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Segmental resection of distal ureter with termino-terminal ureteral anastomosis vs bladder cuff removal and ureteral re-implantation for upper tract urothelial carcinoma: results of a multicentre study

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ABSTRACT

Objectives

To compare overall (OS), cancer-specific (CSS), recurrence free survival (RFS) and post-operative renal function among patients affected by upper tract urothelial carcinoma (UTUC) of the distal (lower lumbar and pelvic) ureter, electively treated with segmental resection and termino-terminal anastomosis (TT) vs bladder cuff removal and ureteral re-implantation (RR).

Patients and methods

A multicentre retrospective study, including 84 patients diagnosed with UTUC of the distal ureter and treated with TT or RR, is presented. The primary endpoint was to compare TT and RR in terms of OS, CSS and RFS. As a secondary outcome we compared the post-operative

creatinine values as an index of renal function in the two groups.

Results

Out of 521 patients with UTUC, 65 (77.4%) and 19 (22.6%) patients underwent RR and TT, respectively. Pre- and post-operative characteristics were not statistically different between the two groups. The median follow-up period was 22.7 months. Patients treated with TT and those treated with RR did not show significantly different 5yOS, 5yCSS and 5yRFS (73.7 vs 92.3%, p = 0.052, 94.7 vs 95.4%, p = 0.970, and 63.2 vs 53.9%, p = 0.489, respectively). No difference in post-operative creatinine variation emerged in association with the surgical technique (p = 0.411).

Conclusion

Patients treated with TT or RR for UTUC showed comparable OS, CSS, RFS and post-operative renal function. Our data suggest that the bladder cuff removal is not imperative in the treatment of distal ureteral UTUC, and TT can be a safe solution in selected cases.

KEYWORDS

Renal function;

Segmental ureterectomy;

Survival;

Termino-terminal ureteroureterostomy;

Upper tract urothelial carcinoma;

Ureteral reimplantation.

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a rare malignancy [1, 2] that can be located in the pyelocaliceal cavities and, although less commonly, in the ureter [3]. Despite the fact that radical nephroureterectomy (RNU) with bladder cuff removal is currently considered as the standard treatment [4], recently kidney-sparing surgery (KSS), and in particular open or laparoscopic segmental ureterectomy (SU), has been proposed in selected cases such as solitary kidney, chronic kidney disease and synchronous bilateral disease, together with endoscopic and percutaneous procedures [5].

It is commonly accepted in reconstructive surgery that short and uncomplicated proximal ureteral defects can be treated with direct ureteroureterostomy, while ureteroneocystostomy or ureteroureterostomy can be performed for distal ones, guarantying a tension-free repair [6]. Short term overall (OS), cancer-specific (CSS) and recurrence free survival (RFS) in a recent meta-analysis in patients treated for UTUC did not significantly differ between SU and RNU [7]. Moreover, RNU could be associated with a significant decrease of renal function in comparison with SU. Data for survival and functional outcome are missing on a long-term follow-up and even less is known about functional outcomes and survival among patients undergoing different surgical techniques of ureteral anastomosis after SU for UTUC.

Considering this gap in literature, the aim of our study was to compare the OS, CSS and RFS among patients undergoing surgery for UTUC, electively treated with segmental resection of the distal ureter and termino-terminal anastomosis (TT) vs bladder cuff removal and ureteral reimplantation (RR). As a secondary endpoint, the impact of the surgical technique on post-operative renal function was evaluated.

