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Urothelial Cancer

Stage-Specific Impact of Tumor Location on Oncologic Outcomes in Patients With Upper and Lower Tract Urothelial Carcinoma Following Radical Surgery

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Abstract

Background: Dissimilarities in management and outcomes exist between upper tract urothelial carcinoma (UTUC) and urothelial carcinoma of the bladder (UCB).

Objective: The aim of this study was to analyze the stage-specific impact of upper or lower urinary tract tumor location on oncologic outcomes.

Design, setting, and participants: Data were collected from 4335 patients with UCB treated with radical cystectomy (RC) and bilateral pelvic lymphadenectomy (PLND), 877 patients with ureteral UTUC, and 1615 with pelvicalyceal UTUC treated with radical nephroureterectomy (RNU). No patient received preoperative chemotherapy or radiation therapy.

Interventions: Patients were treated with RC and bilateral PLND or RNU.

Measurements: Outcomes were assessed according to primary tumor location.

Results and limitations: Compared to UTUC patients, UCB patients had more advanced tumor stage and higher grade, and they were more likely to harbor lymphovascular invasion (LVI) and lymph node metastasis ($p < 0.001$). In non-muscle-invasive tumor stages, UCB patients were more likely to experience disease recurrence and mortality compared to renal pelvicalyceal tumor patients ($p < 0.002$) but not ureteral tumors ($p > 0.05$). In pT2 and pT3 tumors, there was no difference in outcomes between the three tumor locations. In pT4 tumors, patients with ureteral and pelvicalyceal tumors were more likely to experience disease recurrence and mortality compared to UCB patients ($p < 0.004$). These stage-specific findings were unchanged after adjustment for the effects of age, gender, tumor grade, LVI, lymph node

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status, and adjuvant chemotherapy. This study is limited by its retrospective and multicenter nature.

Conclusions: Stage-specific differences in outcomes exist between UCB and UTUC. The differentially worse outcomes by stage between UCB and UTUC patients underline the differences between both cancer entities and the need for individualized stage-specific management for each patient.

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1. Introduction

Urothelial carcinoma (UC) is the second most common genitourinary malignancy after prostate cancer and a major cause of morbidity and mortality in the United States [1]. Radical cystectomy (RC) with pelvic lymphadenectomy (PLND) is the standard surgical treatment for muscle-invasive and high-risk UC of the bladder (UCB) [2,3]. Radical nephroureterectomy (RNU) with excision of an ipsilateral bladder cuff is the standard of care for invasive, bulky, or high-grade upper tract UC (UTUC) of the renal pelvicalyceal system and ureters [4]. The most common site for tumor recurrence after RNU is the bladder; similarly, the greatest risk factor for development of UTUC is previous UCB [5–7].

Both UCB and UTUC are recognized to arise in a background of field-effect change within the urothelial lining precipitated by carcinogens, causing independent genetic alterations in the bladder and upper urinary tract [8,9]. Both tumor entities show similarities in molecular and cytogenetic changes [10] as well as prognostic factors such as tumor stage and grade, lymphovascular invasion (LVI), and lymph node metastasis [5,11]. However, many dissimilarities in the natural history and management of these two entities exist [12]. Such differences include but are not limited to the impact of gender on outcomes [5,13] and anatomic differences resulting in different treatment strategies (ie, the inability to accurately stage UTUC and the lack of effective methods for delivery of intracavitary chemotherapy or bacillus Calmette-Guérin [BCG]) [4,5]. Nevertheless, management decisions in UTUC are often based on extrapolation from UCB data and guidelines. The aim of this study was to evaluate the impact of primary upper or lower urinary tract tumor location on oncologic outcomes in UC patients treated with radical surgery.

2. Methods and materials

2.1. Patient selection

This was an institutional review board–approved, international, multi-institutional, retrospective study, with each participating site providing the necessary institutional data-sharing agreements before study initiation. A computerized database 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 produced for the current analysis.

