



Predictive factors of bladder tumor recurrence after radical treatment of upper urinary tract cancer

Facteurs prédictifs de récurrence vésicale après traitement radical des tumeurs de la voie excrétrice urinaire supérieure

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ABSTRACT

Introduction : The main problem after Radical Nephroureterectomy (RNU) for localized non-metastatic upper urinary tract urothelial cancer (NM-UUT-UC) is bladder recurrence.

Aim : To identify factors of bladder recurrence of localized NM-UUT-UC after radical treatment.

Methods : *It is an analytical and observational study that was conducted in the department of urology of La Rabta Hospital in Tunis. We collected the data of patients diagnosed with localized NM-UUT-UC who had RNU between 2005 and 2019.*

Results : The mean age of the 73 eligible patients was 68 years (± 11). The sex ratio was 5/2. Macroscopic hematuria was the revealing clinical sign in 66% of patients, while low back pain was the most frequent sign in 88% of patients. The most frequent tumor stage was pT1 in 20 patients while 32% of them had a pT2-T3 stage. Bladder recurrence was reported in 22% of patients with a median time of nine months [4-27] and extremes of three and 69 months. Factors of bladder recurrence in the univariate analysis were smoking, tumor localization in the ureter and the extravesical excision of the intramural ureter and bladder cuff. On multivariate analysis, the only independent predictor of bladder tumor recurrence was ureteral location (OR=3.65 ; CI95%=[1.02-13.1] ; p=0.047).

Conclusion : Tumor localization in the ureter was an independent predictor of bladder recurrence after radical treatment for localized NM-UUT-UC.

Key words : Ureteral neoplasms; Nephroureterectomy; Risk factors; Recurrence; Urinary Bladder Neoplasms

RÉSUMÉ

Introduction: La récurrence vésicale après Néphro-Urétérectomie Totale (NUT) pour une Tumeur de la Voie Excrétrice urinaire Supérieure (TVES) constitue un problème majeur.

Objectif : Identifier les facteurs de récurrence vésicale des TVES localisées non métastatiques après traitement radical.

Méthodes : Il s'agit d'une étude analytique et observationnelle qui a été menée au service d'urologie de l'hôpital La Rabta à Tunis. Nous avons recueilli les données des patients diagnostiqués avec une TVES localisée traités par NUT entre 2005 et 2019.

Résultats : L'âge moyen des 73 patients éligibles était de 68 ans (± 11). Le sex-ratio était de 2/5. L'hématurie macroscopique était le signe clinique révélateur chez 66 % des patients, tandis que la lombalgie était le signe le plus fréquent chez 88 % des patients. Le stade tumoral le plus fréquent était pT1 chez 20 patients tandis que 32% d'entre eux avaient un stade pT2-T3. Une récurrence vésicale a été rapportée chez 22% des patients avec une durée médiane de neuf mois [4-27] et des extrêmes de trois et 69 mois. Les facteurs de récurrence vésicale dans l'analyse univariée étaient le tabagisme, la localisation de la tumeur dans l'uretère et l'excision extravésicale de l'uretère intramural et de la coiffe vésicale. En analyse multivariée, le seul facteur prédictif indépendant de récurrence de la tumeur vésicale était la localisation urétérale (OR=3,65 ; IC95%=[1,02-13,1] ; p=0,047).

Conclusion : La localisation tumorale dans l'uretère était un facteur prédictif indépendant de récurrence vésicale après traitement radical pour les TVES localisées non métastatiques.

Mots clés : Tumeurs de l'uretère ; Néphro-urétérectomie ; Facteurs de risque ; Récurrence ; Tumeurs de la vessie.