PATIENTS AND METHODS

Study design

Data from patients treated for UTUC in six Italian tertiary referral centres (Bologna, Genoa, Milan, Palermo, Trieste, Turin) from January 2003 to December 2013 were collected. All consecutive patients underwent TT or RR for UTUC of the distal (lower lumbar and pelvic) ureter were included in the analysis. All patients were diagnosed with UTUC at computed tomography (CT) or magnetic resonance (MR) imaging. Preoperative ureteroscopy with biopsy was performed when indicated for doubtful imaging. Other preoperative data included age, gender, smoking status, creatinine value (mg/dl), symptoms, urine cytology, tumour site, hydronephrosis, stage and grade of previous bladder tumour. Patients with a history of previous UTUC, metastatic disease, radical cystectomy or other malignancies were excluded. Patients were treated with SU and TT or RR according to tumour location. Pathological data included T and N category, carcinoma in situ detection, grade, number of lymph nodes dissected, lymph vascular invasion, tumour necrosis, surgical margin status and the presence of concomitant bladder cancer. Patients underwent follow-up every 3 months the first year after surgery, 4 months the second year, 6 months from the third to the fifth year, and then annually, according to the most recent international guidelines [8]. Creatinine plasmatic levels, recurrence and the necessity of chemotherapy were recorded.

Statistical analysis

Statistical analysis was performed by one of the authors (MS). Patient characteristics were compared at baseline and the end of the follow-up period, using the Student's t-test or Mann-Whitney U test for continuous variables and χ^2 for categorical variables. The primary outcome of the current study was to compare TT and RR in terms of OS, CSS and RFS. Thus un-adjusted 5-year (5y)OS curves of the two groups were compared by using the Kaplan–

Meier method, while CSS and RFS were compared by using the cumulative incidence method [9]. A multivariate Cox regression adjusted for technique, age, gender, chemotherapy and recurrence was used to estimate Hazard Ratios (HR). As a secondary outcome, we investigated the delta creatinine (post-operative minus pre-operative creatinine) in the two groups. In particular, a multivariate Cox regression adjusted for technique, age, gender, tumour side and localization, hydronephrosis, tumour pathological stage, chemotherapy and pre-operative creatinine was used to calculate HR. Post-hoc power analyses for unadjusted analyses were performed by using power calculation methods described by Freedman [10], Schoenfeld [11] and Latouche [12]. In particular, we computed if with our study sample we were able to observe an HR of 8.7, 0.01, and 0.05 for 5yOS, 5yCSS, and 5yRFS between TT and RR, respectively. Statistical analyses were performed with R v3.3.3. A p value < 0.05 was considered as statistically significant.

RESULTS

We retrospectively collected the data of 521 patients treated for UTUC from 2003 to 2013 in six selected Italian centres. Overall, 84 patients underwent segmental resection of the ureter for a distal ureteral UTUC; 65 (77.4%) and 19 (22.6%) patients underwent RR and TT, respectively. In terms of pre-operative characteristics, only the localization of the tumour and the performance of an endoscopic biopsy prior to surgery showed statistically different distribution among patients treated with RR and TT ($p < 0.001$ and $p = 0.046$, respectively; **Table 1**). Overall only four cases of perioperative complications were reported: three Clavien-Dindo grade 2 (fever requiring antibiotics) and one grade 3 (intravesical bleeding requiring endoscopic treatment). Four (3 after RR and 1 after TT) ascertained anastomotic strictures were reported, but endoscopic correction was required in only two of them. Post-operative pathological characteristics including stage, grade, number of lymph nodes

dissected, lymphovascular invasion, necrosis, positive surgical margins and presence of concomitant bladder cancer were not statistically different between the two groups (**Table 2**). The median follow-up period of the study population was 22.7 months (range 0.5 - 120 months). Overall, 9 (10.7%) and 24 (28.6%) patients locally had ureteral and bladder recurrence, while 4 (4.8%) patients developed metastatic disease, showing a comparable distribution between the two groups (p = 0.061, **Table 3**). No statistically significant difference in terms of 5yOS, 5yCSS and 5yRFS was detected among patients treated with TT and RR (73.7 vs 92.3%, p = 0.052, 94.7 vs 95.4%, p = 0.970, and 63.2 vs 53.9%, p = 0.489); (**Figure 1**) respectively. Post hoc power analyses revealed that for expected HRs we had a statistical power of 0.80. At the multivariable adjusted analysis the type of reconstructive technique, gender and age were not significantly associated with OS, CSS and RFS: post-operative chemotherapy was the only significant determinant for CSS with a HR of 9.86 (95%CI 1.31 - 74.42, p = 0.03; **Figure S1**).