Overall, the study collected data from 21 institutions comprising 6827 patients with UCB and UTUC of the ureter or pelvicalyceal system treated

with RC and bilateral PLND or RNU, respectively, according to previously described standards [14] between 1979 and 2008. In RNU, the hilar and regional lymph nodes adjacent to the ipsilateral great vessel were generally resected if palpable intraoperatively or enlarged on preoperative axial imaging. For both RC and RNU patients, extent of lymphadenectomy performed was at the discretion of individual surgeons. Patients with metachronous multifocal tumors or previous history of UC at another site at the time of surgery were excluded from our analysis. None of the patients received preoperative chemotherapy or radiation therapy. At the time of surgery, no patient had known distant metastatic disease. Overall, 1233 patients (18.1%) received adjuvant chemotherapy at the discretion of the investigator based on patient tumor stage and overall health status.

2.2. Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures, and all slides were re-reviewed by genitourinary pathologists blinded to clinical outcomes. Tumors were staged according to the 2002 TNM classification by the American Joint Committee on Cancer for UCB and UTUC. The presence of concomitant carcinoma in situ (CIS) was defined as the presence of CIS in conjunction with another tumor other than CIS alone. LVI was defined as the unequivocal presence of tumor cells within an endothelium-lined space without underlying muscular walls [15,16]. In RC patients, genitourinary pathologists assigned tumor grade according to the 1973 World Health Organization (WHO) grading system at the initial diagnosis. In RNU patients, tumor grading was assessed according to the 1998 WHO/International Society of Urological Pathology consensus classification. Grading information required conversion to a consensus system before combining the site-specific data. Tumor locations were defined as bladder, ureteral, or renal pelvicalyceal. To ensure the validity of pathologic data extraction, two investigators independently reviewed pathology results in a subgroup of patients while blinded to patient clinical parameters and the finding of the other reviewer. Interreader reliability measured using the intraclass correlation coefficient was >0.95 for each pathologic characteristic.

2.3. Follow-up regimen

Follow-up was performed according to institutional protocols. Patients were generally seen every 3–4 mo for the first year after surgery, every 6 mo from the second through fifth years, and annually thereafter. Follow-up generally consisted of a history, physical examination, and serum chemistry evaluation. Diagnostic imaging of both (or the remaining) upper tracts and chest radiography were performed at least annually or when clinically indicated. Additional radiographic evaluations, such as bone scan or computerized tomography, were performed at the discretion of the treating physician. In UTUC patients, urinary cytology and cystoscopy were performed during follow-up.

Disease recurrence was defined as local failure in the operative site, regional lymph nodes, or distant metastasis. Patients who did not experience recurrence were censored at time of last follow-up for recurrence-free survival (RFS) analysis. According to radical surgery, detection of cancer in the ureter and/or urethra in UCB patients or in the bladder in UTUC patients was coded as a second (metachronous) primary

and not as a local or distant recurrence. The cause of death was determined by retrospective physician chart review and corroborated in some cases by death certificates [17]. A patient with disseminated metastases at the time of death was categorized as having died of his disease. Patients who did not die from their disease were censored at time of last follow-up for cancer-specific survival (CSS) analyses. In addition, patients who died within 30 d of surgery were censored at the time of death for CSS analyses.

2.4. Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normal distribution of variables. Fisher exact test and the χ^2 test were used to evaluate the association between categorical variables. Differences in continuously distributed variables across categories were assessed using the Mann-Whitney test (two categories) and Kruskal-Wallis test (three or more categories). The Kaplan-Meier method was used to calculate survival outcomes, and differences were assessed with the log-rank statistic. Multivariable Cox proportional hazards regression models evaluated time to recurrence and cancer-specific mortality after radical surgery. In all models, proportional hazards assumptions were systematically verified using the Grambsch-Therneau residual-based test. All reported *p* values are two-sided, and statistical significance was set at *p* < 0.05. All statistical tests were performed with SPSS v.17 statistical software (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Association with clinical and pathologic characteristics

