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Urothelial Cancer

Impact of Distal Ureter Management on Oncologic Outcomes Following Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

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Abstract

Background: There is a lack of consensus regarding the optimal approach to the bladder cuff during radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC).
Objectives: To compare the oncologic outcomes following RNU using three different methods of bladder cuff management.
Design, setting, and participants: Retrospective analysis of 2681 patients treated with RNU for UTUC at 24 international institutions from 1987 to 2007.
Intervention: Three methods of bladder cuff excision were performed: transvesical, extravesical, and endoscopic.
Outcome measurements and statistical analysis: Univariable and multivariable models tested the effect of distal ureter management on intravesical recurrence, recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS).
Results and limitations: Of the 2681 patients, 1811 (67.5%) underwent the transvesical approach; 785 (29.3%), the extravesical approach; and 85 (3.2%), the endoscopic approach. There was no difference in terms of RFS, CSS, and OS among the three distal

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ureteral management approaches. Patients who underwent the endoscopic approach were at significantly higher risk of intravesical recurrence compared with those who underwent the transvesical ($p = 0.02$) or extravesical approaches ($p = 0.02$); the latter two groups did not differ from each other ($p = 0.40$). Actuarial intravesical RFS estimates at 2 and 5 yr after RNU were 69% and 58%, 69% and 51%, and 61% and 42% for the transvesical, extravesical, and endoscopic approaches, respectively. In multivariate analyses, distal ureteral management ($p = 0.01$), surgical technique (open vs laparoscopic; $p = 0.02$), previous bladder cancer ($p < 0.001$), higher tumor stage (trend; $p = 0.01$), concomitant carcinoma in situ (CIS) ($p < 0.001$), and lymph node involvement (trend; $p < 0.001$) were all associated with intravesical recurrence. Excluding patients with history of previous bladder cancer, all variables remained independent predictors of intravesical recurrence.

Conclusions: The endoscopic approach was associated with higher intravesical recurrence rates. Interestingly, concomitant CIS in the upper tract is a strong predictor of intravesical recurrence after RNU. The association of laparoscopic RNU with intravesical recurrence needs to be further investigated.

1. Introduction

Radical nephroureterectomy (RNU) with excision of the bladder cuff is the standard of care for high-risk noninvasive and invasive urothelial carcinoma of the upper tract (UTUC) [1]. The outcomes of different bladder cuff management approaches remain poorly investigated [2,3]. Recently, Li et al. [4] reported no difference in oncologic outcomes among three different approaches of the distal ureter (transvesical, extravesical, and endoscopic) in a retrospective single-center study of 301 patients. This study had a relatively small sample size and short follow-up, limiting its statistical power to assess the impact of distal ureteral management approaches on intravesical recurrence. The aim of the current study was to assess the impact of the three, different, distal ureter management approaches on intravesical recurrence-free survival, recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) in a large, international, multicentric cohort of patients treated with RNU.

2. Materials and methods

2.1. Patients

In this institutional review board-approved study, all participating sites provided necessary institutional data-sharing agreements prior to study initiation. A total of 24 centers worldwide provided data. A computerized databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Prior to final analysis, the database was frozen and the final data set was produced for the current analysis.

From 1987 to 2007, 2681 patients underwent RNU with bladder cuff excision for UTUC. None of the patients received preoperative chemotherapy or radiotherapy, and none had previous muscle-invasive bladder cancer. Adjuvant chemotherapy was administered at the clinicians' discretion based on tumor stage and overall health status as well as patient preference.

2.2. Surgical technique

RNU was performed either open or laparoscopically, based on the surgeon's preference. The distal bladder cuff was removed either through a transvesical, extravesical, or endoscopic approach. The transvesical technique was performed via an incision in the lower quadrant or midline. It involved creating an anterior cystotomy in the bladder, confirming the contralateral ureteral orifice, and circumferentially incising the ipsilateral ureteral orifice through the full thickness of the bladder. The RNU specimen with the bladder cuff was removed en bloc and the anterior cystotomy was closed in two layers.