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INTRODUCTION

Upper Urinary Tract Urothelial Cancer (UUT-UC) account for 5 to 10% of Urothelial Carcinomas (UC) with an approximate incidence of 1-2/100,000 inhabitants/year (1). When it is diagnosed at late stages, the survival rate is pejorative with five-year survival rates for stage IV being around 10-15% (1). Bladder recurrence after radical treatment occurs in 30 to 50% of cases which requires regular and restrictive cystoscopy monitoring (2). In the literature, there is no validated nomogram that predicts risk factors for bladder recurrence especially since the incidence of UUT-UCs can vary depending on several factors, including genetics, environmental exposures, and lifestyle factors. It would therefore be beneficial to study these factors of recurrence in many populations worldwide in order to identify the patients most at risk and to adapt surveillance.

The aim of our study was to identify the factors of bladder cancer recurrence after radical treatment of high risk localized non-metataic upper urinary tract urothelial cancer (NM-UUT-UC).

METHODS

It is an analytical and observational study that was conducted in the department of Urology of La Rabta Hospital in Tunis. We collected the data of all patients diagnosed with NM-UUT-UC who had radical surgical treatment between January 2005 and December 2019. Data collection was conducted in December 2021.

We included in our study patients who met all the following criteria : the diagnosis of UUT-UC was made after Computed Tomography Urography (CTU) or ureteroscopy; high-risk UUT-UC defined by muscle invasive lesion on imaging, hydronephrosis, multifocal lesions or tumor size greater than 2 cm (3) ; the treatment was an open Radical NephroUreterectomy (RNU) with excision of the perimeatal bladder cuff ; confirmatory diagnosis of UUT-UC by anatomopathological examination ; patients who had postoperative surveillance by CTU (+ chest CT) every 6 months for 4 years then annually and by cystoscopy every 3 months for 1 year then every 6 months for 2 years then every year and post-operative monitoring period of at least 12 months.

Patients with one or more of the following criteria were not included in the study : history of bladder carcinoma or presence of concomitant neoplasia ; T4 primary tumor according to TNM UIIC 2017 classification of UUT-UC or metastatic disease at the time of diagnosis on imaging or after histological examination of the surgical specimen ; treatment with induction chemotherapy before surgery; postoperative chemotherapy in case of confirmed metastatic disease.

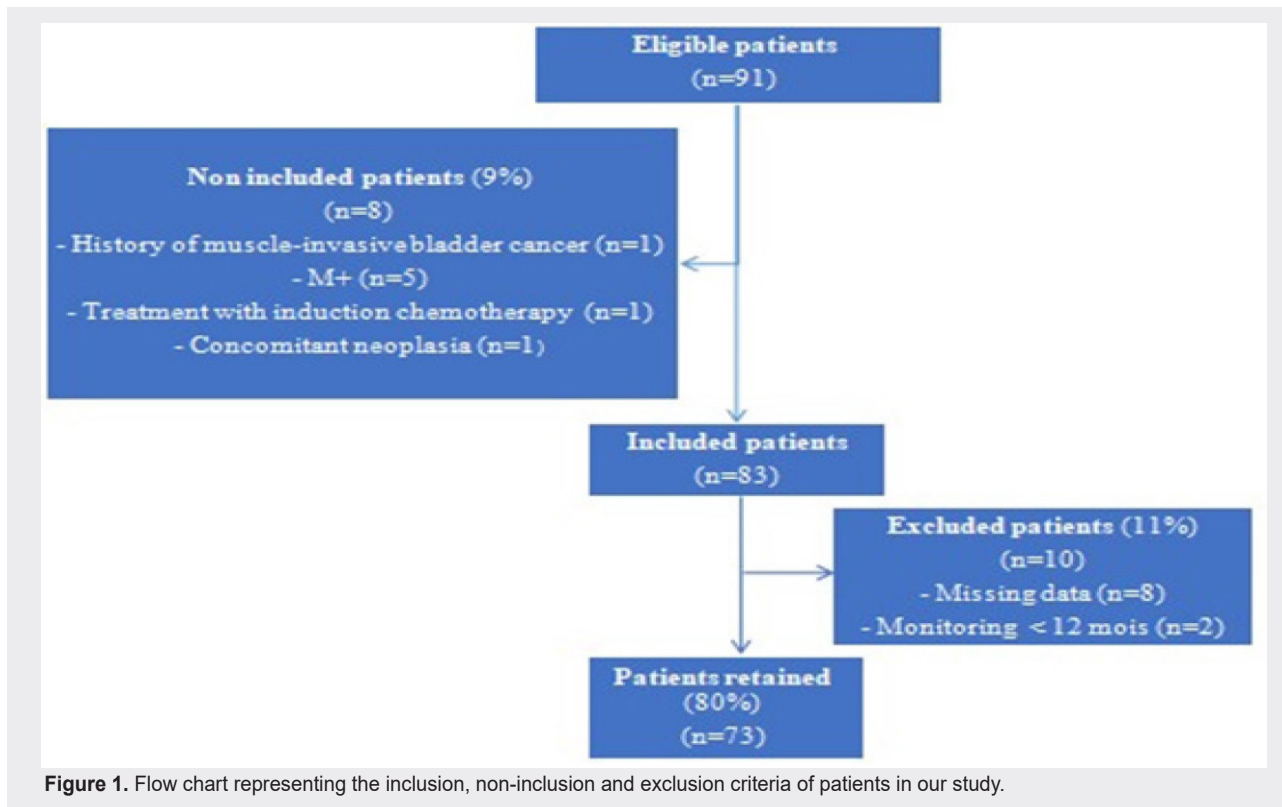
Patients with at least one missing data item related to the inclusion and non-inclusion criteria were excluded from the study.

