cystectomy**

	Overall*	Cold cup	Transurethral
Sensitivity	80.6%	72%	80%
Specificity	81.9%	88.8%	81.6%
Positive predictive value	61.7%	64.2%	60.1%
Negative predictive value	92.1%	91.9%	92.2%

*overall= cold cup or transurethral biopsy

While preoperative urethral biopsy had a NPV of 91.2%, the PPV was comparably lower at 61.7%. When stratified by biopsy method (TUR versus cold cup), however, the sensitivity and specificity as well as both positive and negative predictive measures comparable between the two methods of biopsy, Table 3.

The NPV of the frozen section intra-operative biopsies was estimated at 100% while the PPV was estimated at 11.1%. Thirty-eight patients (16.2%) in our sample had at least one urethral frozen section performed. Thirty-seven patients (97%) had negative frozen sections. Only one patient was found to have a suspicious finding on frozen section. In this instance, another frozen section was taken, which proved to be definitively negative. Notably this patient did not recur within in urethra and remains. Three patients (8%) with negative frozen sections were found to have involvement of the urethra on final pathological analysis. Only one patient with a negative frozen section (3%) had a recurrence in the pendulous urethra which resulted in a delayed urethrectomy 26 months after cystectomy. Frozen section analysis was found to have a higher NPV than preoperative biopsy (100% versus 91.2%) while having a lower PPV (11.1% versus 62.8%). The frozen sections performed were able to predict the final urethral margin status with 100% sensitivity and 78.9% specificity.

Urethrectomy at RC

Of the 234 patient cohort, 52 had a urethrectomy at the time of RC because of positive endoscopic preoperative urethral biopsy. On final pathologic review of these subjects 37 (71.1%) had urethral tumor involvement and 15/52 (28.8%) urethra was absolutely normal. From the total (29/81) patients with a positive preoperative biopsy who did not have urethrectomy at time of RC, only two patients 2/182 (1.1%) had a recurrence in the pendulous urethra requiring subsequent surgery, Table 4.

TABLE 4. **Urethra management and pathological results**

Management of pendulous urethra	
Urethrectomy at radical cystectomy	52/234 (22.2)
Urethrectomy pts w/ pos prostatic urethra	37/52 (71.1)
Pendulous urethral recurrence	2/182 (1.1)

Discussion

Decision-making regarding the urethra before and after RC for UCC has always been controversial. Many recommend empiric urethrectomy at the time of RC; however the development of orthotopic diversions has complicated this blanket approach. Prior studies have established risk factors for urethral recurrence, such as a previous history of non muscle-invasive bladder cancer, pT2 disease or greater, positive urethral margins, multifocal disease, diffuse carcinoma in situ, as well as involvement of the upper tract and bladder neck localiton.[3,5,11] The most important of these predictors, however, is prostatic urethral involvement, particularly at the level of the stroma.[11,12] Nevertheless, if patients exhibiting any one of these risk factors were excluded from neobladder candidacy, only 30% of patients would qualify for an orthotopic diversion.[7] Accordingly, this study appraised the adequacy of prostatic urethral sampling both preoperative and intra-operatively.

We found that preoperative prostatic urethral biopsy afforded a relatively high NPV of 92.1%, although the PPV was only 61.7%. There was no appreciable variation in the accuracy of biopsy when stratified by the cold cup or TUR technique. Kassouf and colleagues published a report of their experience with 252 patients undergoing TURBT for urothelial carcinoma. A preoperative TUR was performed in 177 of these patients and then compared to the results of final pathology. Within this series, they reported a NPV of 99.4% with a relatively lower PPV of 12.5%. Our population contained more patients with high grade disease means that a negative preoperative biopsy would be more likely to be positive on final pathology in comparison to a cohort with lower grade disease. In contradistinction, Kassouf and colleagues showed that within their cohort, 118 of who received intra-operative frozen section, both the PPV and NPV were 100%.[9] Implying that radical urethrectomy and the choice of urinary diversion should not be performed on the basis of prostatic urethral biopsy status but rather frozen section analysis, as the perioperative and long term recurrence rates within the pendulous urethra correlated poorly with the results of the preoperative results. As such, frozen section analysis of the prostatic apical urethral margin has been suggested as a substitute to preoperative prostatic biopsy given its improved ability to correctly determine the urethral status.[9]

While our evidence suggests that preoperative sampling alone should not guide the decision to undertake a urethrectomy or not, there still remains a place for the preoperative endoscopic sampling.