In the extravesical technique, the intramural portion of the ureter was completely dissected. With gentle traction on the ureter, a right-angle clamp or stapler was used to transect the distal ureter with its bladder cuff. The bladder was also closed with a two-layer suture.

In the endoscopic approach, the patient was placed in the lithotomy position and underwent cystoscopy. A resectoscope was inserted into the bladder via the urethra using sterile water for irrigation and the ipsilateral ureteral orifice was endoscopically coagulated. The bladder was kept semidistended to prevent excessive extravasations during the procedure. A hook electrode was used to incise a circumferential 10-mm cuff of bladder mucosa around the ureteral orifice. Endoscopic-guided dissection and incision deep to the level of perivesical fat and detachment of the intramural ureter were performed. After complete hemostasis, the bladder was catheterized. The patient was repositioned for RNU. The first step of RNU was to identify and ligate the ureter below the level of the tumor prior to mobilizing the kidney. After completing nephrectomy, the distal ureter, including the bladder cuff, was gently retracted and removed. The ureter was checked for complete removal by identifying the coagulated edge of the bladder cuff at the distal ureteral end.

2.3. Pathologic analysis

All surgical specimens were processed according to standard pathologic procedures at each institution [5]. Tumors were staged according to the 2002 American Joint Committee on Cancer–Union Internationale Contre le Cancer (AJCC/UICC) TNM classification [6]. Tumor grade was assessed according to the 1998 World Health Organization/International Society of Urologic Pathology consensus classification [7]. Tumor location was defined as either renal pelvic or ureteral [8,9]. Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed tumors in any location (renal pelvis or ureter) [10,11]. Lymphovascular invasion (LVI) was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls [12].

2.4. Follow-up

Patients were followed, generally, every 3–4 mo for the first year following RNU, every 6 mo from the second through the fifth year, and annually thereafter. Follow-up consisted of a history, physical examination, routine

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blood work, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest computerized tomography, or magnetic resonance imaging were performed when clinically indicated [13].

Disease recurrence was defined as tumor relapse in the operative field, regional lymph nodes, and/or distant metastasis; it excluded bladder cancer occurrences. Bladder cancer occurrences were coded as intravesical recurrence. Cause of death was determined by treating physicians, by chart review corroborated by death certificates, or by death certificates alone. To reduce bias in attribution of cause of death, only patients who had UC listed on the death certificate were considered to have died of UTUC for this study [14]. All patients who were coded as dead of cancer had previous disease recurrence. Patients who died in the perioperative period (ie, within 30 d of surgery) were censored at time of death for UTUC-specific survival analyses.

2.5. Statistical analysis

Differences in continuous variables across distal ureter management were assessed using the Kruskal-Wallis test. The chi-square test was used to evaluate the association between categorical variables and the three procedures (transvesical, extravesical, and endoscopic). RFS, intravesical RFS, CSS, and OS curves were generated using the Kaplan-Meier method and compared using the log-rank test. Univariable and multivariable Cox regression models addressed outcomes after RNU. Finally, to support our conclusions, a matched-pair comparative analysis was performed based on the 85 patients who underwent endoscopic distal ureteral management in a 3:1 model. Patients were matched regarding TNM stage and lymph node status. All reported p values were two sided and statistical significance was set at 0.05. Statistical analyses were performed with SPSS v.20.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Association between distal ureteral management and clinicopathologic characteristics in all patients

Of the 2681 patients, 1811 (67.5%) underwent the transvesical approach, 785 (29.3%) underwent the extravesical approach, and 85 (3.2%) underwent the endoscopic approach. Endoscopic management was performed at eight institutions (2 to 54 cases per institution). The distribution of clinicopathologic features and their association with distal ureteral management is shown in Table 1. Compared to patients who underwent the transvesical or extravesical approaches, those who underwent the endoscopic approach were more likely to have been treated using laparoscopic RNU ($p < .01$) and to harbor pelvicaliceal tumors ($p < .01$), and less likely to exhibit tumor multifocality ($p \leq .02$).