No statistically significant difference was observed for post-operative creatinine variation among patients treated with TT and RR (delta creatinine 0.0 ± 0.3 and 0.1 ± 0.2 mg/dl, respectively; p = 0.383). In the adjusted analysis, statistically significant determinants for post-operative creatinine variation were preoperative creatinine level (HR 0.35, 95%CI 0.10 - 0.60; p = 0.010), male gender (HR 0.31, 95%CI 0.10 - 0.52; p = 0.006), left side location (HR 0.37, 95%CI 0.09 - 0.64; p = 0.012) and pT3 disease (HR 0.50, 95%CI 0.09 - 0.91; p = 0.020), irrespective of the surgical technique (p = 0.411; **Figure 2**).

DISCUSSION

In this multicentre retrospective study we compared the OS, CSS and RFS of two different ureteral reconstruction techniques after SU for distal ureteral UTUC. Interestingly, patients treated with TT and RR showed comparable 5yOS, 5yCSS and 5yRFS.

Although it is known that up to 70% of ureteral tumours occur in the distal ureter, 25% in the mid-ureter, and 5% in the proximal ureter [13], RNU is widely indicated as the standard treatment for UTUC, regardless of tumour localization [4], and the removal of the entire ureter seems to be mandatory. In fact, it has been discussed that total excision of the distal ureter with its intramural portion, including the ipsilateral ureteric orifice and bladder cuff, is essential for optimal treatment of UTUC [14]. Clearly the rationale for the indication of excising all the affected upper urinary tract derives from the observation of a high disease recurrence rate in the remaining ureteral stump after a simple nephrectomy [15].

However, chronic kidney disease has been reported in 52% of patients with UTUC at diagnosis, with this rate significantly increasing to 78% after RNU with a median relative reduction in renal function of 21% [16] and an estimated glomerular filtration rate decrease of 9.32 ml/1.73 m^2 ($p = 0.007$) after RNU in comparison with SU [7]. Nowadays, KSS is acceptable in selected cases of anatomical or functional solitary kidney, bilateral disease or severe renal insufficiency to avoid the morbidities frequently following RNU [17]. KSS and RNU have been compared on heterogeneous patients' population and the available data are therefore highly variable and difficult to adapt to common clinical practice [18].

Recently, a meta-analysis published by Fang et al. in 2016 found no significant differences between SU and RNU in terms of CSS (unadjusted HR 0.90, 95%CI 0.73 - 1.11; $p = 0.33$) [7]. Although some concerns have been raised about the dissimilar distribution of T stage and grade between the two treatment groups, no significant differences were detected in terms of CSS in patients with non-muscle invasive UTUC [19] and high-grade disease [20]. Also OS (HR 0.98, 95%CI 0.63 - 1.53; $p = 0.93$) and RFS (HR 1.06, 95%CI 0.76 - 1.48; $p = 0.72$) appeared to be comparable between SU and RNU [7].

Translating the experience from the RNU to the KSS, it is common practice to excise the bladder cuff also for the distal ureteral UTUC with consequent ureteral re-implantation.

However it has not yet clearly been demonstrated if any differences exist–for functional and oncological outcomes among patients treated with RR and TT for UTUC.

Both ureteroneocystostomy or ureteroureterostomy have been suggested with good outcomes for benign and malignant ureteral diseases. Wenske et al [21] reported excellent functional outcomes without significant morbidity in a population of 100 patients undergoing ureteral re-implantation by psoas-hitch, Boari flap, or ureteroneocystostomy for benign ureteral obstruction or UTUC, with no statistically significant difference between the three different surgical techniques. On the other hand, open end-to-end ureteroureterostomy resulted to be effective and safe in treating iatrogenic lower ureteral injury at 33.7 months median follow-up [22]. A ureteral patency rate of 96% has also been reported in patients treated with open ureteroneocystostomy or ureteroureterostomy with no significant difference adopting a laparoscopic approach ($p = 0.544$) at a mean follow-up of 43 months [23]. Moreover ureteroureterostomy showed significantly less estimated blood loss ($p < 0.001$) and lower incidence of vesicoureteral reflux (grade I) on cystography ($p = 0.031$) in comparison with ureteroneocystostomy at a follow-up of 36.5 months [24].

