Predictive role of preoperative hydronephrosis on poor pathological outcomes and prognosis in upper tract urothelial carcinoma patients: Experience from a nationwide high-volume center in China

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Abstract. To validate the predictive value of preoperative hydronephrosis (HN) with regard to clinicopathological outcome and prognosis in a large cohort of upper tract urothelial carcinoma (UTUC) patients, a retrospective analysis was conducted using the clinicopathological data of 520 consecutive patients treated between 2000 and 2010 at a nationwide high-volume center in China. Preoperative computed tomography or magnetic resonance imaging scans were evaluated for the presence of ipsilateral HN, and the associations between HN and pathological outcomes, patient survival and urinary tract recurrences were assessed. Ipsilateral HN was present in 271 patients (52.1%). Preoperative HN was associated with advanced age (P=0.007), sessile tumor architecture (P<0.001), ureteral location (P<0.001), higher tumor stage (P<0.001) and higher histological grade (P=0.002). Univariate and multivariate analyses revealed that poorer cancer-specific survival (CSS) and overall survival (OS) times were correlated with preoperative HN (P=0.004 and P=0.009, respectively). The 5-year CSS and OS rates for patients with HN were 86.9 and 86.2%, respectively, compared to 93.3 and 91.9% for patients without HN. For patients with muscle-invasive disease, HN remained a risk factor for poor CSS and OS (P=0.009 and P=0.012, respectively). No association was identified between HN and bladder recurrence (P=0.552) or the development of contralateral upper tract carcinoma (P=0.164). The findings indicated that preoperative HN is prevalent in UTUC. The presence of preoperative HN predicted poorer pathological outcomes and was a significant risk factor affecting survival. The evaluation of HN may be informative for decisions concerning surgical options, and the presence of HN should raise the possibility of employing an aggressive treatment approach.

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Introduction

Urothelial carcinoma is the second most common urological malignancy worldwide, after prostate cancer (1). A distinguishing feature of urothelial carcinomas is their multiple foci, which cause the tumors to appear synchronously or sequentially throughout the urinary tract, including the upper urinary tracts (renal pelvis or ureter), bladder and urethra (2). Upper tract urothelial carcinomas (UTUC) are uncommon and account for only 5-10% of urothelial carcinomas (3). At present, tobacco exposure is considered the most important risk factor for urothelial carcinoma (4,5). Gross or microscopic hematuria is the presenting symptom in 70-80% of UTUC patients (6). Furthermore, at the time of diagnosis 40-50% of patients exhibit *in situ* [pTa to pT1 (7)] disease, 50-60% of patients exhibit invasive or advanced disease [p≥T2 (7)], and ~25% patients already exhibit regional metastasis (8,9). Radical nephroureterectomy (RNU) with excision of the bladder cuff is the gold-standard treatment for UTUC (3). However, alternative treatments include ureteroscopic ablation, percutaneous resection and segmental resection (10). The oncological outcomes for patients with high-grade or non-organ-confined disease remain poor, with 5-year cancer-specific survival rates of <60%; while for patients with non-muscle-invasive lesions, the 5-year recurrence-free survival rate is 88.0-91.8% (11). For patients with low-grade carcinomas, conservative strategies, including segmental ureterectomy or endoscopic management, provide cancer-specific survival (CCS) and overall survival

(OS) rates equivalent to that achieved using RNU (12,13), with a 5-year cancer-specific survival rate of >93% (14), whereas patients at high-risk (pT3 or N+) may benefit from neoadjuvant chemotherapy (15,16). The ability to accurately predict pathological outcomes prior to initiating therapy may aid in clinical risk stratification and the selection of therapeutic strategies.

