Resection of the Intramural Portion of the Distal Ureter during Transurethral Resection of Bladder Tumors: Predictive Factors for Secondary Stenosis and Development of Upper Urinary Tract Recurrence

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Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin

CIS = carcinoma in situ

CTU = computerized tomography urography

IMPDU = intramural portion of distal ureter

MMC = mitomycin C

NMIBC = nonmuscle invasive bladder cancer

TURBT = transurethral resection of bladder tumor

UO = ureteral orifice

UTUC = upper urinary tract urothelial carcinoma

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Purpose: We analyzed the incidence of and predictive factors for ureteral stenosis and recurrent upper urinary tract urothelial carcinoma after resection of tumors located in the intramural portion of the distal ureter.

Materials and Methods: We retrospectively analyzed the records of 2,317 patients who underwent transurethral resection of bladder tumor for nonmuscle invasive bladder cancer, including 112 (4.83%) with tumors involving the intramural portion of the distal ureter. Multivariate Cox regression analysis was done to determine predictive factors for ureteral stenosis and recurrent urinary tract urothelial carcinoma.

Results: At a mean followup of 56 months 17 patients (15.2%) presented with recurrent upper urinary tract urothelial carcinoma and ureteral stenosis had developed in 13 (11.6%). On univariate analysis previous recurrences were associated with both events. On multivariate analysis tumor size 1.5 cm or greater (HR 4.521, p = 0.023) and T1 tumor stage (HR 8.525, p = 0.005) were independent predictive factors for stenosis. Stage T1 in the bladder (HR 7.253, p = 0.001) and carcinoma in situ in the intramural portion of the distal ureter (HR 6.850, p = 0.005) increased the risk of recurrent upper urinary tract urothelial carcinoma. The main study limitation was the lack of information on vesicoureteral reflux due to the retrospective design.

Conclusions: Involvement of the intramural portion of the distal ureter is uncommon. In patients with nonmuscle invasive bladder cancer and involvement of the intramural portion of the distal ureter a stage T1 tumor and a tumor size 1.5 cm or greater are independent predictive factors for distal ureteral stenosis. Moreover, stage T1 and carcinoma in situ in the intramural portion of the distal ureter significantly increase the risk of recurrent upper urinary tract urothelial carcinoma. The urinary tract should be more closely followed in this patient subgroup.

Key Words: ureter; urinary bladder neoplasms; carcinoma; constriction, pathologic; recurrence

Upper urinary tract urothelial carcinoma develops in 2% to 7% of patients with primary bladder cancer.[1] Patients who present with a history of bladder cancer are at higher risk for multifocal and higher stage UTUC recurrences.[1–3] Additionally, patients with tumors located at the trigone

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and distal ureter are more likely to have synchronous UTUC.[4] Despite this, it is unusual to diagnose a tumor in the IMPDU. This normally happens based on the isolated visualization of papillae in the UO or as a finding of tumor in the UO during TURBT.[5] In these cases complete TURBT, including the underlying bladder wall with detrusor muscle or the remaining distal ureter macroscopically free of tumor, must also include wide resection of the ureteral orifice. As a result there is a potentially higher risk of ureteral scarring with subsequent development of a UO/distal ureteral stricture with consequent upper urinary tract obstruction during followup. There is also a higher risk of recurrent UTUC.[5–7]

We analyzed predictive factors for the development of UO/distal ureteral stricture as well as the incidence of recurrent UTUC after TURBT/excision of tumors located in the IMPDU and/or associated bladder cancer.

MATERIALS AND METHODS

This is a retrospective analysis of longitudinal followup data from our database of 2,317 patients who underwent TURBT for NMIBC between February 2004 and September 2011. A total of 112 medical records of patients treated with tumors involving the IMPDU were reviewed. In accordance with our specific institutional protocol and current European guidelines tumor resection was performed in fractions, including the exophytic part of the tumor, the underlying bladder wall with detrusor muscle and the edges of resection areas for tumors greater than 1 cm in diameter.[8] The TURBT specimen of the IMPDU was always sent separately for histological analysis. Muscle invasive bladder tumors were excluded from study. To rule out a synchronous tumor in the more proximal ureter or the renal pelvis our protocol recommends perioperative imaging of the upper urinary tract. Specifically, excretory urography or CTU was done in all of our cases.

The surgical technique consisted of complete transurethral resection of the bladder tumor and the IMPDU, avoiding ureteral detachment. Generally, when the single UO was resected and the distal ureter was macroscopically free of tumor, a Double-J® stent was not deemed necessary. In cases with extensive resection of the trigone area or with macroscopic tumor remaining in the distal ureter after resection a Double-J catheter was left in place for 2 weeks.