In case of UTUC the different reconstruction techniques are often analysed all together and, to our knowledge, there are no comparative studies between RR and TT in terms of oncologic outcomes. Interestingly in our experience TT and RR showed similar 5yOS, 5yCSS and 5yRFS (**Figure 1**), quite better than those after RNU (data not shown), with a low rate of ureteral (10.7%) and bladder (28.6%) recurrence (**Table 3**). Accordingly, a 5yOS of 40 – 72%, 5yCSS of 54 – 90%, 5yRFS of 28 - 84% and an intravesical recurrence-free survival of 54 - 69% have been reported in patients treated with SU for UTUC [7].

There is no consensus on the role of tumour location in terms of oncologic outcomes for ureteral cancer: in our experience the choice of the reconstructive technique primarily depended on the tumour location and this reflected its different distribution in the two groups

(RR vs TT). This could also explain the different (although not significant) distribution of recurrence reported in the two groups.

We also detected a comparable distribution of post-operative pT stage and grade, reducing the concern about selection bias. Noteworthy, the rate of positive surgical margin is similar between the groups with a slightly higher rate in the RR group in contrast with the common thought.

Considering the post-operative variation of renal function in terms of serum creatinine levels, we found that pre-operative creatinine, male gender, pT3 stage and left side were associated with a significant HR for post-operative creatinine variation. This observation could be partially explained considering that in our population male patients and those with left side tumours also had higher pre-operative creatinine levels (although not statistically significant). Conversely pathological stage had already been associated to renal function [25].

Finally, the main limitation of our study is its retrospective design and the small sample size, partially due to the rarity of the disease. Consequently some probably interesting data, such as the dimensions of the disease at CT scan or previous intravesical chemotherapy, were not available. No pathological data on the concomitant or recurrent bladder cancer and the chemotherapy protocol were available. Another limitation is the lack of data on administration of postoperative instillation after surgery at the Centres included in our study. On the contrary the main strength of our study is its multicentre approach with a validated and shared follow-up scheme. Instead an exhaustive comparison between RNU and SU in terms of oncologic and functional outcomes was beyond the intents of this study.

In conclusion, we report that patients treated with TT or RR for UTUC showed comparable 5yOS, 5yCSS and 5yRFS. Moreover, no significant differences were found in terms of post-operative creatinine variation between the two surgical techniques. Our results could suggest that the bladder cuff removal is not imperative in the treatment of distal ureteral UTUC, and

TT can be a safe solution when feasible in selected cases of common clinical practice.

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CONFLICTS OF INTEREST

None declared.

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LEGENDS TO ILLUSTRATIONS

Figure 1. Comparison between RR and TT techniques in terms of 5-years OS (A), CSS (B) and RFS (C).

Figure 2. Multivariate Cox regression adjusted analysis for post-operative creatinine variation.

Figure S1. Multivariate Cox regression adjusted analysis for OS (A), CSS (B) and RFS (C).

Table 1. Pre-operative descriptive characteristics of the study population.