Ipsilateral hydronephrosis (HN) is common in UTUC patients, and may be attributed to one of several factors, including luminal obstruction, intramural invasion or extrinsic compression (17). The presence of ipsilateral HN in patients with bladder cancer is a predictive factor for poor pathological outcome and poor prognosis (18-20); however, at present, no consensus has been reached regarding the predictive role of the presence of HN in UTUC patients. Although HN has been reported to be associated with advanced disease (17,21-24), only two studies demonstrated a correlation between HN and poor prognosis based on small sample (17,25).

Our previous work has revealed associations between HN and muscle-invasive and grade 3 diseases (21). In the present study, after revising our database to include the follow-up information of patients treated between 2000 and 2010, we sought to validate the predictive value of preoperative HN on clinicopathological outcome and prognosis with the aim of improving clinical risk stratification and, thus, the ability to provide more optimal and personalized risk-informed therapeutic options.

Materials and methods

Patient selection. The clinicopathological data of consecutive UTUC patients treated between 2000 and 2010 at Peking University First Hospital (Beijing, China) were collected. Among the 631 patients with complete follow-up, 111 were excluded from the analysis: 25 with bilateral synchronous UTUCs, 54 who underwent alternative surgeries rather than RNU, 28 with a follow-up period of <12 months, 2 with metastatic disease and 2 with positive surgical margins. A total of 520 patients were finally enrolled for evaluation. All patients were diagnosed using computed tomography (CT) or magnetic resonance imaging (MRI), urological ultrasound and ureteroscopy with or without biopsy. None of these patients received neoadjuvant chemotherapy, however, for certain patients, adjuvant chemotherapy or radiotherapy was administered when evidence of distant metastasis or retroperitoneal recurrence was documented. All patients underwent surgery within two months after the occurrence of symptoms. Ethical approval was obtained from Peking University Institutional Review Board (IRB00001052-13057).

Ipsilateral HN status. Ipsilateral HN was assessed by upper urinary tract imaging, including CT with or without intravenous contrast in 510 patients, and MRI with or without intravenous contrast in 10 patients. Only imaging studies performed within 6 weeks of RNU and which were evaluated for HN by radiologists blinded to clinical outcomes were considered. As ~100 CT films were not available for re-evaluation, two authors (Dr Xuesong Li and Dr Gengyan Xiong) blinded to the radiology reports reviewed the 10 MRI films and 100 CT films independently. The concordance between the two observers in assessing presence or absence of HN was 95.5% and, by consensus decision, the concordance between re-evaluation and primary reports was 97.3%.

The evaluation criteria for assessing the presence or absence of HN were similar to those of a previous study (23). For renal pelvic lesions, patients with hydrocalycosis were included in the cohort of patients considered to have HN. A hydrocalyx was defined as any degree of dilation within a focal calyx, with or without the presence of obvious obstruction at the draining infundibulum. For ureteral tumors, any degree of dilation in any component of the ureter or associated renal unit was classified as HN. To avoid small subgroups and heterogeneity with respect to the grading of HN, the status of HN was evaluated strictly as present or absent in the current analysis.

Patients evaluation. All pathological specimens were re-reviewed by a dedicated genitourinary pathologist (Dr Qun He) to unify the reproducibility of the diagnosis. Tumor stage was assessed according to the 2002 Union for International Cancer Control TNM classification of malignant tumors (10). Tumor grade was assessed according to the World Health Organization classification of 1973 (10). Tumor architecture was defined as papillary or sessile by examination of the final specimen. Tumor location was divided into two areas (renal pelvis and ureter) based on the site of the dominant lesion. Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed macroscopic tumors in any location. The estimated glomerular filtration rate was calculated using the modified glomerular filtration rate estimating equation for Chinese patients (26).

Follow-up schedule. Of the total cohort (n=631), 520 patients were included in the current analyses. For patients who were followed-up at our institute, the follow-up regimen of the affected patients included cystoscopy every 3 months for the first 3 years; cystoscopy intervals were extended to 1 year thereafter. Chest X-ray, serum creatinine level and abdominal ultrasound or CT were examined concurrently. The impact of preoperative HN on CSS, OS, bladder recurrence-free survival and contralateral carcinoma-free survival times was determined. Bladder recurrence was defined as the detection of a subsequent bladder tumor during cystoscopy and confirmation by pathology, while contralateral carcinoma was defined as urothelial carcinoma in the contralateral upper urinary tract. The causes of patient mortality were determined by the treating physicians.