All cases underwent adjuvant treatment with BCG while MMC was considered only in cases of BCG intolerance.[9]

The study was performed according to the guidelines and principles of the Declaration of Helsinki and standard ethical conduct for research involving humans. The study also guaranteed compliance at all times with Law 15/1999 on Protection of Personal Data (Spanish Government). The ethics committees for clinical research at the center approved this study.

Followup

All patients underwent ultrasound 1 month after Double-J stent removal/UO resection. When hydronephrosis was noted, CTU was performed. Followup comprised CTU at 3 months and every 6 months thereafter. Ureterorenoscopy after adjuvant BCG was performed in cases of remaining tumor in the IMPDU after UO resection or during followup when the diagnosis was doubtful or positive cytology was found.

We defined the presence of a UO/distal ureter stricture as unequivocal ureteral obstruction requiring intervention. Bladder followup comprised cystoscopy and cytology every 3 months for the first 2 years and every 6 months thereafter. Pathological staging was performed according to the TNM system and grades were assigned using 2004 WHO criteria.

Statistical Analysis

Descriptive statistics are expressed as the mean $\pm$ SD, and median and IQR with valid percents for continuous and categorical data, respectively. Relationships between principal outcomes (stenosis and UTUC recurrence) and relevant variables were analyzed using the chi-square test (the Fisher exact test for observed frequencies less than 5) for categorical variables. Continuous variables were tested using the t-test. The Mann-Whitney U test was used when variables were not normally distributed.

Sociodemographic and clinical variables that showed $p < 0.2$ in the association with outcomes on univariate analysis were used to construct the corresponding 2 backward stepwise multivariate Cox regression models. Some qualitative variables with more than 2 categories (ie pathology findings, tumor grade, tumor size and number of previous recurrences) included in the final models were recoded into 2 categories to increase statistical power. Statistical significance was considered at $p < 0.05$. Statistical analysis was performed with SPSS®, version 19.

RESULTS

From our database of 2,317 patients with NMIBC 112 (4.83%) with a mean age of 69 years and a mean followup of 56 $\pm$ 46 months underwent resection of the IMPDU. Recurrence developed in the bladder in 17 patients (15.2%). Of the resected tumors 65 (58%) were primary and 68 (61%) were symptomatic at diagnosis (supplementary table, http://jurology.com/). In 102 patients (91%) perioperative excretory urography was performed and 12 (10.7%) underwent CTU to rule out synchronous UTUC.

Pathological examination of intramural tumors revealed Ta in 64% of cases, T1 in 27.7% and CIS in 17% (supplementary table, http://jurology.com/). Due to extensive resection in the trigone area a Double-J catheter was placed in 36 cases (31%). Based on EAU (European Association of Urology) guidelines[8] 74 patients (66.1%) received an immediate postoperative MMC instillation. Furthermore, 25 (22.3%) and 85 patients (75.9%) received adjuvant MMC and BCG, respectively.

UTUC developed in 17 patients (15.2%) at a median of 22 months (IQR 9–116). The location was the distal ureter in 65.4% of cases. Ten UTUC recurrences (59%) were invasive or high grade and they were treated with nephroureterectomy. Distal ureteral stenosis developed in 13 patients (11.6%) at a median of 47 days (IQR 16–268). Seven of these patients (54%) also presented with recurrent UTUC during followup ($p < 0.0001$), which was located in the distal ureter in 6 of 7 patients. Furthermore, on univariate analysis we observed no statistically significant differences in catheter placement with respect to the incidence of recurrent UTUC (7 of 36 vs 10 of 76, $p = 0.387$) or ureteral stenosis (3 of 36 vs 10 of 76, $p = 0.457$).

Immediate postoperative MMC instillation was administered in 74 patients (66.1%). On univariate analysis we observed a tendency toward higher UTUC recurrence in patients who did not receive the postoperative instillation (8 of 74 vs 9 of 38, $p = 0.072$).

Recurrent Tumor Association with Ureteral Stenosis and UTUC

Of the tumors 47 (42%) were recurrent, including 37 (33%) with 2 or more recurrences. On univariate analysis we observed statistically significant differences between primary and recurrent tumors with respect to the incidence of symptoms at diagnosis (60% vs 26%, $p < 0.001$), development of ureteral stenosis (4.6% vs 21.3%, $p = 0.007$) and incidence of UTUC (4.6% vs 29.8%, $p < 0.001$). Among the 13 patients with ureteral stenosis the treatment was de-obstructive TURBT in 6 (46%), ureteral reimplantation in 5 (38%) and balloon dilation in 2 (15%).

