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Original Article

Comparisons of prognosis between urothelial carcinoma of the upper urinary tract and bladder with pT3-4 cancer

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Abstract: The oncological outcomes of upper tract urothelial carcinoma (UTUC) and bladder cancer (BC) in patients treated with radical surgeries remains controversial. A retrospective analysis of the clinicopathologicla data of 228 consecutive UTUC patients and 174 BC patients treated with radical surgeries from 2000 to 2012 at a high-volume center in China was conducted. Kaplan-Meier method and Cox regression were used to compare overall survival (OS) and cancer-specific survival (CSS) and to find prognostic factors. In this cohort of patients, BC were associated with male sex (P<0.001), multifocality (P<0.001), positive lymph node (P=0.002), no hydronephrosis (P<0.001) and open surgical approach (P<0.001). UTUC have statistically significant better 5-year CSS rate (61.0% vs. 49.8%, P=0.008) and OS rate (58.3% vs. 37.4%, P<0.001) than BC. Bladder tumor location (UTCU vs. BC: hazard ratio (HR)=0.703 and HR=0.462) and positive lymph node status (HR=1.919 and HR=1.667) were independent risk factors of cancer-specific death and overall mortality, respectively. Our data suggest that locally invasive urothelial carcinomas (UC) behave differently in the upper and lower urinary tracts. UTUC has a better prognosis than BC when stage and grade are considered simultaneously and lymph node involvement has significant influences on clinical outcomes of urothelial carcinoma.

Keywords: Bladder cancer, upper tract urothelial carcinoma, radical cystectomy, radical nephroureterectomy, prognosis

Introduction

Urothelial carcinoma is a disease of the entire urothelium. Primary upper tract urothelial carcinomas (UTUC) are relatively rare compared to bladder cancer. These tumors only account for a total of 5-10% of all upper tract tumors (UTT), compared with 90-95% of the bladder tumors which are the most common malignancy of the urinary tract [1-3]. In the literature, the frequency of invasive tumors at diagnosis in the bladder and UTT varies approximately from 15% to 25% and 60%, respectively [4-6]. Due to patients with UTUC generally have more advanced disease at the initial diagnosis, we only focus on pT3-4cM0 diseases in this study based on this consideration.

Traditionally, radical nephroureterectomy (RNU) with excision of the bladder cuff is the gold-standard treatment for UTUC [5]. Radical cystectomy (RC) is recommended in T2-T4aN0M0 and high-risk non-muscle invasive bladder cancer [7]. There are many differences between the two types of tumor in respect to anatomy and molecular mechanism. Anatomically the smooth muscle covering of the UUT, especially the renal pelvis, is much thinner than that of the bladder. Thus, theoretically less organ-confined tumors could be found in the UUT than in the bladder. Recently molecular insights suggest that the biology of some upper urinary tract and bladder urothelial carcinoma differ [8-10]. The prognostic effect that urothelial carcinoma tumor location has on outcomes prediction is a matter of debate.

Recent observational studies found that anatomical location didn't affect the prognosis of urothelial carcinoma with comparable stage

and grade [11-13]. We sought to compare the clinical outcomes of high-stage UTUC and BC with homogenous treatment protocols at a high-volume center in China.

Methods

Patient population

Following institutional review board approval, we initially collected the clinicopathological data of 731 consecutive UTUC and 466 BC patients who underwent surgery from 2000 to 2012 with complete follow-up information. We excluded 503 (68.8%) UTUC and 292 (62.7%) BC patients with pT1-2 tumors. Two hundred and twenty-eight (31.2%) UTUC and 174 (37.3%) BC patients with pT3-4cM0 tumors were finally enrolled for survival comparisons. None of these patients received neoadjuvant chemotherapy, although for some patients adjuvant chemotherapy or radiotherapy was administered when evidence of distant metastasis or retroperitoneal recurrence was documented. Routine lymph node dissection (LND) was not performed unless enlarged lymph nodes were showed on the preoperative CT or MRI scan.

Patient's evaluation

All patients were diagnosed by combining preoperative imaging, direct visualization with final pathology. RC was the treatment for all BC and RNU with excision of the bladder cuff was performed for all UTUC cases in this series. Hydronephrosis was determined by preoperative imaging. Tumor stage was assessed according to the 2002 Union for International Cancer Control TNM classification of malignant tumors. Tumor grade was assigned according to the 2004 World Health Organization classification grading system. Tumor location was defined as UTUC (including renal pelvic and ureteral carcinoma) or BC. Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed macroscopic tumors in any location. Tumor size was defined as the diameter of the lesion. The status of regional lymph node was based on the pathological specimens, CT, MRI or even PET-CT and no distant metastases were found before surgery. Patient survival was computed from the day of surgery until the most recent follow-up visit or until death.