Statistical analysis. All statistical tests were performed using SPSS software version 20.0 (IBM SPSS, Armonk, NY, USA), and the threshold for statistical significance was set at $P<0.05$. The Pearson test and χ^2 test were used to assess the distribution of categorical variables, and the Mann-Whitney U test was used for continuous variables. Univariate analysis using the log-rank test and multivariate analysis using Cox's proportional hazards regression model were also conducted. Only variables that were indicated to be significant upon univariate analysis were considered for the multivariate analysis.

Results

Patient clinical and pathological characteristics and HN. The clinical and pathological data of the included patients and their association with HN are shown in Table I. Of the 520 patients enrolled, ipsilateral HN was present in 271 patients (52.1%).

Table I. Patient clinical and pathological characteristics and ipsilateral hydronephrosis.

Characteristic	Ipsilateral hydronephrosis, n (%)		χ^2	P-value
	Absent	Present		
Gender			0.004	0.951
Male	110 (21.15)	119 (22.88)		
Female	139 (26.73)	152 (29.23)		
Age, years			7.320	0.007[a]
<70	157 (30.19)	139 (26.73)		
≥70	92 (17.69)	132 (25.38)		
Preoperative renal function			3.221	0.522
CKD1 (eGFR≥90)	26 (5.00)	18 (3.46)		
CKD2 (90>eGFR≥60)	88 (16.92)	96 (18.46)		
CKD3 (60>eGFR≥30)	106 (20.38)	117 (22.50)		
CKD4 (30>eGFR≥15)	13 (2.50)	19 (3.65)		
CKD5 (eGFR<15)	16 (3.08)	21 (4.04)		
Urinary cytology			0.675	0.714
Negative	57 (10.96)	58 (11.15)		
Positive	122 (23.46)	128 (24.62)		
Missing data	70 (13.46)	85 (16.35)		
Tumor architecture			16.604	0.000[a]
Papillary	219 (42.12)	200 (38.46)		
Sessile	30 (5.77)	71 (13.65)		
Multifocality			2.788	0.095
No	205 (39.42)	207 (39.81)		
Yes	44 (8.46)	64 (12.31)		
Location			145.028	0.000[a]
Ureter	54 (10.38)	202 (38.85)		
Pelvis	195 (37.50)	69 (13.27)		
Tumor stage			24.199	0.000[a]
Ta	22 (4.23)	8 (1.54)		
T1	76 (14.62)	74 (14.23)		
T2	75 (14.42)	127 (24.42)		
T3	76 (14.62)	59 (11.35)		
T4	0 (0.00)	3 (0.58)		
Node stage			2.066	0.356
N0	20 (3.85)	31 (5.96)		
Nx	225 (43.27)	233 (42.88)		
N+	4 (0.77)	6 (1.15)		
Tumor grade			12.568	0.002[a]
G1	10 (1.92)	9 (1.73)		
G2	167 (32.12)	143 (27.50)		
G3	72 (13.85)	119 (22.88)		
Tumor necrosis			0.286	0.593
No	225 (43.27)	241 (46.35)		
Yes	24 (4.62)	30 (5.77)		
Tumor size, cm			1.205	0.272
≤3	156 (30.00)	157 (30.19)		
>3	93 (17.88)	114 (21.92)		
CIS			0.030	0.863
Absent	241 (46.35)	263 (50.58)		
Present	8 (1.54)	8 (1.54)		

[a]Statistically significant. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; CIS, carcinoma *in situ*.

Table II. Univariate and multivariate analysis of risk factors for cancer-specific survival.