Ureteral Stenosis and Recurrent UTUC Predictive Factors

Univariate analysis revealed that previous recurrence, a recurrent tumor 1.5 cm or greater, and stage T1 disease in the bladder and the IMPDU compared to Ta and CIS in the IMPDU were associated with a higher risk of ureteral stenosis during followup. When backward stepwise multivariate Cox logistic regression analysis was applied to identify variables related to stenosis, it showed that primary tumors were associated with a significantly decreased risk of stenosis (HR 0.106, $p = 0.025$). Tumor size 1.5 cm or greater (HR 4.521, $p = 0.023$) and stage T1 in the IMPDU (HR 8.525, $p = 0.005$) increased the probability of stenosis (see table).

The same methodology was used to identify variables related to recurrent UTUC. Univariate analysis revealed that previous recurrence, tumor size 1.5 cm or greater, stage T1 tumor in the bladder and IMPDU (vs stage Ta), high grade in the bladder and IMPDU (vs low grade), and associated CIS in the bladder and IMPDU were associated with a higher risk of UTUC recurrence. In the final multivariate Cox model primary tumors were also associated with a decreased probability of recurrent UTUC (HR 0.039, $p = 0.003$) while stage T1 in the bladder (vs Ta) (HR 7.253, $p = 0.001$) and CIS in the IMPDU (HR 6.850, $p = 0.005$) increased the risk of recurrent UTUC (see table).

DISCUSSION

Resection of the IMPDU is necessary when primary papillary lesions are present at that location whether as presenting symptoms or as an incidental finding during TURBT adjacent to the IMPDU. It is difficult to assess the specific incidence of such involvement of the IMPDU, given that most studies of the issue are outdated, included only a limited number of patients and were subject to important selection biases.[10–12] Contemporary series from single institutions indicate an incidence of up to 10%.[13] In our study, which to our knowledge is the largest published series of this specific subset of patients, the incidence was 4.83%. On this basis involvement of the IMPDU represents an uncommon event in the setting of primary and recurrent bladder carcinoma.

The most important issues to be evaluated in these tumors are the risks of 1) ureteral stenosis after secondary scarring by TURBT and 2) UTUC development during followup. We evaluated independent predictive factors in our large series of patients.

Several previous groups have suggested that resection of the distal ureter during TURBT does not increase the risk of ureteral stenosis during followup.[10,12,14] However, these studies were again subject to the limitations mentioned. The most recent publications of larger series that applied a specific definition of ureteral obstruction after TURBT demonstrated an incidence of up to 16%.[5,7,13]

The principal issues to be considered with respect to secondary stenosis after TURBT are 1) the incidence, 2) the factors predictive of stenosis during followup and 3) the potential benefit of ureteral stenting during the postoperative period. We defined secondary ureteral stenosis as the presence of unequivocal ureteral obstruction requiring intervention. Using this definition 13 patients (11.6%) in our series experienced secondary stenosis, a finding in accordance with the most recent literature.[13] The intervention performed to resolve ureteral stenosis was de-obstructive transurethral resection in 6 cases (46%).

Backward stepwise univariate and multivariate Cox regression models of ureteral stenosis and recurrent UTUC

	Ureteral Stenosis				Recurrent UTUC			
	Crude HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Crude HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Age	0.957 (0.916–1.001)	0.055	—	—			—	—
Sex:								
Female (referent)	1		—	—	1		—	—
Male	0.741 (0.198–3.519)	0.741	—		0.523 (0.163–1.682)	0.001		
Previous recurrence:			—	—			—	—
No (referent)	1				1			
Yes	5.586 (1.444–11.609)	0.013			4.768 (2.350–8.707)	0.001		
Primary tumor:								
No (referent)	1		1		1		1	
Yes	0.179 (0.046–0.693)	0.013	0.106 (0.015–0.751)	0.025	0.114 (0.031–0.425)	0.001	0.039 (0.003–0.375)	0.003
Size (cm):							—	—
Less than 1.5 (referent)	1		1		1			
1.5 or Greater	5.122 (2.332–8.187)	0.001	4.521 (1.879–7.234)	0.023	4.280 (1.300–9.097)	0.017		
Complete TURBT:			—	—			—	—
No (referent)	1				1			
Yes	0.198 (0.05–0.788)	0.022			0.299 (0.079–1.135)	0.076		
Ureteral stent:			—	—			—	—
No (referent)	1				1			
Yes	1.667 (0.429–6.469)	0.460			0.628 (0.217–1.812)	0.389		
Bladder tumor stage:			—	—				
Ta (referent)	1				1		1	
T1	4.608 (1.379–9.398)	0.014			5.862 (3.485–7.381)	0.001	7.255 (4.251–10.280)	0.001
Bladder tumor 2004 grade:			—	—			—	—
Low (referent)	1				1			
High	1.435 (0.540–3.816)	0.469			10.027 (2.175–26.228)	0.003		
Associated bladder CIS:			—	—			—	—
No (referent)	1				1			
Yes	1.756 (0.490–6.288)	0.387			6.000 (1.996–11.034)	0.001		
IMPDU stage:							—	—
Ta, Tis (referent)	1		1		1			
T1	6.870 (1.997–11.641)	0.002	8.525 (1.257–15.252)	0.005	4.922 (1.664–7.732)	0.004		
IMPDU 2004 grade:			—	—			—	—
Low (referent)	1				1			
High	1.191 (0.373–3.809)	0.469			10.000 (2.159–26.250)	0.003		
Associated IMPDU CIS:			—	—				
No (referent)	1				1		1	
Yes	5.670 (1.646–10.528)	0.006			7.501 (5.825–9.250)	0.001	6.850 (4.202–8.253)	0.006
Treatment:	—	—	—	—			—	—
Mitomycin (referent)					1			
BCG					2.464 (0.525–11.596)	0.300		