Follow up schedule

For patients with UTUC who were followed at our institute, the follow-up regimen of the affected patients included cystoscopy every 3 months for the first 3 years. The cystoscopy intervals were extended to 1 year thereafter. Chest X-ray, urine cytology, serum creatine, and abdominal ultrasound or CT/MRI were examined at the same time for all patients.

Statistical analyses

The Pearson's test and *the chi-square test* were used for comparisons between groups in categorical and continuous variables, respectively. Cancer-specific and overall survival curves were derived by the Kaplan-Meier method with the log-rank test. Univariate analysis with the log-rank test and multivariate analysis with Cox hazards regression were applied to evaluate the value of prognostic factors in predicting overall and cancer-specific survival. Only variables that were significant according to univariate analysis were considered for the multivariate analysis. All test were two sided with a statistical significance limit set at $P<0.05$. Statistical analyses were performed using SPSS v.19.0.

Results

The clinicopathological features are summarized in **Table 1**. No significant difference of age (P=0.692) and tumor size (P=0.496) were found in the two groups. Fifty-four patients (31.0%) with BC and 51 patients (22.4%) with UTUC received adjuvant chemotherapy after operation (P=0.050). Patients who received chemotherapy were remained in this cohort of patients for the univariate and multivariate analyses. There was significant difference in male sex (53.5% vs. 82.8%, P<0.001), multifocality (27.2% vs. 53.4%, P<0.001), lymph nodal invasion (19.3% vs. 32.8%, P=0.002), hydronephrosis (48.2% vs. 1.1%, P<0.001) and surgical approach (open: 31.1% vs. 79.3%, P<0.001) between the two group.

The median follow-up time was 53 months (interquartile range [IQR], 27-64 months) for BC and 44 months (IQR, 27-81 months) for UTUC (P=0.993). At the end of follow-up, 76 (33.4%) UTUC and 65 (37.4%) BC patients had died due to cancer-related causes, while 6 (2.6%) UTUC

Table 1. Clinicopathologic features of the 402 patients with high-stage UTUC and BC

	All	BC	UTUC	Pearson χ^2	*P* value
No. of patients	402	174	228		
Age (years, n (%))				0.213	0.645
<65 years	174 (43.3)	64 (36.8)	89 (39.0)		
≥65 years	228 (56.7)	110 (63.2)	139 (61.0)		
Age, mean ± SD, y		66.3±10.6	65.9±11.0		0.692
Gender				37.717	<0.001*
Male	266 (66.2)	144 (82.8)	122 (53.5)		
Female	136 (33.8)	30 (17.2)	106 (46.5)		
Tumor grade					
High grade	402 (100.0)	174 (100.0)	228 (100)		
Low grade	0 (0)	0 (0)	0 (0)		
Multifocality				28.715	<0.001*
Yes	155 (38.6)	93 (53.4)	62 (27.2)		
No	247 (61.4)	81 (46.6)	166 (72.8)		
Tumor size				0.463	0.496
≤3 cm	161 (40.0)	73 (42.0)	88 (38.6)		
>3 cm	241 (60.0)	101 (58.0)	140 (61.4)		
Mean ± SD, cm		3.819±2.017	4.149±2.302		0.135
Lymph node (n (%))				9.505	0.002*
pN+	101 (25.1)	57 (32.8)	44 (19.3)		
cN0-x	301 (74.9)	117 (67.2)	184 (80.7)		
Hydronephrosis (n%)				108.909	<0.001*
Yes	112 (27.9)	2 (1.1)	110 (48.2)		
No	290 (72.1)	172 (98.9)	118 (51.8)		
Surgical approach				91.740	<0.001*
Open	209 (52.0)	138 (79.3)	71 (31.1)		
Laparoscopic	193 (48.0)	36 (20.7)	157 (68.9)		
Adjuvant chemotherapy					
Yes	105 (26.1)	54 (31.0)	51 (22.4)	3.841	0.050
No	297 (73.9)	120 (69.0)	177 (77.6)		

UTUC = upper tract urothelial carcinoma. BC = bladder cancer. SD = standard deviation. *P<0.05, significant difference was reached.

and 28 (16.1%) BC patients had died from other causes.

The Kaplan-Meier curves for CSS and OS of the two groups are shown in **Figure 1**. Five year CSS and OS rates of the UTUC and BC groups were 61.0% vs. 49.8% (P=0.008) and 58.3% vs. 37.4% (P<0.001), respectively. Univariate and multivariate analyses to predict cancer-specific and overall death in all patients are summarized in **Table 2**. In the univariate analysis, bladder tumor location and lymph nodal involvement were highly significant predictors of cancer-specific mortality and overall mortality. In the multivariate analysis, bladder tumor location and lymph nodal involvement remained independent predictors of cancer-specific mortality and overall mortality.