3.2. Association between distal ureteral management and clinical outcomes in all patients

The median follow-up in patients alive at last follow-up was 57.5 mo (range: 1–271 mo). Disease recurrence occurred in 748 patients (27.9%), while intravesical recurrence occurred in 577 patients (21.5%); 605 patients (22.6%) died of UTUC, and 966 patients (36%) died of any cause. Actuarial RFS estimates at 2 and 5 yr after RNU were 71% and 66%, 73% and 66%, and 77% and 69% for the transvesical, extravesical, and endoscopic approaches, respectively (Fig. 1). Actuarial CSS

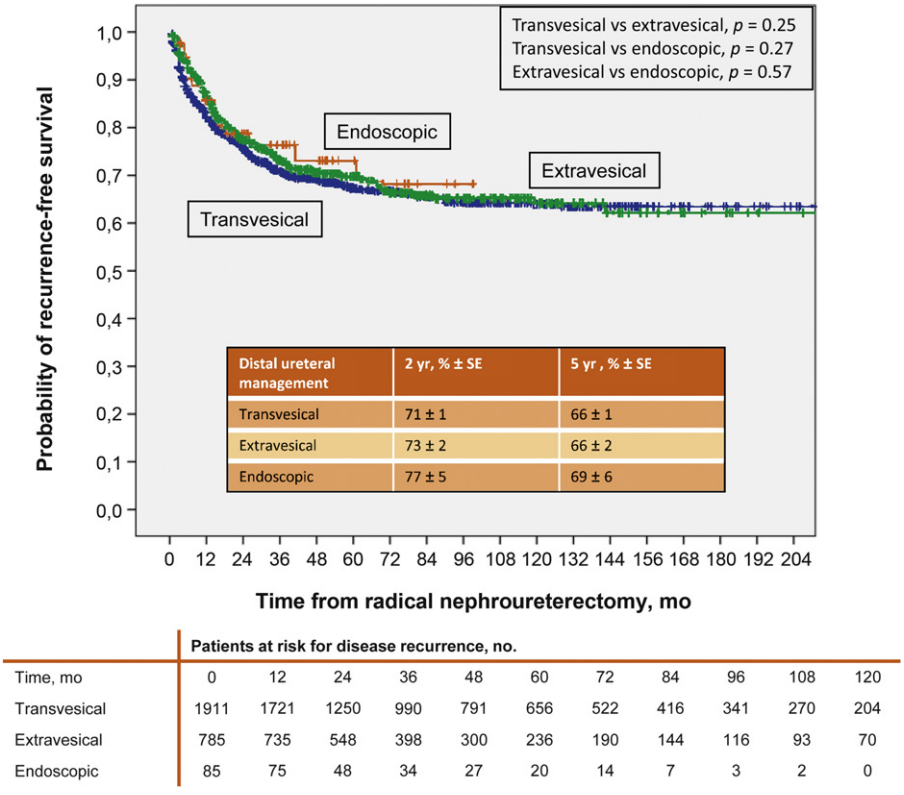

Fig. 1 – Recurrence-free survival. SE = standard error.

Table 1 – Association between distal ureteral management during radical nephroureterectomy and clinicopathologic characteristics of 2681 patients treated for upper tract urothelial carcinoma