Overall, 4335 patients (63.5%) had tumors located in the bladder, 877 patients (12.8%) had tumors located in the

ureter, and 1615 patients (23.7%) had tumors located in the renal pelvicalyceal system. Table 1 displays the descriptive characteristics of the patients. Univariable comparison of all three groups showed statistically significant differences in all analyzed parameters (all *p* < 0.001). UCB patients were more likely to have advanced tumor stage (pT3–4 in UCB vs ureter vs renal pelvicalyceal UC: 44.6% vs 27.3% vs 39.4%), higher grade, concomitant CIS, LVI, and lymph node metastases (*p* < 0.001). Moreover, UCB patients were more likely to receive adjuvant chemotherapy (22.7% vs 9.4% vs 10.2%; *p* < 0.001). Median number of lymph nodes removed in UCB patients was 18 (IQR: 20). In UTUC patients who underwent lymph node dissection (33.5% renal pelvicalyceal and 31.5% ureteral tumor patients, respectively), the median number of lymph nodes removed was 4 (IQR: 7) and 5 (IQR: 9) in renal pelvicalyceal and ureteral tumors. UCB patients were mostly males, whereas female gender prevalence was highest in renal pelvicalyceal UTUC.

3.2. Association with disease recurrence and survival

The median follow-up was 44 (IQR: 63; range: 1–271), 46 (IQR: 57; range: 1–246), and 42 mo (IQR: 69; range: 1–324) in patients with renal pelvicalyceal, ureteral, and bladder tumors, respectively. Overall, 428 (26.5%), 231 (26.3%), and 1456 (33.6%) patients with renal pelvicalyceal, ureteral, and bladder tumors experienced disease recurrence; 571 (35.4%), 313 (35.7%), and 2031 (46.9%) patients with renal pelvicalyceal, ureteral, and bladder tumors died of any

Table 1 – Association of tumor location with clinical and pathologic characteristics of 4335 urothelial carcinoma (UC) of the bladder patients treated with radical cystectomy and 2492 upper tract UC patients treated with radical nephroureterectomy

	Renal pelvicalyceal (<i>n</i> = 1615)	Ureter (<i>n</i> = 877)	Bladder (<i>n</i> = 4335)	<i>p</i> value
Age, yr, median (IQR)	69 (15.4)	70 (13.0)	67 (13.4)	<0.001
Gender, no. (%):				<0.001
Male	1062 (65.8)	619 (70.6)	3464 (79.9)	
Female	553 (34.2)	258 (29.4)	871 (20.1)	
Pathologic stage, no. (%):				<0.001
T0, Ta, Tis	395 (24.5)	197 (22.5)	774 (17.9)	
T1	330 (20.4)	223 (25.4)	585 (13.5)	
T2	254 (15.7)	219 (25.0)	1042 (24.0)	
T3	529 (32.8)	225 (25.7)	1371 (31.6)	
T4	107 (6.6)	13 (1.5)	563 (13.0)	
Grade, no. (%):				<0.001
Low	264 (16.3)	128 (14.6)	74 (1.7)	
High	1338 (82.8)	745 (84.9)	4034 (93.1)	
No grading (pT0 disease)	13 (0.8)	4 (0.5)	227 (5.2)	
Concomitant CIS, no. (%):				<0.001
Absent	1282 (79.4)	632 (72.1)	2181 (50.3)	
Present	333 (20.6)	245 (27.9)	2154 (49.7)	
LVI, no. (%):				<0.001
Absent	1214 (75.2)	691 (78.8)	2860 (66.0)	
Present	401 (24.8)	186 (21.2)	1475 (34.0)	
Lymph node status, no. (%):				<0.001
Negative	378 (23.4)	217 (24.7)	3216 (74.2)	
Positive	163 (10.1)	59 (6.7)	1119 (25.8)	
No dissection performed	1074 (66.5)	601 (68.5)	0 (0)	
Adjuvant chemotherapy, no. (%):				<0.001
Not administered	1450 (89.8)	795 (90.6)	3349 (77.3)	
Administered	165 (10.2)	82 (9.4)	986 (22.7)	

IQR = interquartile range; CIS = carcinoma in situ; LVI = lymphovascular invasion.