Discussion

We found significant differences in outcomes between patients with BC and UTUT. As a group, BC patients have worse pathological features (multifocality and positive lymph nodes) than UTUC patients. Similar to our findings, Michael Rink et al. reported that BC patients were more likely to experience disease recurrence and cancer-specific mortality compared UTUC patients. Tung et al. recently showed that patients with UTUC had higher frequencies of poor differentiation than BC [14]. Conversely, other

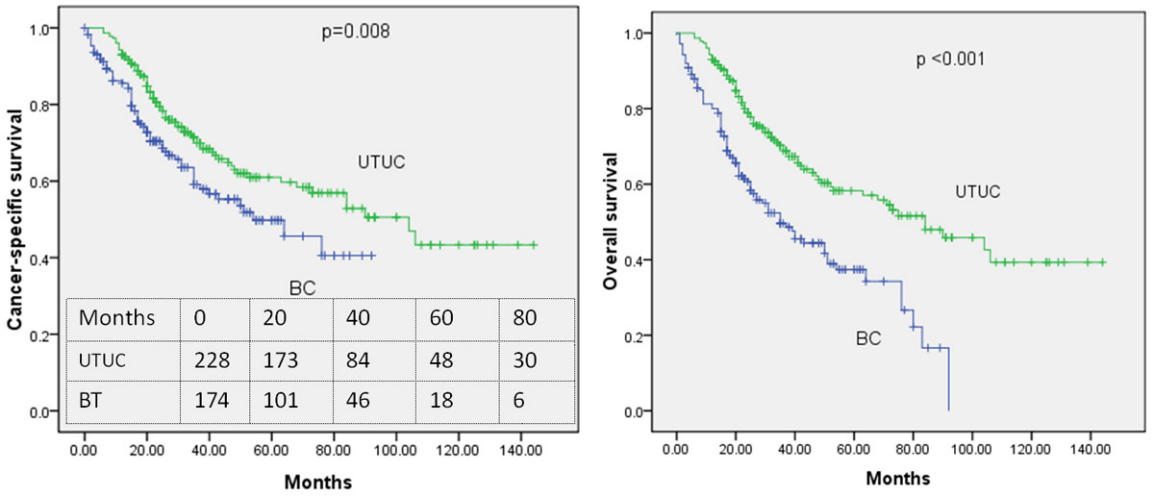

Figure 1. Kaplan-Meier curves for cancer-specific survival (CSS) and overall survival (OS) in patients with upper tract urothelial carcinoma (UTUC) and bladder cancer (BC). Between UTUC and BC groups, 5 year-CSS (61.0% vs. 49.8%, P=0.008) and OS (58.3% vs. 37.4%, P<0.001) rates were significantly different in pathological T stage ≥3.

studies found that UTUC patients had worse pathologic features [11, 15]. However, the study by Catto et al. reported comparable oncologic outcomes between UTUC and lower tract UC patients [11]. These disparate findings may be explained by differences between study populations and patient cohort sizes.

In this cohort, BC patients were tend to receive open surgical approach (P<0.001). Compared to upper urinary tract, the anatomies of lower urinary tract and adjacent organs were more complicated and dangerous. For safety and efficiency, especially when laparoscopic RC wasn't widely used, open surgical approach would be a more appropriate choice. However, open surgery must be a harder attack to the patient than laparoscopy. And moreover, radical cystectomy would encounter the inevitable urinary diversion, including ileal conduit diversion and cutaneous ureterostomy which would affect the patient's quality of life (QoL). It would take more time to recovery from the surgical trauma after surgery, especially receiving ileal conduit diversion. On the contrary, laparoscopic RNU for UTUC, especially retroperitoneal laparoscopic RNU, would be a minimal invasive trauma to patients, including decreasing the time of hospital stay and bowel recovery.

Based on our study, BC group shows a more frequent male sex than the UTUC group. The gender-related oncological outcomes of the two diseases from different studies are controversial. Women who present with BC present with more advanced disease and have worse survival than men [16]. However, sex is no longer considered an independent prognostic factor that influences UTUC mortality [17]. But a recent study considered the male sex as a significant predictor of a poor CSS in UTUC in the Chinese population [18]. The most plausible explanation for this could be the use of traditional Chinese medicine (TCM) containing aristolochic acid (AA). According to TCM theory, AA-containing preparations are mostly used by women for weight loss, regulating the menstrual cycle, increasing breast milk production and reducing the secretion of leucorrhea. Consequently, it was widely used by Chinese women until the State Drug Administration of PR China forbade its use in April of 2003. In one retrospective study of UTUC in Balkan endemic nephropathy patients, a lower tumor stage predominated among UTUC patients from the endemic settlements from 1957 to 1986 [19]. This phenomenon led to the prediction that UTUCs caused by AA might have lower malignancy and better CSS rates which would be helpful to explain our conclusion. Another reason for the gender disparity is that BC is usually the result of environmental carcinogens, whereas UTUC is often the result of genetic problems such as microsatellite instability. Environmental carcinogens affect men more wheras MSI is an equal-opportunity problem.