During the postoperative surveillance period, we recorded for each eligible patient the date of bladder tumor occurrence at follow-up cystoscopy to determine risk factors for bladder cancer recurrence. The setback period was recorded as the date last seen in the medical record.

The data of our study were analyzed using the statistical software SPSS® (official version available at the Faculty of Medicine of Tunis). Categorical variables were described according to their percentage distribution with the 95% confidence interval. For quantitative variables, the data were presented by their means and standard deviations when the distribution was normal and otherwise by the median with the interquartile range [Q1-Q3]. The normality of the distribution was verified by the Kolmogorov-Smirnov test. The search for factors of cancer bladder recurrence after surgical treatment was performed by comparing patients with and without recurrence. They were divided into factors depending on the patient, the tumor and the surgical treatment. The search for these factors was performed by multivariate logistic regression analysis using Wald's top-down method and introducing all risk factors for bladder recurrence in univariate analysis with p values <0.2. Each identified factor was then presented with its adjusted odds ratio (OR) and 95% confidence interval. The 5% significance level (p<0.05) was used for all statistical tests performed in our study.

RESULTS

Of the 91 eligible patients, 73 were retained after applying the non-inclusion and exclusion criteria of our study (Figure 1).



The mean age of the patients was 68 years (± 11) with extremes ranging from 47 to 92 years, of whom 34 (47%) had an age ≥ 70 years. The sex ratio was 5/2. Fifty-three percent of patients were smokers. Ten percent had occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated solvents. Macroscopic hematuria was the revealing clinical sign in 66% of patients, while low back pain was the most frequent sign in 88% of patients. A Performance Status score ≥ 1 was noted in 53% of patients. Forty-one patients had hydronephrosis on CT with right-side involvement in 56% of cases.

The excision of the intramural ureter and bladder cuff was performed by two surgical techniques. An endoscopic approach was carried out on 26 patients and an extravesical open management was performed on 47 patients. Regarding operative complications, an accidental opening of the operating room was observed in two patients and a bleeding requiring a blood transfusion in four. Two patients had a surgical site infection.

A single tumor location (ureteral or in the pyelocalyceal cavities) was found in 88% of patients. The most frequent tumor stage was pT1 in 20 patients while 32% of them had a pT2-T3 stage. High grade tumor was the most frequent in 55% of patients. Three patients had lymph node involvement on the surgical specimen (Table 1).

Table 1. Characteristics of patients diagnosed with clinically localized non metastatic upper urinary tract urothelial carcinoma treated with radical nephroureterectomy between 2005 and 2019.