Variable	Patients, n	Recurrence, n	Univariate analysis P-value	Multivariate analysis		
				Hazard ratio	95% CI	P-value
Presence of hydronephrosis			0.004[a]	1.932	1.294-2.883	0.001[a]
Absence	249	39				
Presence	271	66				
Gender			0.000[a]	0.491	0.327-0.738	0.001[a]
Female	291	43				
Male	229	62				
Age, years			0.028[a]			0.437
<50	28	7				
50-60	92	15				
60-70	175	31				
70-80	187	40				
≥80	38	12				
Preoperative renal function			0.940			
No CKD (eGFR≥60)	228	44				
Early CKD (60>eGFR≥15)	255	52				
End-stage CKD (eGFR<15)	37	9				
Urinary cytology			0.648			
Negative	115	22				
Positive	250	57				
Missing data	155	26				
Surgical approach			0.743			
Open	348	76				
Laparoscopic	172	29				
Tumor architecture			0.008[a]			0.364
Papillary	419	79				
Sessile	101	26				
Multifocality			0.560			
No	412	84				
Yes	108	21				
Location			0.060			
Ureter	256	58				
Pelvis	264	47				
Tumor stage			0.000[a]	1.663	1.289-2.145	0.000[a]
Ta	30	0				
T1	150	13				
T2	202	46				
T3	135	41				
T4	3	2				
Node stage			0.284			
N0	51	10				
Nx	458	91				
N+	10	3				
Tumor grade			0.010[a]			0.172
G1	19	0				
G2	310	56				
G3	191	49				
Tumor necrosis			0.021[a]	2.069	1.162-3.686	0.014[a]
No	466	90				
Yes	54	15				

Table II. Continued.

Variable	Patients, n	Recurrence, n	Univariate analysis P-value	Multivariate analysis		
				Hazard ratio	95% CI	P-value
Tumor size, cm			0.165			
≤3	313	59				
>3	207	46				
CIS			0.318			
Absent	504	103				
Present	16	2				
Adjuvant therapy			0.470			
No	485	95				
Yes	30	8				

[a]Statistically significant. CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; CIS, carcinoma *in situ*.

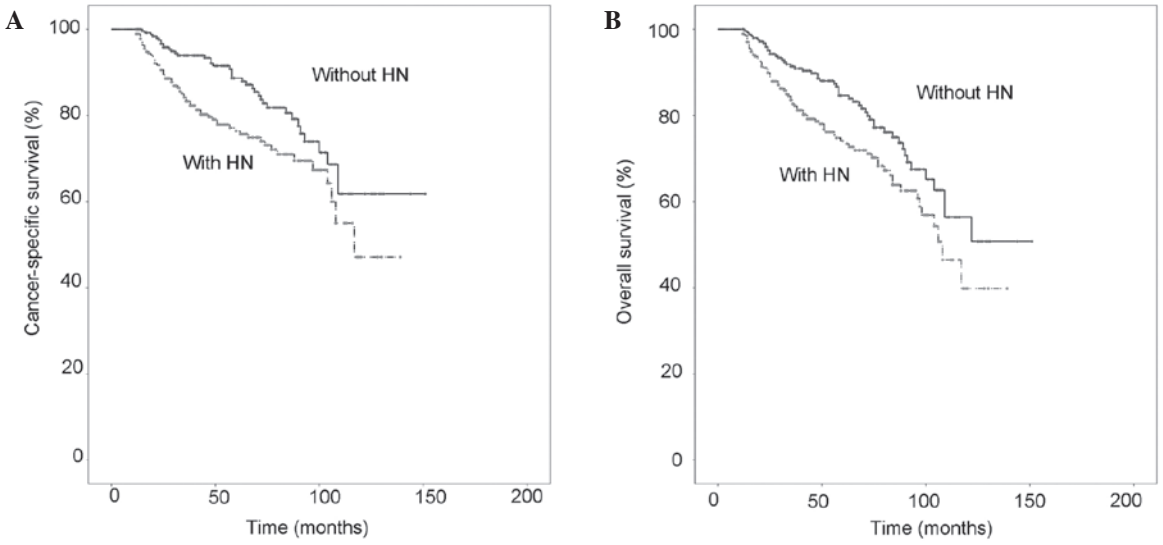

Figure 1. (A) Kaplan-Meier estimated cancer-specific survival curves stratified by the presence of HN (P=0.004). (B) Kaplan-Meier estimated overall survival curves stratified by the presence of HN (P=0.009). HN, hydronephrosis.