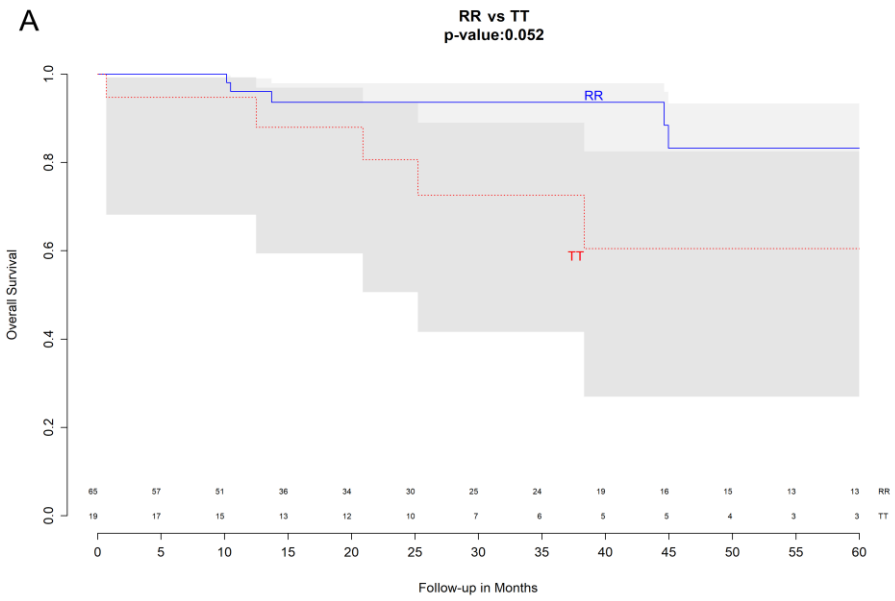
Variable	Total	RR	TT	p-value
Patients	84	65 (77.4)	19 (22.6)	
Age, yr	69.5 ± 9.1	69.8 ± 9.7	68.7 ± 6.8	0.651
Gender				
Male	65 (77.4)	52 (80.0)	13 (68.4)	0.454
Female	19 (22.6)	13 (20.0)	6 (31.6)	
Smoking status – 30 pts				
No	12 (40.0)	11 (45.8)	1 (16.7)	0.402
Yes	18 (60.0)	13 (54.2)	5 (83.3)	
Preoperative serum creatinine, mg/dl	1.04 ± 0.37	1.04 ± 0.39	1.05 ± 0.34	0.964
Symptoms – 43pts				
No	15 (34,9%)	11 (32.4)	4 (44.4)	0.777
Yes	28 (65,1%)	23 (67.6)	5 (55.6)	
Prior endoscopic biopsy				
No	65 (77.4)	54 (83.1)	11 (57.9)	0.046
Yes	19 (22.6)	11 (16.9)	8 (42.1)	
Negative	4 (21.1)	3 (27.3)	1 (12.5)	0.834
Positive	15 (78.9)	8 (72.7)	7 (87.5)	
Prior urine cytology				
No	64 (76.2)	50 (76.9)	14 (73.7)	0.988
Yes	20 (23.8)	15 (23.1)	5 (26.3)	
Negative	12 (60.0)	11 (73.3)	1 (20.0)	0.114
Positive	8 (40.0)	4 (26.7)	4 (80.0)	
Tumor localization				
Intramural	27 (32.1)	27 (41.5)	0 (0.0)	< 0.001
Pelvic	46 (54.8)	33 (50.8)	13 (68.4)	
Lower lumbar	11 (13.1)	5 (7.7)	6 (31.6)	
Tumor side				
Right	31 (36.9)	26 (40.0)	5 (16.3)	0.414
Left	53 (63.1)	39 (60.0)	14 (73.7)	
Hydronephrosis – 44 pts				
No	11 (25.0)	11 (32.4)	0 (0.0)	0.097
Yes	33 (75.0)	23 (67.6)	10 (100.0)	
History of bladder tumor				
No	54 (64.3)	40 (61.5)	14 (73.7)	0.484
Yes	30 (35.7)	25 (38.5)	5 (26.3)	
Prior bladder tumor pT stage – 29 pts				
pTa	11 (36.6)	9 (36.0)	2 (50.0)	0.663
pT1	14 (46.6)	12 (48.0)	2 (50.0)	
CIS	4 (13.8)	4 (16.0)	0 (0.0)	
Prior bladder tumor grade – 28 pts				
G1	7 (25.0)	5 (20.8)	2 (50.0)	0.285
G2	8 (28.6)	8 (33.3)	0 (0.0)	
G3	13 (46.4)	11 (45.8)	2 (50.0)	
Continuous variables are expressed as mean ± SD; nominal variables are expressed as No. (%)				