Our analysis demonstrated that cold cup biopsy and prostatic urethral TUR are comparable techniques for predicting final pathological status of the prostatic urethra. These findings are intuitively surprising given that TUR theoretically removes a deeper portion of the prostatic parenchyma, containing more tissue layers than cold-cup biopsy. This is confounded since TUR loop biopsy may completely remove tumor from the prostatic urethra, thereby eliminating cancer from the specimen. Furthermore, although cold cup biopsy and TUR were no different in their ability to determine positive urethral involvement, this study was not designed to determine whether one technique or the other afforded a better staging mechanism (i.e. the ability to detect pT4a disease). Indeed, this study established that TUR biopsy afforded better stromal sampling. Involvement of the prostatic stroma is associated with a higher risk of urethral recurrence in the long term.[3,7] Given its ability to provide a deeper sample of the prostatic tissue, a TUR loop biopsy may thus prove to be a better prognostic tool.

Urethrectomy is often done in patients with a positive prostatic urethra, at any level, due to concern for a higher risk of UCC recurrence in the pendulous urethra.[1-5,7,10,11,13,14] We observed in our study 28.8% (15/52) of patients underwent uretrectomy at time of RC has a normal urethra in the final pathological review of RC and urerectomy specimen. That means a high number of patients overtreated who did not benefit for uretrectomy. Moreover, of the 182 patients who did not undergo simultaneous urethrectomy with radical cystectomy, only 2 recurred during long term follow up (1.09%). This rate is slightly higher than that reported in the literature of 0.5%-0.7%, although it underscores the point that the rates of urethral recurrence overall are low.[1,9] As seen in our data as well as in prior series, even when endoscopic biopsy is positive, the urethral recurrence rate is low; in fact, in a study by Donat and colleagues, only 11/99 (11%) of the patients who had a positive cold cup biopsy developed a recurrence during the 10 year follow up.[15] Cumulatively, the low PPV of prostatic urethral biopsy and the low rate of pendulous urethral recurrence suggest that urethrectomy is not indicated as a routine pairing with radical cystectomy; and, importantly, the candidate pool for orthotopic urinary diversion may be larger than previously thought.

Despite the importance of the findings described in this work, several limitations warrant further discussion. First, this study is retrospective in nature and thus subject to the variability of different practice patterns and pathologic evaluation over time. Also, despite noting important trends in upstaging rates, we do not have sufficient power to evaluate the impact preoperative biopsy depth has on the correlation with urethra status on final pathology. Frozen section data was also not available to be correlated with preoperative and pathological urethral status as a further comparative variable. Despite these shortcomings, this study sets an important precedent for future evaluation regarding the efficacy of prostatic urethral sampling and patient selection for urethrectomy, which are frequent procedures in urological practice.

Based on the conclusions of our study, endoscopic biopsy in the form of either cold cup or TUR sampling before RC should not be used to determine candidacy for orthotopic diversion. Rather, the biopsy should be used to risk stratify patients in order to optimize perioperative planning and patient counseling. When a prostatic urethral endoscopic biopsy is negative, because of the high NPV and low incidence of late recurrence, perioperative frozen section is not necessary and orthotopic diversion can be performed with minimal risk. When the endoscopic biopsy is positive, neobladder construction is not contraindicated. In this case, a frozen section should be obtained, and, if positive, a urethrectomy and cutaneous diversion is advisable.