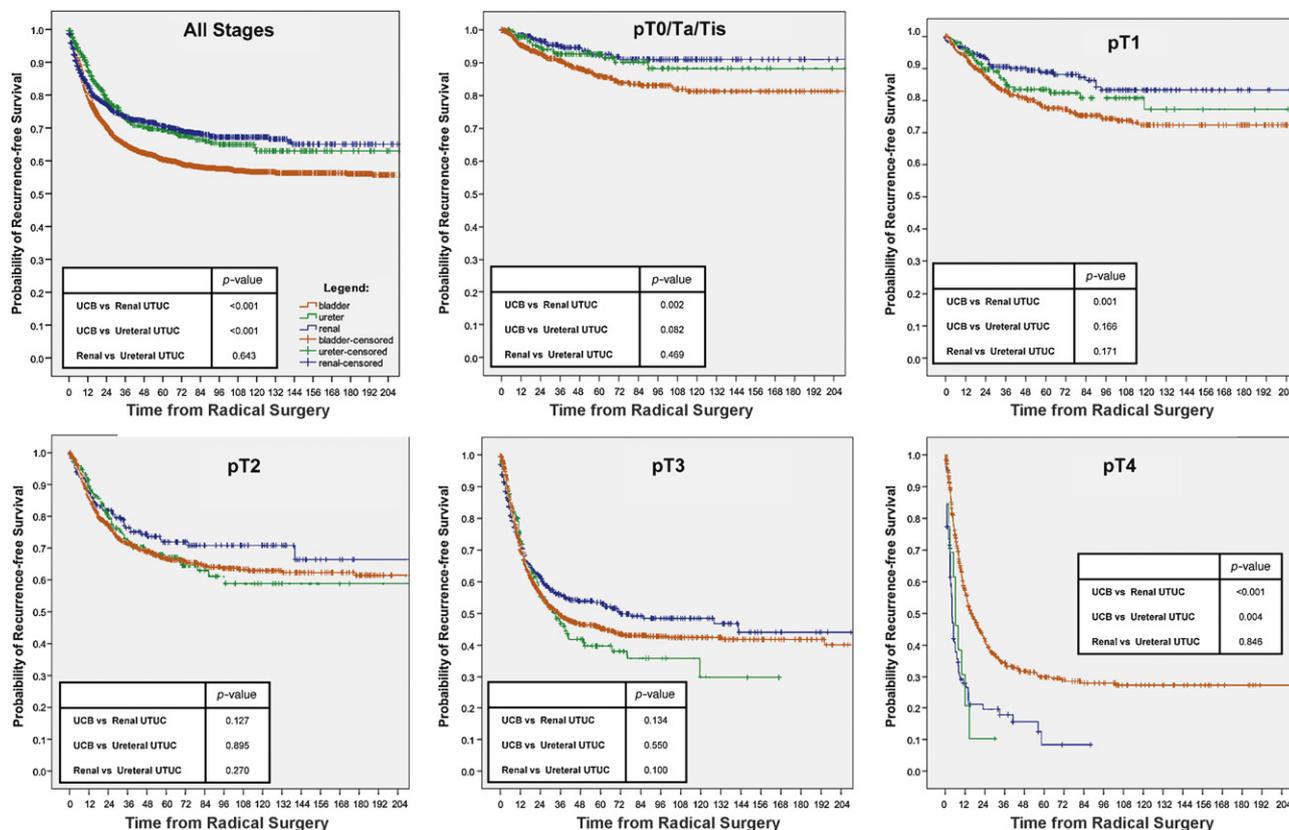


Fig. 1 – Kaplan-Meier plots of recurrence-free survival stratified according to tumor location in 4335 urothelial carcinoma of the bladder patients treated with radical cystectomy as well as 877 ureteral and 1615 renal upper-tract urothelial carcinoma patients treated with radical nephroureterectomy. UCB = urothelial carcinoma of the bladder; UTUC = upper-tract urothelial carcinoma.