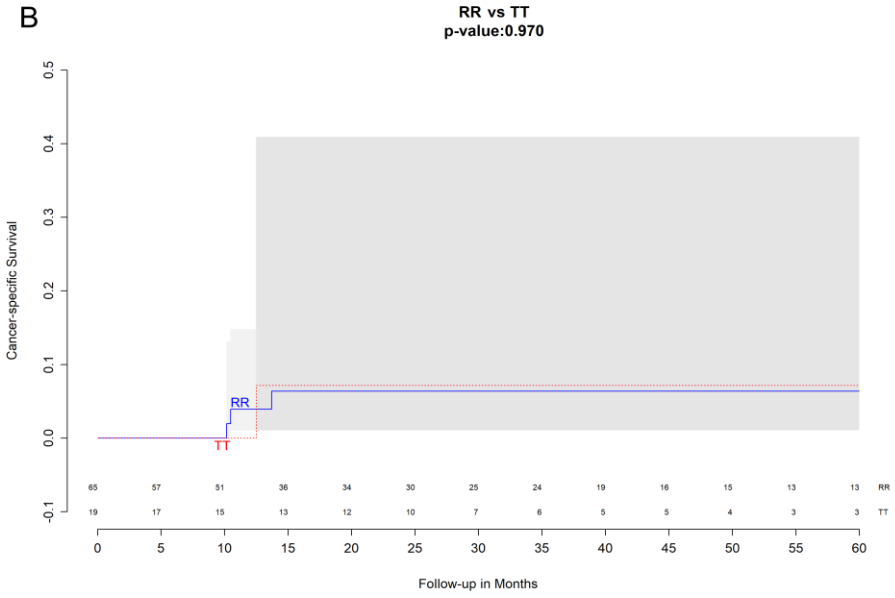
Table 2. Pathological characteristics.

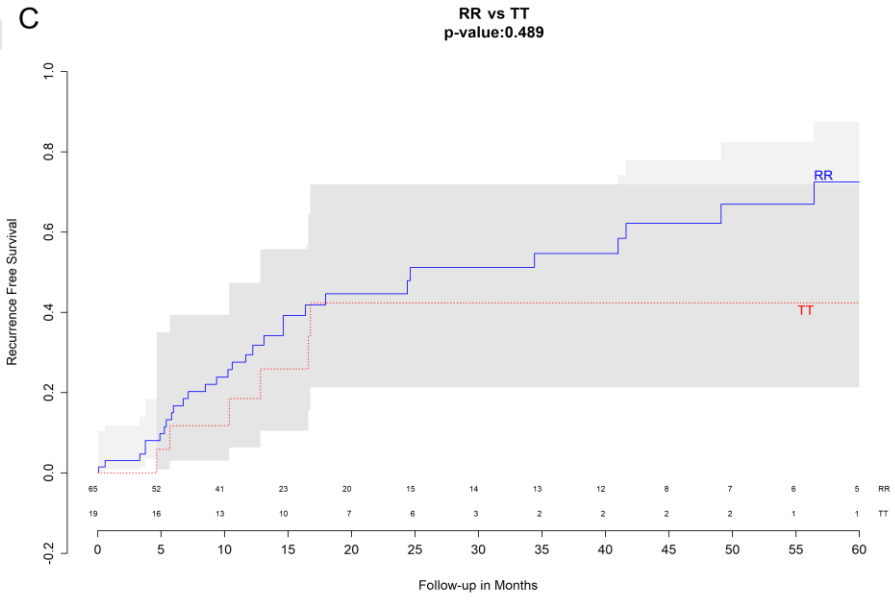
Variable	Total	RR	TT	p-value
Patients	84	65 (77.4)	19 (22.6)	
Pathological T-stage				
pT0	2 (2.4)	1 (1.5)	1 (5.3)	0.721
pTa	30 (35.7)	21 (32.3)	9 (47.4)	
pT1	21 (25.0)	17 (26.2)	4 (21.0)	
pT2	19 (22.6)	16 (24.6)	3 (15.8)	
pT3	11 (13.1)	9 (13.8)	2 (10.5)	
CIS	1 (1.2)	1 (1.5)	0 (0.0)	
CIS associated				
No	81 (96.4)	62 (95.4)	19 (100.0)	0.802
Yes	3 (3.6)	3 (4.6)	0 (0.0)	
Lymph node dissection				
No	65 (77.4)	48 (73.8)	17 (89.5)	0.262
Yes	19 (22.6)	17 (26.2)	2 (10.5)	
No. lymph nodes dissected	1.1 ± 2.9	1.4 ± 3.2	0.1 ± 0.2	0.089
Pathological N-stage				
pN0	17 (20.2)	15 (23.1)	2 (10.5)	0.334
pN1	2 (2.4)	2 (3.1)	0 (0.0)	
pNx	65 (77.4)	48 (73.8)	17 (89.5)	
Grade – 81 pts				
G1	12 (14.8)	7 (11.1)	5 (27.8)	0.173
G2	21 (25.9)	16 (25.4)	5 (27.8)	
G3	48 (59.3)	40 (63.5)	8 (44.4)	
Limph vascular invasion – 46 pts				
No	42 (91.3)	32 (91.4)	10 (90.9)	0.576
Yes	4 (8.7)	3 (8.6)	1 (9.1)	
Necrosis – 83 pts				
No	80 (96.4)	62 (96.9)	18 (94.7)	0.794
Yes	3 (3.6)	2 (3.1)	1 (5.3)	
Surgical margins				
Negative	69 (82.1)	55 (84.6)	14 (73.7)	0.451
Positive	15 (17.9)	10 (15.4)	5 (26.3)	
Concomitant bladder cancer				
No	67 (79.8)	49 (75.4)	18 (94.7)	0.128
Yes	17 (20.2)	16 (24.6)	1 (5.3)	
Continuous variables are expressed as mean ± SD; nominal variables are expressed as No. (%).				