Conclusions

Preoperative prostatic urethral biopsy has a low PPV and thus does not adequately predict final prostatic urethral status at radical cystectomy. Also, there was no difference in predictive capacity between cold cup or TUR sampling techniques. Because of the limited prognostic value of preoperative biopsy, as well as the low overall rate of recurrence in the pendulous urethra, urethrectomy should be performed in a carefully selected and well-informed patient population; as a corollary to these findings, the candidate pool for neobladder creation may be larger than previously thought. Further investigation is warranted in a larger subset of patients regarding the relative merits of cold cup versus TUR biopsy techniques, in addition to the long term oncologic/quality-of-life consequences of a retained urethra among patients with a positive prostatic urethra preoperative biopsy. □

References

1. Hassan J, Cookson M, Smith J, Chang S. Urethral recurrence in patients following orthotopic urinary diversion. *J Urol* 2004; 172(4):1338-1341.

2. Nieder AM, Sved PD, Gomez P, Kim SS, Manoharan M, Soloway MS. Urethral recurrence after cystoprostatectomy: implications for urinary diversion and monitoring. *Urology* 2004;64(5):950-954.
3. Stein JP, Clark P, Miranda G, Cai J, Groshen S, Skinner DG. Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. *J Urol* 2005;173(4):1163-1168.
4. Varinot J, Camparo P, Roupret M et al. Full analysis of the prostatic urethra at the time of radical cystoprostatectomy for bladder cancer: impact on final disease stage. *Virchows Archiv* 2009;455(5):449-453.
5. Cho KS, Seo JW, Park SJ et al. The risk factor for urethral recurrence after radical cystectomy in patients with transitional cell carcinoma of the bladder. *Urol Int* 2009;82(3):306-311.
6. Donat S, Wei D, McGuire M, Herr H. The efficacy of transurethral biopsy for predicting the long-term clinical impact of prostatic invasive bladder cancer. *J Urol* 2001;165(5):1580-1584.
7. Freeman JA, Esrig D, Stein JP, Skinner DG. Management of the patient with bladder cancer. Urethral recurrence. *Urol Clin North Am* 1994;21(4):645-651.
8. Wood DP, Montie JE, Pontes JE, Levin HS. Identification of transitional cell carcinoma of the prostate in bladder cancer patients: a prospective study. *J Urol* 1989;142(1):83-85.
9. Kassouf W, Spiess PE, Brown GA et al. Prostatic urethral biopsy has limited usefulness in counseling patients regarding final urethral margin status during orthotopic neobladder reconstruction. *J Urol* 2008;180(1):164-167.
10. Lebret T, Herv JM, Barr P et al. Urethral recurrence of transitional cell carcinoma of the bladder. Predictive value of preoperative latero-montanal biopsies and urethral frozen sections during prostatocystectomy. *Eur Urol* 1998;33(2):170-174.
11. Huguet J, Monllau V, Sabate S et al. Diagnosis, risk factors, and outcome of urethral recurrences following radical cystectomy for bladder cancer in 729 male patients. *Eur Urol* 2008;53(4):785-792 discussion 792-783.
12. Hardeman SW, Soloway MS. Urethral recurrence following radical cystectomy. *J Urol* 1990;144(3):666-669.
13. Freeman JA, Esrig D, Stein JP, Skinner DG. Management of the patient with bladder cancer. Urethral recurrence. *Urol Clin North Am* 1994;21(4):645-651.
14. Huguet J, Monllau V, Sabate S et al. Diagnosis, risk factors, and outcome of urethral recurrences following radical cystectomy for bladder cancer in 729 male patients. *Eur Urol* 2008;53(4):785-792.
15. Donat SM, Wei DC, McGuire MS, Herr HW. The efficacy of transurethral biopsy for predicting the long-term clinical impact of prostatic invasive bladder cancer. *J Urol* 2001;165(5):1580-1584.