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

Accepted for publication January 12, 2016.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

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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

0022-5347/16/1961-0052/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2016.01.038
Vol. 196, 52-56, July 2016
Printed in U.S.A.

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.