Table 3. Post-operative follow-up.

Variable	Total	RR	TT	p-value
Patients	84	65 (77.4)	19 (22.6)	
Follow-up period, mo	22.7 (14.0 – 29.0)	21.5 (12.2 – 33.3)	25.2 (12.4 – 39.9)	0.769
Post-operative creatinine, mg/dl	1.1 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	0.580
Delta creatinine, mg/dl	0.1 ± 0.3	0.1 ± 0.2	0.0 ± 0.3	0.383
Recurrence				
No	47 (56,0%)	35 (53.8)	12 (63.2)	0.648
Yes	37 (44,0%)	30 (46.2)	7 (36.8)	
Omolateral	7 (18,9%)	3 (10.0)	4 (57.1)	0.061
Contralateral	1 (2,7%)	1 (3.3)	0 (0.0)	
Bilateral	1 (2,7%)	1 (3.3)	0 (0.0)	
Vesical	24 (64,9%)	22 (73.3)	2 (28.6)	
Metastasis	4 (10,8%)	3 (10.0)	1 (14.3)	
Systemic chemotherapy				
No	76 (90,5%)	59 (90.8)	17 (89.5)	0.783
Yes	8 (9,5%)	6 (9.2)	2 (10.5)	
Continuous variables are expressed as median (95%CI) or mean ± SD; nominal variables are expressed as No. (%).				







Variable		Estimate	p
Technique	RR	Reference	
	TT	-0.08 (-0.29, 0.13)	0.411
Gender	Female	Reference	
	Male	0.31 (0.10, 0.52)	0.006
Age		0.01 (-0.00, 0.02)	0.098
Hydronephrosis	No	Reference	
	Yes	-0.18 (-0.46, 0.09)	0.183
pT	pTa	Reference	
	pT0	-0.21 (-0.57, 0.14)	0.218
	pT1	0.00 (-0.20, 0.21)	0.968
	pT2	0.02 (-0.22, 0.26)	0.864
	pT3	0.50 (0.09, 0.91)	0.020
Chemoterapy	No	Reference	
	Yes	0.16 (-0.18, 0.49)	0.338
Cancer localization	Intramural	Reference	
	Pelvic	-0.05 (-0.25, 0.14)	0.575
	Middle	0.13 (-0.25, 0.51)	0.475
Cancer side	Right	Reference	
	Left	0.37 (0.09, 0.64)	0.012
Pre-operative creatinine		0.35 (0.10, 0.60)	0.010