cause during follow-up ($p < 0.001$); and 351 (21.7%), 194 (22.1%), and 1204 (27.8%) patients died from their disease, respectively.

Figures 1 and 2 show the Kaplan-Meier plots for RFS and CSS estimates stratified by tumor location and pathologic stage. Overall, UCB patients were more likely to experience disease recurrence and cancer-specific mortality compared to ureteral and renal pelvicalyceal tumor patients ($p < 0.001$), who in turn were not different from each other ($p > 0.05$). In a multivariable analysis that adjusted for the effects of age ($p = 0.001$), gender (female vs male: $p = 0.025$), tumor stage ($p < 0.001$), grade ($p = 0.69$), lymph node metastasis (NX vs N0: $p = 0.67$; N+ vs N0: $p < 0.001$), LVI ($p = 0.001$), and adjuvant chemotherapy ($p = 0.24$), tumor location (UCB vs ureter: $p = 0.066$; UCB vs renal pelvicalyceal system: $p = 0.13$) was not associated with disease recurrence. In a multivariable analysis that adjusted for the effects of age ($p = 0.001$), gender (female vs male: $p = 0.022$), tumor stage ($p < 0.001$), grade ($p = 0.54$), lymph node metastasis (NX vs N0: $p = 0.10$; N+ vs N0: $p < 0.001$), LVI ($p = 0.001$), and adjuvant chemotherapy ($p = 0.28$), tumor location (UCB vs ureter: $p = 0.098$; UCB vs renal pelvicalyceal system: $p = 0.89$) was not associated with CSS.

When restricted to patients with non-muscle-invasive tumor stages, UCB patients were more likely to experience disease recurrence (Fig. 1) and die of their cancer (Fig. 2)

compared to renal pelvicalyceal UTUC but not compared to ureteral UTUC patients. In pT2 and pT3 tumors, there was no difference in disease recurrence between the three locations. Patients with pT3 tumors located in the bladder ($p = 0.047$) or ureters ($p = 0.019$), however, were more likely to die of their cancer compared to patients with renal pelvicalyceal UTUC. In pT4 tumors, patients with ureteral and renal pelvicalyceal tumors were more likely to experience disease recurrence and cancer-specific mortality than UCB patients ($p < 0.004$; Figs. 1 and 2).

Multivariable Cox regression analyses adjusting for standard clinical and pathologic characteristics confirmed the statistical findings of the univariable analyses (examples of analyses for non-muscle-invasive and pT4 patients provided in Tables 2 and 3).

4. Discussion

We found significant differences in outcomes between patients with UCB and UTUC. As a group, UCB patients had worse pathologic features than UTUC patients. To date, only limited data exist comparing upper- and lower-tract UC, with controversial results. Similar to our findings, Moussa et al. [18] reported in 280 patients that UCB patients had worse clinical features and overall survival compared to UTUC patients grouped together. Conversely, other studies