To our knowledge our report represents the first study of predictive factors associated with the development of ureteral stenosis during followup. In cases in which complete TURBT of small tumors was achieved, the risk of stenosis did not increase. Nevertheless, the presence of large T1 bladder tumors (vs Ta) and associated CIS in the IMPDU increased the risk on univariate analysis.

On multivariate analysis only tumor size 1.5 cm or greater and stage T1 in the IMPDU were significantly associated with ureteral stenosis. This indicates that specifically large tumors requiring extensive resection in the trigone area to achieve complete TURBT are associated with a significantly increased risk of scarring and stenosis of the distal ureter during followup.

The association of recurrent NMIBC with a higher risk of ureteral stenosis was previously reported in 19 cases in a study from our institution.[5] In the current update we confirmed this association in univariate and multivariate analyses (see table). In our series a Double-J catheter was left in place for 2 weeks only in cases requiring extensive resection in the trigone area. Despite this selection bias ureteral stenting was not predictive of ureteral stenosis and UTUC recurrence on multivariate analysis. Our results confirm previous findings by Mano et al, who avoided stent placement in the majority of cases and concluded that a ureteral stent does not affect the risk of stenosis during followup.[13]

Our results may also suggest that catheter placement does not increase the risk of tumor spilling. Nevertheless, the real value of stenting cannot be determined according to our results due to selection bias since stents were placed only in cases of extensive resection. Other studies in which the decision to perform ureteral stenting was made according to the magnitude of surgical damage to the orifice have also confirmed the lack of benefit.[7] Thus, according to our results stenting may be recommended only to prevent acute pain and edema

during the first 48 hours after surgery, and not for reasons relating to late fibrosis.

Another interesting issue is the incidence of recurrence in the upper tract following initial treatment. The reported incidence of UTUC recurrence in recent studies during followup after TURBT of the IMPDU ranges between 1.2% and 13%.[7,13] In a previous series in 19 cases from our institution we found a 42% incidence of recurrent UTUC.[5] Based on this fact and a meta-analysis demonstrating that BCG was superior to MMC for intermediate and high risk NMIBC we decided to administer BCG in all of our IMPDU cases.[9]

Most of these patients had a history of multiple bladder recurrences. On univariate analysis in this study, in addition to previous recurrence, large tumor size (greater than 1.5 cm), tumor stage T1, high tumor grade, and associated CIS in the bladder and IMPDU were associated with a higher risk of recurrent UTUC (see table). However, on multivariate analysis only recurrent tumors, T1 tumor stage in the bladder and CIS in the IMPDU were independent predictive factors for UTUC recurrence.

Our study has several limitations. The most important one could be the low number of patients who presented with recurrence or ureteral stenosis. That is why the results of multivariate analysis must be considered carefully. To our knowledge our results represent the first approach to future research on this topic. Another limitation is that we did not routinely leave a ureteral catheter in place after TURBT of the ureteral orifice. This represents a selection bias when assessing the predictive role of ureteral stenting with respect to ureteral stenosis.

Moreover, tumor size is often overestimated or reported with lower accuracy. Also, due to the retrospective review of our data we were unable to record updated information that would permit analysis of the effect of vesicoureteral reflux. In this context it was not possible to associate recurrent UTUC with cancer cell implantation due to the presence of reflux or primary multifocal disease.[6,15,16]

CONCLUSIONS

Nonmuscle invasive bladder cancer of the IMPDU is an uncommon event in NMIBC. Recurrent tumors are associated with a higher risk of ureteral stenosis and UTUC recurrence. Nevertheless, on multivariate analysis only tumor stage T1 and tumor size greater than 1.5 cm were independent predictive factors for distal ureteral stenosis. Moreover, T1 nonmuscle invasive bladder cancer and CIS in the IMPDU significantly increased the risk of recurrent UTUC. Therefore, we conclude that closer followup of the urinary tract should be performed in such cases.

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