Variables	Total, no. (%)	Transvesical, no. (%)	Extravesical, no. (%)	Endoscopic, no. (%)	*p* value		
					T vs Ex	T vs En	Ex vs En
Patients, no.	2681 (100)	1811 (67.5)	785 (29.3)	85 (3.2)	–	–	–
Age, yr, median (IQR)	68.4 (54–84)	68.7 (53–83)	67.7 (53–82)	69.6 (54–86)	0.08	0.06	0.09
Male	1808 (67.4)	1208 (66.7)	546 (69.6)	54 (63.5)	0.08	0.31	0.16
Female	873 (32.6)	603 (33.3)	239 (30.4)	31 (36.5)			
ECOG*							
0	1101 (66.7)	552 (64.2)	497 (69.8)	52 (65.8)	0.01	0.20	0.86
1–3	550 (33.3)	308 (35.8)	215 (30.2)	27 (34.2)			
Previous bladder cancer							
Yes	770 (28.7)	555 (30.6)	193 (24.6)	22 (25.9)	<0.001	0.21	0.44
No	1911 (71.3)	1256 (69.4)	592 (75.4)	63 (74.1)			
Primary tumor location							
Renal pelvis	1730 (64.5)	1152 (63.6)	508 (64.7)	70 (82.4)	0.31	<0.01	<0.01
Ureter	951 (35.5)	659 (36.4)	277 (35.3)	15 (17.6)			
Multifocality							
Yes	629 (23.5)	428 (23.6)	189 (24.1)	12 (14.1)	0.42	0.02	0.02
No	2052 (76.5)	1383 (76.4)	596 (75.9)	73 (85.9)			
Surgical approach							
Open	2170 (80.9)	1533 (84.6)	624 (79.5)	13 (15.3)	<0.01	<0.01	<0.01
Laparoscopic	511 (19.1)	278 (15.4)	161 (20.5)	72 (84.7)			
pT Stage							
pT0-pTa-pTis-pT1	1221 (45.5)	858 (47.4)	313 (39.9)	50 (58.8)			
pT2	519 (19.4)	336 (18.6)	173 (22.0)	10 (11.8)	0.017	<0.01	<0.01
pT3	810 (30.2)	525 (29.0)	262 (33.4)	23 (27.1)			
pT4	131 (4.9)	92 (5.1)	37 (4.7)	2 (2.4)			
Grade							
No tumor	24 (0.9)	18 (1.0)	4 (0.5)	2 (2.4)			
Low	415 (15.5)	282 (15.6)	99 (12.6)	34 (40.0)	0.062	<0.01	<0.01
High	2242 (83.6)	1511 (83.4)	682 (86.9)	49 (57.6)			
Lymph node status							
pN0	760 (28.3)	538 (29.7)	213 (27.1)	9 (10.6)			
pNx	1662 (62.0)	1099 (60.7)	490 (62.4)	73 (85.9)	0.38	<0.01	<0.01
pN+	259 (9.7)	174 (9.6)	82 (10.5)	3 (3.5)			
Concomitant CIS							
Present	676 (25.2)	471 (26.0)	189 (24.1)	16 (18.8)	0.16	0.09	0.17
Absent	2005 (74.8)	1340 (74.0)	596 (75.9)	69 (81.2)			
Lymphovascular Invasion**							
Present	579 (24.5)	369 (24.4)	193 (24.9)	17 (20.7)	0.42	<0.01	0.24
Absent	1787 (75.5)	1141 (75.6)	581 (75.1)	65 (79.3)			
Adjuvant chemotherapy							
Yes	264 (9.8)	148 (8.2)	103 (13.1)	13 (15.3)	<0.01	0.02	0.33
No	2417 (90.2)	1663 (91.8)	682 (86.9)	72 (84.7)			
Follow-up, mo	57.5	61.1	52.3	36.1	<0.01	<0.01	0.01
Intravesical recurrence	577 (21.5)	388 (21.4)	160 (20.3)	29 (34.1)	–	–	–
Time to intravesical recurrence, mo	38.3	39.9	36.7	23.9			
Recurrence	748 (27.9)	526 (29)	204 (25.9)	18 (21.2)	–	–	–
Time to recurrence, mo	46.4	48.3	43.6	29.6			
Death of disease	605 (22.6)	419 (23.1)	175 (22.3)	11 (12.9)	–	–	–
Time to death, mo	50.1	52.5	46.3	31.5			