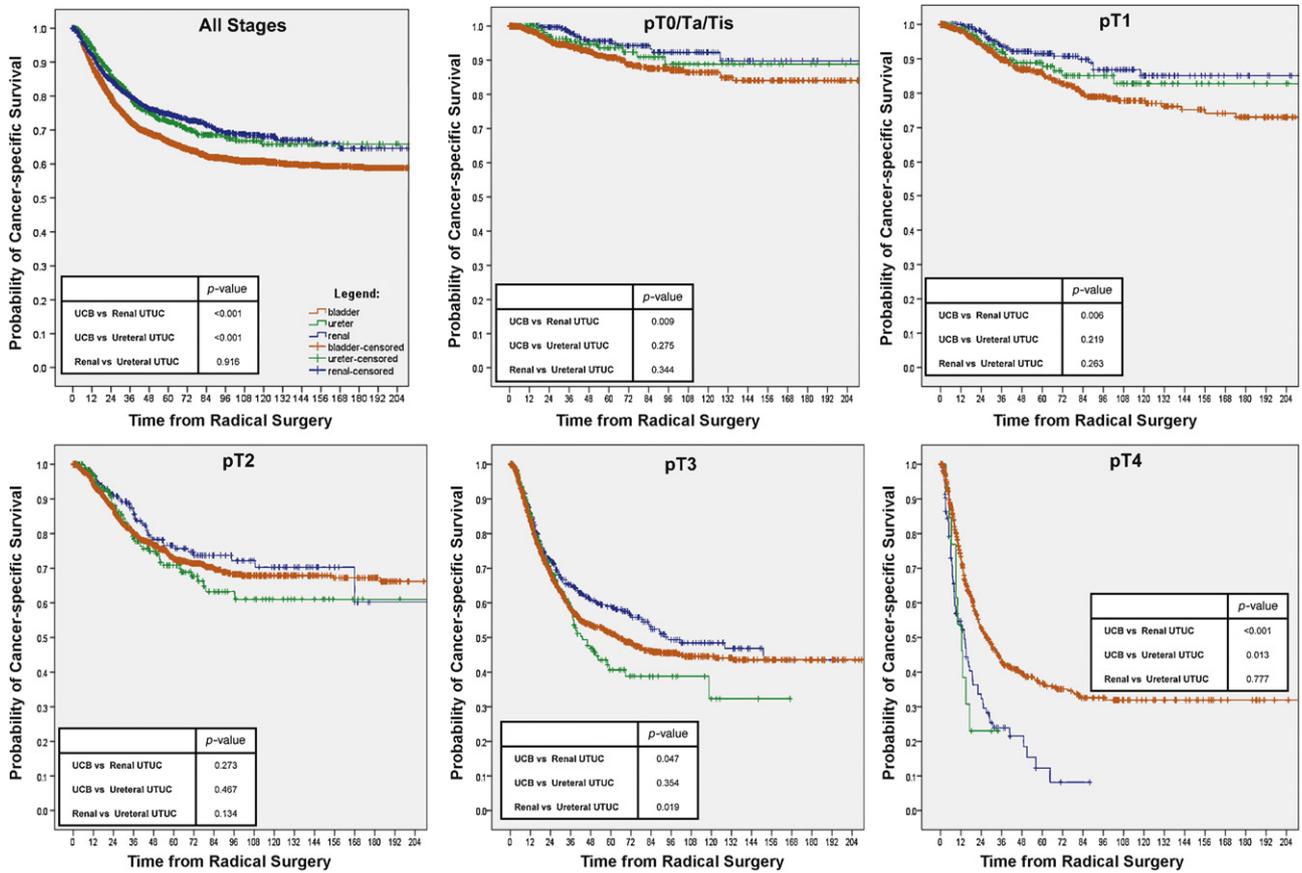


Fig. 2 – Kaplan-Meier plots of cancer-specific survival stratified according to tumor location in 4335 urothelial carcinoma of the bladder patients treated with radical cystectomy as well as 877 ureteral and 1615 renal upper-tract urothelial carcinoma patients treated with radical nephroureterectomy. UCB = urothelial carcinoma of the bladder; UTUC = upper-tract urothelial carcinoma.

found that UTUC patients had worse pathologic features [19,20]. However, the study by Catto et al. reported comparable oncologic outcomes between UTUC and lower tract UC patients [19]. These disparate findings may be explained by differences between study populations and patient cohort sizes. Using our large, international cohorts, we confirmed that oncologic outcomes do not differ between

ureteral and renal pelvicalyceal tumors when adjusted for the effects of clinicopathologic features [21–23]. In contrast, UCB patients had worse tumor features and survival than UTUC patients. However, these differences were more nuanced when stratified by tumor stage.