Variables	Values
Mean Age (years \pm SD)	68 \pm 11
Smoking N (%)	39 (53.42)
Notion of exposure to carcinogens N (%)	7 (9.58)
PS* N (%)	
0	35 (47.94)
≥ 1	38 (52.05)
ASA** N (%)	
1	37 (50.68)
2	35 (47.94)
3	1 (1.36)
Clinical signs N (%)	
Lower back pain	32 (43.83)
Renal colic	8 (10.95)
Macroscopic hematuria	48 (64.75)
Tumoral stage N (%)	
pTa	18 (24.65)
pT1	20 (27.93)
pT2	18 (24.65)
pT3	14 (19.17)
pT4	3 (4.10)
Tumoral grade N (%)	
Low grade	33 (45.2)
High grade	40 (54.79)
Side N (%)	
Right	41 (56.16)
Left	32 (43.83)
Lymphovascular emboli N (%)	12 (16.43)
Tumor necrosis N (%)	12 (16.43)
Carcinoma in situ N (%)	5 (6.84)
Positive surgical margin N (%)	14 (19.17)

At the end of our study period, 50 patients (68%) were still alive. At one year, two patients had died, i.e. a one-year survival rate of 97%.

The follow-up period was less than three years in 22 patients (30%). At five years, 20 patients (27%) had died, 19 patients (26%) were alive and 34 patients (47%) had a follow-up period of less than five years. The median survival was 36 months [20-61] with extremes ranging from eight to 145 months.

During postoperative surveillance, bladder recurrence was reported in 22% of patients with a median time of nine months [4-27] and extremes of three and 69 months.

Of the 38 patients who had tumor localization in the ureter (52%), 12 patients (31.57%) had bladder recurrence. Five patients had tumors in the lumbar ureter, 3 patients in the iliac ureter, and 4 patients in the pelvic ureter. There was no statistically significant association between the tumor portion of the ureter and the occurrence of bladder recurrence.

The univariate analysis of factors of bladder cancer recurrence after RNU was significant for smoking ($p = 0.049$), ureteral location ($p = 0.038$) and the excision of the intramural ureter and bladder cuff by open extravesical surgery ($p = 0.004$). On multivariate analysis, ureteral tumor location was the only independent factor associated with risk of bladder recurrence with $p = 0.047$ (Tables 2 and 3).

Table 2. Univariate analysis of bladder cancer recurrence predictive factors after surgical radical treatment in patients with clinically localized non metastatic upper urinary tract urothelial carcinoma

	Bladder recurrence		OR*	CI95%**	p
	No (N=57)	Yes (N=16)			
Age \geq 70 Years	26	8	1.192	0.393 - 3.618	0.756
Gender					
Male	39	13	0.5	1.005 - 11.580	0.370
Female	18	3			
Smoking	27	12	3.333	1.005 - 11.580	0.049
Hydronephrosis	30	11	1.980	0.610 - 6.431	0.251
Ureteral localisation	26	12	3.577	1.029 - 12.433	0.038
History of bladder tumor	21	10	2.857	0.908 - 8.990	0.067
Tumor stage \geq pT2	26	9	1.533	0.502 - 4.683	0.452
High tumor grade	31	9	1.078	0.353 - 3.294	0.895
Tumor necrosis	10	2	0.671	0.131 - 3.431	0.97
Lymphovascular emboli	8	4	2.042	0.526 - 7.924	0.444
Positive margins	9	5	2.424	0,678 - 8,671	0.278
Intramural ureter excision					
Extravesical	31	16	1.667	1.005 - 2.765	0.004
Endoscopic approach	26	0			

*OR : Odds Ratio ; **CI95% : 95% Confidence Interval

Table 3. Multivariate analysis of bladder cancer recurrence predictive factors after surgical radical treatment in patients with clinically localized non metastatic upper urinary tract urothelial carcinoma.