T = transvesical; Ex = extravesical; En = endoscopic; IQR = interquartile range; ECOG = Eastern Cooperative Oncology Group; CIS = carcinoma in situ.
* ECOG status available only in 1651 patients (62%).
** Lymphovascular invasion information was available only in 2366 patients (88%).

estimates at 2 and 5 yr after RNU were 80% and 71%, 79% and 70%, and 82% and 82% for the transvesical, extravesical, and endoscopic approaches, respectively. Actuarial OS estimates at 2 and 5 yr after RNU were 71% and 66%, 73% and 66%, and 77% and 69% for the transvesical, extravesical, and endoscopic approaches, respectively. Actuarial intravesical RFS estimates at 2 and 5 yr after RNU were 69% and 58%, 69% and 51%, and 61% and 42% for the transvesical, extravesical, and endoscopic approaches, respectively (Fig. 2a). In multivariable Cox regression analysis, endoscopic distal ureter management, male sex, laparoscopic surgical technique, previous bladder cancer, higher tumor stage, concomitant carcinoma in situ (CIS), and lymph node involvement were all associated with intravesical recurrence (Table 2). Institution was not a predictor of intravesical disease recurrence (hazard ratio [HR]: 1.004; 95% confidence interval [CI], 0.992–1.017; $p = 0.52$). Exclusion of patients who received adjuvant

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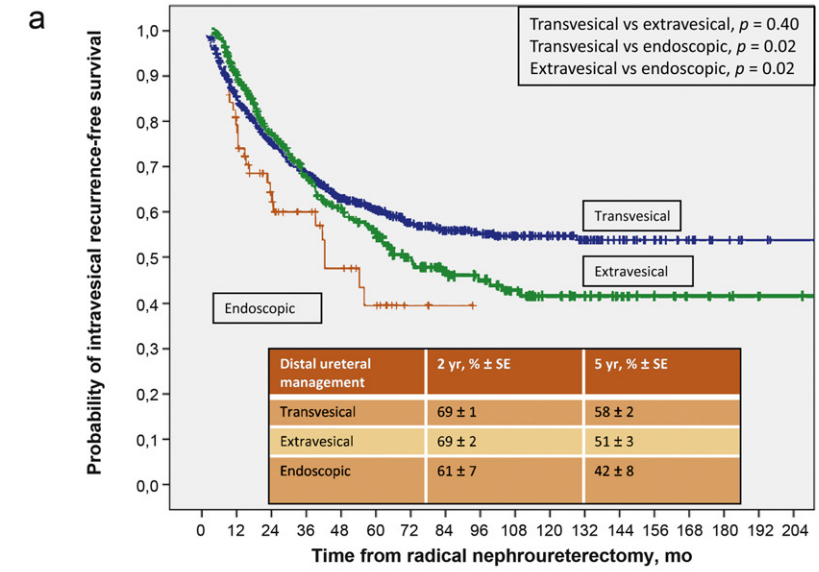
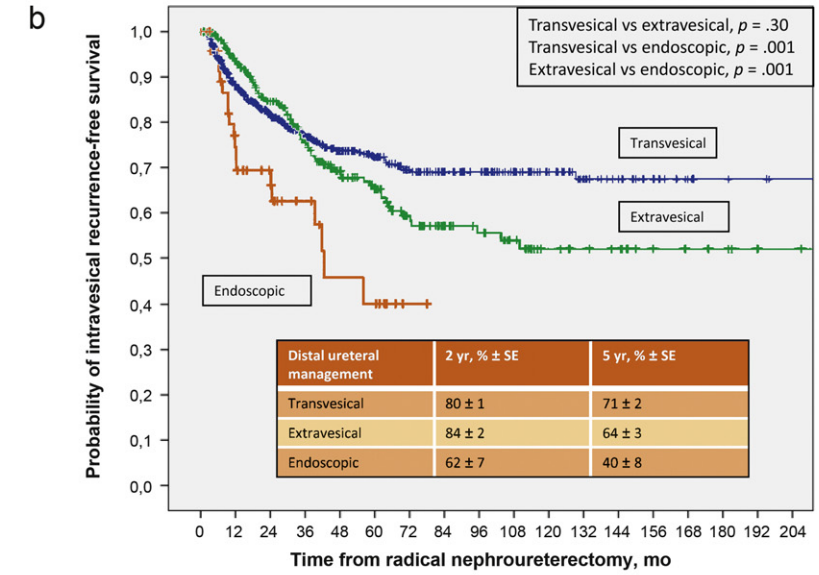