In non-muscle-invasive disease, UCB patients had worse outcomes compared to both UTUC locations; in pT2 and pT3

Table 2 – Multivariable Cox regression analyses predicting disease recurrence and cancer-specific mortality in 2504 non-muscle-invasive patients with upper and lower tract urothelial carcinoma treated with radical cystectomy and bilateral lymphadenectomy or radical nephroureterectomy

Parameter	Disease recurrence			Cancer-specific mortality		
	HR	95% CI	p value	HR	95% CI	p value
Age (continuous)	1.017	1.005–1.029	0.006	1.030	1.015–1.045	<0.001
Female gender	1.198	0.920–1.559	0.180	1.333	0.985–1.804	0.063
Tumor location:						
UCB vs ureteral UTUC	0.747	0.540–1.034	0.079	0.748	0.510–1.096	0.136
UCB vs renal pelvicalyceal UTUC	0.540	0.400–0.730	<0.001	0.502	0.351–0.719	<0.001
Pathologic grade	1.341	1.100–1.635	0.004	1.427	1.120–1.817	0.004
Lymph node metastasis	2.681	1.700–4.226	<0.001	3.925	2.397–6.429	<0.001
LVI	1.641	1.132–2.377	0.009	1.709	1.135–2.574	0.010
Adjuvant chemotherapy	2.562	1.696–3.869	<0.001	2.349	1.473–3.747	<0.001

HR = hazard ratio; CI = confidence interval; UCB = urothelial carcinoma of the bladder; UTUC = upper tract urothelial carcinoma; LVI = lymphovascular invasion.

Table 3 – Multivariable Cox regression analyses predicting disease recurrence and cancer-specific mortality in 683 pT4 patients with upper and lower tract urothelial carcinoma treated with radical cystectomy and bilateral lymphadenectomy or radical nephroureterectomy

Parameter ^a	Disease recurrence			Cancer-specific mortality		
	HR	95% CI	p value	HR	95% CI	p value
Age (continuous)	0.998	0.989–1.008	0.745	1.005	0.995–1.016	0.339
Female gender	1.162	0.910–1.483	0.229	1.296	1.008–1.667	0.044
Tumor location:						
UCB vs ureteral UTUC	2.542	1.386–4.662	0.003	2.459	1.300–4.648	0.006
UCB vs renal pelvicalyceal UTUC	2.237	1.732–2.904	<0.001	1.633	1.237–2.156	0.001
Lymph node metastasis	1.894	1.521–2.358	<0.001	2.015	1.595–2.546	<0.001
LVI	1.394	1.118–1.740	0.003	1.598	1.257–2.031	<0.001
Adjuvant chemotherapy	0.936	0.761–1.152	0.535	0.887	0.712–1.105	0.286

HR = hazard ratio; CI = confidence interval; UCB = urothelial carcinoma of the bladder; UTUC = upper-tract urothelial carcinoma; LVI = lymphovascular invasion.

^a Grade not included in multivariable model, as all pT4 patients had high-grade disease.

disease, there were no statistically significant differences among all tumor locations. The inferior outcomes of non-muscle-invasive UCB patients in our cohort might be attributable to the selection process, as non-muscle-invasive UCB patients undergo RC because of features of aggressive biology, such as tumor recurrence, failure to respond to intravesical therapy, or aggressive pathologic features [24,25]. In UTUC, endoscopic management is more challenging [26], and the use of intracavitary chemotherapy or BCG therapy is uncommon [4,5,12]. The lack of appropriate staging and grading, poor selection, and treatment of non-muscle-invasive UTUC leads to high rates of RNU for these tumors. Delay in diagnosis and/or treatment may also differentially affect outcomes in these patients [27,28].