Variables	OR*	CI95%**	p
Smoking	3.411	0.949 – 12.263	0.06
History of bladder tumour	1.535	0.409 – 5.758	0.525
Ureteral localization	3.655	1.020 – 13.101	0.047
Extravesical ureter excision	3.352	0.952-11.015	0.059

*OR : Odds Ratio ; **CI95% : 95% Confidence Interval

DISCUSSION

In this study, the mean age of the 73 patients was 68 years (± 11). The sex ratio was 5/2. Macroscopic hematuria was the revealing clinical sign in 66% of patients, while low back pain was the most frequent sign in 88% of patients. The most frequent tumor stage was pT1 in 20 patients while 32% of them had a pT2-T3 stage. Bladder recurrence was reported in 22% of patients with a median time of nine months [4-27] and extremes of three and 69 months. Factors of bladder recurrence in the univariate analysis were smoking, tumor localization in the ureter and the extravesical excision of the intramural ureter and bladder cuff. On multivariate analysis, the only independent predictor of bladder tumor recurrence was ureteral location (OR=3.65 ; CI95%=[1.02-13.1] ; $p=0.047$).

The frequency of bladder recurrence has been explained in the literature by several hypotheses. The first hypothesis is the theory of the effect of the terrain associated with urothelial carcinogenesis. The second hypothesis is the intraluminal seeding and implantation of a single transformed cell (4,5).

In the multivariate analysis of our study, only ureteral location was an independent factor for bladder recurrence after RNU. This finding was found in the meta-analysis of Seisen et al. in which it was found that the anatomical proximity between the ureteral location of the primary tumor and the bladder could largely favor the intravesical implantation of an oncogenic cell resulting in bladder recurrence (2). In contrast, Fradet et al. found that ureteral location alone was not a risk factor, but the concomitant presence of UUT-UC in the ureteral and pyelocal cavities was a risk factor for bladder recurrence (6).

In our study, we performed NUT by double approach with extravesical dissection of the bladder neck or by a lumbar approach with endoscopic resection. We compared these two techniques for the removal of the intramural ureter and the bladder neck in terms of bladder recurrence. In this respect, we excluded tumors of ureteral localization, because only the double approach was recommended in this situation. When comparing these two techniques, extravesical dissection increased the risk of bladder recurrence compared with patients who had endoscopic resection (OR=1.667; p=0.004).

In the meta-analysis of Seisen et al. it was shown that extravesical dissection during double-port NUT was a predictive factor for bladder recurrence (2). In contrast, Xylinas et al. found that the endoscopic approach to bladder removal during NUT was a factor in bladder recurrence (7). Another study found that the rate of bladder recurrence was comparable in patients who had endoscopic resection or extravesical dissection via dual-port NUT (8). It is therefore obvious that prospective and randomized studies are necessary to validate the technique that is the least likely to cause bladder recurrence (9).

Through our review of the literature, we have individualized 3 groups of risk factors for bladder recurrence. Patient-dependent factors were male gender, a history of bladder lesions and preoperative chronic renal failure. Tumour-dependent factors were a positive preoperative urine cytology, ureteral localisation, stage \geq pT2 and necrosis. Treatment-dependent factors were laparoscopic approach, extravesical bladder cuff approach and positive surgical margin (10-13). We are aware of the limitations of our study where the main source of bias is the number of patients. This is due on the one hand to the rarity of the studied pathology. On the other hand, we have applied numerous non-inclusion criteria in order to homogenize our population. Nevertheless, this work has reassured us that the endoscopic technique for pyelocaliceal tumors is not only associated with less operative morbidity but also with less bladder recurrence.

In our study which included patients who have had radical nephroureterectomy for localized non-metataic upper urinary tract urothelial cancer, factors of bladder recurrence in the univariate analysis were smoking, tumor localization in the ureter and extravesical excision of the intramural ureter and bladder cuff. On multivariate analysis, the only independent predictor of bladder tumor recurrence was ureteral location

CONCLUSION

Postoperative metamorphopsia could be related to a major macular displacement, which may result in retinal distortions. Thus, the main interest would be to find out how to reduce the macular slide during the pars plana vitrectomy.

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