Distal ureteral management	2 yr, % ± SE	5 yr, % ± SE
Transvesical	69 ± 1	58 ± 2
Extravesical	69 ± 2	51 ± 3
Endoscopic	61 ± 7	42 ± 8

Patients at risk for intravesical recurrence, no.											
Time, mo	0	12	24	36	48	60	72	84	96	108	120
Transvesical	1911	1721	1250	990	791	656	522	416	341	270	204
Extravesical	785	735	548	398	300	236	190	144	116	93	70
Endoscopic	85	75	48	34	27	20	14	7	3	2	0



Distal ureteral management	2 yr, % ± SE	5 yr, % ± SE
Transvesical	80 ± 1	71 ± 2
Extravesical	84 ± 2	64 ± 3
Endoscopic	62 ± 7	40 ± 8

Patients at risk for intravesical recurrence, no.											
Time, mo	0	12	24	36	48	60	72	84	96	108	120
Transvesical	1152	822	594	446	344	271	206	160	121	88	38
Extravesical	459	331	224	156	117	89	64	50	42	31	13
Endoscopic	70	42	27	21	14	7	2	1	1	0	0

Fig. 2 – (a) Intravesical recurrence-free survival. (b) Intravesical recurrence-free survival excluding previous bladder cancer. SE = standard error.

chemotherapy did not change the statistical significance of the variables except for tumor stage, which became nonsignificant, and female sex, which became significant. Subgroup analyses in patients who underwent laparoscopic RNU and those who underwent open RNU showed similar results (data not shown).

3.3. Association between distal ureter management and clinical outcomes in patients without previous bladder cancer

When excluding patients with a history of previous bladder cancer, actuarial intravesical RFS estimates at 2 and 5 yr after RNU were 81% and 71%, 84% and 64%, and 62% and 40%

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Table 2 – Multivariable Cox regression analyses predicting intravesical recurrence in 2681 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma

	All patients ($N = 2681$)			Patients without previous bladder cancer ($n = 1911$)		
	HR	95% CI	p value	HR	95% CI	p value
Distal ureteral management			0.02			0.005
Transvesical	1	Referent	–	1	Referent	–
Extravesical	1.16	0.96–1.40	0.12	1.14	0.87–1,48	0.35
Endoscopic	1.74	1.14–2.64	0.01	2.42	1.42–4.12	0.001
Age (continuous)	1.01	0.99–1.02	0.40	1.02	1.01–1.04	0.30
Female	0.82	0.68–1.01	0.66	0.80	0.62–1.03	0.83
Tumor location (renal pelvis vs ureter)	1.19	0.99–1.41	0.053	1.09	0.84–1.41	0.52
Tumor multifocality	1.14	0.94–1.37	0.19	0.78	0.58–1.04	0.89
Previous bladder cancer	2.15	1.81–2.55	<0.001	–	–	–
Open vs laparoscopic RNU	1.30	1.04–1.63	0.02	1.46	1.08–1.97	0.01
Pathologic T classification trend			0.01			0.04
pT0-pTa-pT1-pTis	1	Referent	–		Referent	–
pT2	1.17	0.93–1.48	0.18	1	0.77–1.57	0.62
pT3	1.32	1.06–1.65	0.012	1.09	0.93–1.76	0.12
pT4	2.04	1.27–3.26	0.003	1.28 2.33	1.27–4.28	0.006
High tumor grade	0.67	0.33–1.38	0.26	1.03	0.25–4.25	0.97
Concomitant carcinoma in situ	2.14	1.79–2.56	<0.001	3.12	2.40–4.05	<0.001
Lymphovascular invasion	1.14	0.88–1.48	0.31	0.98	0.68–1.43	0.95
Lymph node status			<0.001			0.001
LN0	1	Referent	–	1	Referent	–
LNx	0.75	0.63–0.90	0.002	0.64	0.49–0.83	0.001
LN+	1.31	0.96–1.78	0.09	1.18	0.77–1.81	0.44