We found that pT4 UTUC patients fared worse than their UCB counterparts. This finding could be the result lower perioperative chemotherapy rates resulting from renal function deterioration after RNU [12,29]. Another explanation could be the low rate and limited extent of lymphadenectomy in UTUC patients, possibly squandering a chance for cure in patients with low-volume lymph node metastasis [30]. A reduced barrier effect in muscle-invasive, advanced UTUC patients might be another explanation, as there is a thinner smooth muscle covering in the upper urinary tract compared to the bladder. Moreover, a significant number of pT4 tumors in UCB are adjacent prostatic infiltrations [31], allowing for potential cure by removal during RC. Finally, other reasons, such as variabilities inherent to the patient (eg, age or gender, as shown in our multivariable analysis) [13,32,33] or genetic profiles [5], may account for the stage-specific differences between UCB and UTUC.

Our study shows subtle stage-dependent differences between UCB and UTUC patients, substantiating that physicians cannot indiscriminately extrapolate lessons learned from UCB to UTUC [12]. Thus, these findings should be included for patient counseling, management guidance, and follow-up scheduling, as they support individualized management with respect to tumor location. For example, similar to UCB, a more frequent use of neoadjuvant chemotherapy might further improve outcomes of patients

with advanced UTUC [34,35]. Recent research in UTUC has already shed more light on this rare disease regarding treatment optimization. Nevertheless, embryologic, biologic, and genetic variability in both malignancies might play a fundamental role in differential outcomes [5], which have to be elucidated by continued research. Besides fundamental research into molecular mechanisms, only well-performed clinical research can improve our knowledge and understanding of the biology underlying disease progression and metastasis in these disparate twins.

Our study is not devoid of limitations. First and foremost are limitations inherent to its multicenter and retrospective design, including a lack of data regarding prior treatments, delay between diagnosis and surgery, patient preferences, and comorbidities. We also could not adjust for the number of surgeons at each institution or surgeons' preferences, experience, or surgical techniques. However, all surgeons operated at tertiary care centers with experience in UC. We did not control for the anatomic template of PLND in RC patients. In addition, the low rate of lymph node dissections in UTUC patients might lead to an undefined bias regarding clinical outcomes. Another source of limitation includes possible interobserver variability among pathologists; we did not perform a central pathology review. Differences in the indication for and protocols of adjuvant chemotherapy were not controlled for in our study. Conversely, the purpose of this study was to reflect a real-world multicenter scenario, and we believe that this positively affects the generalizability of our results. Only a prospective study with standardized inclusion criteria may shed more light on this issue.

5. Conclusions

Our study identified significant differences in clinicopathologic features and outcomes between UCB and UTUC patients. Because of the retrospective study design, the reasons for the differences in UCB and UTUC outcomes remain ambiguous and have to be elucidated in a prospective study. The differentially worse outcomes of UCB patients in non-muscle-invasive disease could be the result of better staging and endoscopic treatment selection,

resulting in higher-risk patients undergoing radical surgery in UCB compared to UTUC patients. The differentially worse outcomes of UTUC patients with pT4 tumors could be the result of differences in TNM staging categories, among other reasons. These data underline the differences between the nonidentical twins—UCB and UTUC—and the need for individualized stage-specific management for each patient.

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.

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Analysis and interpretation of data: Shariat, Rink, Ehdaie.

Drafting of the manuscript: Rink, Shariat, Ehdaie, Cha, Green.

Critical revision of the manuscript for important intellectual content: Shariat, Ehdaie, Rink, Cha, Svatek, Green, Hansen, Fisch, Fajkovic, Novara, Daneshmand, Lotan, Kassouf, Fritsche, Karakiewicz, Scherr, Babjuk, Margulis, Raman, Lee, Pycha.

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