Table 2. Univariate and multivariate Cox proportional hazard regression analyses of cancer-specific mortality (A) and overall mortality (B)

	Univariate analysis				Multivariate analysis			
	A		B		A		B	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	1.052 (0.750-1.477)	0.768	1.306 (0.955-1.786)	0.094				
gender	1.270 (0.885-1.823)	0.195	1..314 (0.948-1.822)	0.101				
Tumor location (UTUC vs. BC)	0.640 (0.457-0.896)	0.009	0.468 (0.345-0.633)	<0.001	0.703 (0.499-0.989)	0.043	0.462 (0.316-0.673)	<0.001
Tumor size	1.248 (0.882-1.767)	0.211	1.223 (0.895-1.670)	0.207				
Multifocality	0.768 (0.539-1.092)	0.141	1.007 (0.743-1.366)	0.963				
Lymph node	2.049 (1.430-2.935)	<0.001	1.886 (1.356-2.623)	<0.001	1.919 (1.332-2.764)	<0.001	1.667 (1.194-2.329)	0.003
Hydronephrosis	1.152 (0.804-1.649)	0.441	0.915 (0.651-1.285)	0.608				
Surgical approach	1.167 (0.835-1.631)	0.364	1.408 (1.041-1.905)	0.026			0.866 (0.595-1.259)	0.450
Adjuvant chemotherapy	1.075 (0.742-1.556)	0.703	0.903 (0.637-1.280)	0.567				

Abbreviation: HR = hazard ratio, CI = confidence interval.

The field cancerization hypothesis might play a more important role in the development of multifocal lesions of urothelial carcinoma and the recurrence in the urinary tract. Independent multiclonal tumor development after carcinogenic exposure of the entire urothelial is the mechanism suggested. Chinese herbal nephropathy might introduce nephrotoxic and carcinogenic toxins into the system, inducing neoplasms within the entire urothelial field [20]. Considering that the bladder stores urine, its urothelium is exposed for longer to carcinogens than the upper tract, which receives transient urine exposure [21]. In addition, the surface area of the bladder is much greater than the surface area of the UUT is another important reason for tumor multifocality. As a consequence, it might be easier to develop multifocal lesions in the bladder than in the upper urinary tract.

Genetic variability in both malignancies might play a fundamental role in different outcomes, which have to be elucidated by continued research. Recent molecular studies showed a difference in genetic alterations between UTUC and bladder cancers. A meta-analysis showed that UTUC had specific etiologies (e.g., Balkan nephropathy and phenacetin abuse) and genetic hereditary nonpolyposis colorectal cancer risk factors, microsatellite instability, and epigenetic hypermethylation compared with BC [22]. For example, microsatellite instability-high (MSI-H, instability at >30% of loci) is more frequent in UTUC than in bladder cancer. An Indian research showed that MSI-H was frequently observed in high stage (40.6%) and high grade (59.4%) bladder tumors [23]. Another research also reported that high MSI indicates a better prognosis, especially in patients younger than 71 years with stage T2-T3N0M0 [24]. 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 two different urothelial carcinomas.

Preoperative hydronephrosis is more prevalent in UTUC than in BC in our study. The presence of preoperative hydronephrosis predicted poorer pathological outcomes and was a significant risk factor affecting survival [25]. Chung PH et al. [26] also showed that the degree of hydronephrosis predicts adverse pathological features and worse oncologic outcomes in patients with high-grade urothelial carcinoma of the upper urinary tract. The evaluation of hydronephrosis may be informative for decisions concerning surgical options, and the presence of hydronephrosis should raise the possibility of employing an aggressive treatment approach.

Our subjects were comprised only of patients with high-stage disease who received radical surgery for UTUC or UCB. Also, all of the patients were treated in one single institute which would improve the accuracy of this study. However, our study is not devoid of limitations. This study was limited by the retrospective nature of the analysis with a relatively small number of patients, finite proportion and vague indication of lymph node dissection. In addition, because patients with UTUC generally have more advanced disease at the initial diagnosis, we only focus on pT3-4cM0 diseases in this study. But we balanced the stage and grade, the results of our study may be better improved than those of other studies.

Conclusion

Our data suggest that locally invasive UC behaves differently in the upper and lower urinary tracts, which is different from the relative previous studies. For pathological stage 3 and above, UTUC has a better prognosis than BC when stage and grade are considered simultaneously. However, due to the retrospective study design, our results should be verified in a prospective study.

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of their medical records. The institutional review board approved this study.

Disclosure of conflict of interest

None.

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