HR = hazard ratio; CI = confidence interval; RNU = radical nephroureterectomy.

for the transvesical, extravesical, and endoscopic approaches, respectively (Fig. 2b). Endoscopic distal ureter management, concomitant CIS, lymph node involvement, higher tumor stage, and laparoscopic surgical technique remained independent predictors of intravesical recurrence (Table 2).

3.4. *Matched-pair comparative analysis*

We performed a matched-pair comparative analysis based on the 85 patients who underwent endoscopic distal ureter management on a 3:1 model ($n = 595$ patients). Patients were matched for TNM stage and lymph node status. Endoscopic distal ureteral management (HR: 10.8; CI, 5.27–22.2; $p < .001$) and concomitant CIS (HR: 2.08; CI, 1.35–3.20; $p = .01$) remained independent predictors of intravesical recurrence in a multivariable analysis.

4. Discussion

No difference in RFS, CSS, and OS was reported between patients managed with either transvesical, extravesical, or endoscopic bladder cuff approach. Total excision of the distal ureter with its intramural portion, the ipsilateral ureteral orifice, and bladder cuff is necessary for optimal management of UTUC [2,15]. While the transvesical approach has been the standard for ensuring complete bladder cuff excision, several newer techniques, such as transurethral resection of the intramural ureter, intussusception techniques, and stripping, have been described to simplify resection of the distal ureter [16]. Apart from ureteral stripping, these novel techniques have been shown to be not inferior to the transvesical approach, albeit the follow-up of these studies was too short to make definitive conclusions, specifically with regard to intravesical recurrence. Indeed, studies have reported the risk of tumor recurrence within the residual ureteral stump/periureteral meatal region in cases of incomplete bladder cuff removal to be 30–64% [17–21]. While RFS and CSS are major end points in patients treated with RNU for UTUC, intravesical recurrence is a significant, yet underevaluated, end point to be considered in decision making regarding the optimal treatment and follow-up for UTUC patients.

We found that endoscopic management of the distal ureter results in significantly higher intravesical recurrence rates as compared to the transvesical or extravesical approaches. This association was independent when adjusted for the effect of established outcome predictors in UTUC and remained even after exclusion of patients with past history of non–muscle-invasive bladder cancer. Possible causes for the higher rate of intravesical recurrence in patients treated with the endoscopic approach include tumor spillage and/or incomplete tumor removal. This is in contrast to Li et al, who reported no difference in intravesical recurrence rates among the three approaches [4]. Conclusions from the Li et al. study were limited by the small sample size, short follow-up, low number of events, and single-center nature of their study. Conversely, our study suffered from heterogeneity in management and selection of patients, imbalance in the type of ureteral management technique between centers, and unadjusted biases inherent to retrospective studies.

We found a higher, but not statistically significantly different, rate of late intravesical recurrence in patients who underwent an extravesical approach (either stapling or clamping) compared with those who underwent a transvesical approach. The *blind* extravesical stapling or clamping

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does not inevitably guarantee adequate bladder cuff retrieval [3,21]. Patients treated with the extravesical approach had a higher rate of laparoscopic RNU and adjuvant chemotherapy and those with a transvesical approach had a higher rate of non–muscle-invasive UTUC and previous bladder cancer. The failure to reach statistical significance could be due to the relatively short follow-up time and biases inherent to retrospective studies, such as patient selection. The transvesical approach is not without pitfalls either. For example, an anterior cystotomy must be avoided in the presence of active bladder UC as it retains the potential to seed tumor into the extravesical space. Moreover, early ligation/clipping of the ureter during the nephrectomy seems theoretically preferential. In addition, prior pelvic surgery or irradiation and obesity may render the open procedure more challenging. Notwithstanding these potential concerns, the transvesical approach to distal ureter removal is not only oncologically sound, it has withstood the test of time [16]. While the absolute intravesical recurrence rate was different between the transvesical and extravesical approaches, based on the statistical analyses, we found no difference in any of the outcomes between these approaches.

We found that, in addition to distal ureteral approach, features of disease stage (T stage and lymph node involvement), male sex, laparoscopic surgical approach, concomitant CIS, and history of previous non–muscle-invasive bladder cancer were independent predictors of intravesical recurrence. Exclusion of patients with previous bladder cancer did not change the association of the other predictors except sex. Concomitant CIS in the bladder has been associated with UTUC development [22]. In RNU patients with organ-confined UTUC, concomitant CIS has been shown to be a predictor of disease recurrence and CSS [23,24]. One single study to date reported that concomitant CIS is associated with intravesical recurrence [25]. We found that laparoscopic RNU is associated with a higher risk of intravesical recurrence compared with open RNU. In contrast, Favaretto et al. did not find any difference in the rate of intravesical recurrence between laparoscopic and open RNU in a relatively smaller (324 patients) single-center study [26]. In our study, most patients who underwent endoscopic resection of bladder cuff also had concomitant laparoscopic surgery, thereby, perhaps, confounding the impact of laparoscopic surgery on intravesical recurrence. Moreover, several studies reported no difference in nonbladder recurrence and survival between laparoscopic and open RNU, provided there was adherence to the same oncologic principles [26–28]. Certainly, future studies have to assess the differential effect of minimal invasive RNU on intravesical recurrence.

The current study suffers from several limitations. First and foremost are the limitations inherent to retrospective multicentric study design. We did not perform a centralized pathologic review, which could have led to misinterpretations of pathologic specimens and underreporting of features such as concomitant CIS. In addition, small differences in surgical technique not captured by our data may have profound effects on the measured outcomes. Furthermore, differences in the postoperative follow-up of the bladder between participating centers may have affected outcomes. Moreover, immediate, postoperative, single, intraoperative chemotherapy may lower the intravesical recurrence rate, thereby abrogating the effects seen in our study [29]. Finally, information on complications, operative time, blood loss, and recovery were not available in our multicenter database and this information could balance our findings.

5. Conclusions

While there are no differences in nonbladder recurrence and survival between transvesical, extravesical, and endoscopic management of the bladder cuff, the endoscopic approach results in higher intravesical bladder cancer recurrences. Concomitant CIS of the upper tract is a strong predictor of intravesical recurrence after RNU. After further validation, a risk-based follow-up strategy needs to be developed to determine follow-up scheduling (ie, cystoscopy) and management.

Author contributions: Shahrokh F. Shariat had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Xylinas, Shariat.
Acquisition of data: Fajkovis, Comploj, Novara, Margulis, Raman, Lotan, Kassouf, Fritsche, Weizer, Martinez-Salamanca, Matsumoto, Zigeuner, Pycha, Scherr, Seitz, Walton, Trinh, Karakiewitcz, Matin, Montorsi.
Analysis and interpretation of data: None.
Drafting of the manuscript: Xylinas, Rink, Cha, Shariat.
Critical revision of the manuscript for important intellectual content: Fritsche, Raman, Lotan, Matsumoto, Walton, Matin, Novara, Zerbib.
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