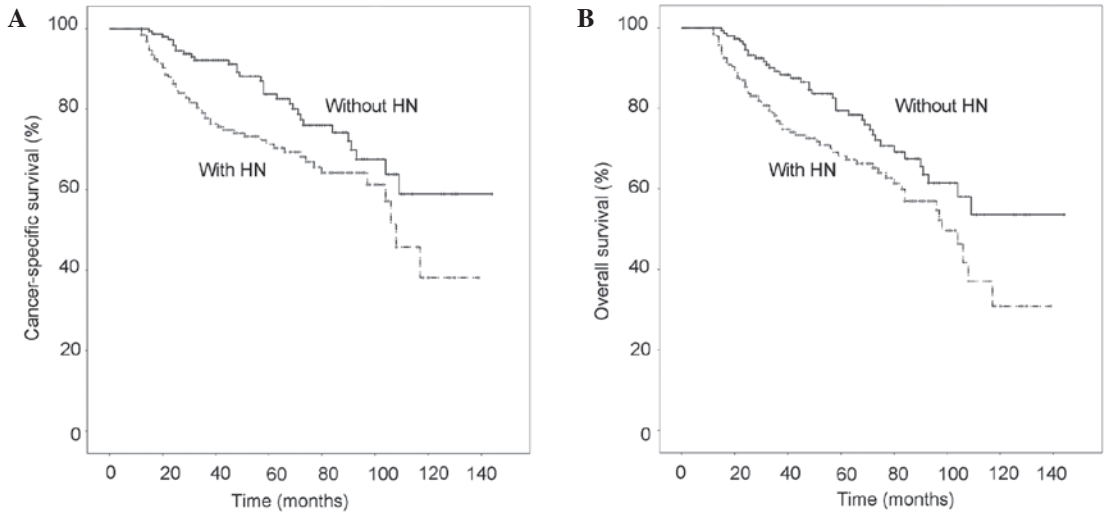

Figure 2. (A) Kaplan-Meier estimated cancer-specific survival curves in patients with muscle-invasive disease stratified by the presence of HN (P=0.009). (B) Kaplan-Meier estimated overall survival curves in patients with muscle-invasive disease stratified by the presence of HN (P=0.012). HN, hydronephrosis.

Table III. Univariate and multivariate analysis of risk factors for overall survival.

Variables	Patients, n	Recurrence, n	Univariate analysis P-value	Multivariate analysis		
				Hazard ratio	95% CI	P-value
Presence of hydronephrosis			0.009[a]	1.587	1.111-2.265	0.011[a]
Absence	249	52				
Presence	271	78				
Gender			0.000[a]	0.604	0.426-0.858	0.005[a]
Female	291	57				
Male	229	73				
Age, years			0.005[a]	1.284	1.068-1.542	0.008[a]
<50	28	8				
50-60	92	17				
60-70	175	38				
70-80	187	53				
≥80	38	14				
Preoperative renal function			0.260			
No CKD (eGFR≥60)	228	48				
Early CKD (60>eGFR≥15)	255	68				
End-stage CKD (eGFR<15)	37	14				
Urinary cytology			0.385			
Negative	116	26				
Positive	250	73				
Missing data	155	31				
Surgical approach			0.503			
Open	348	96				
Laparoscopic	172	34				
Tumor architecture			0.015a			0.262
Papillary	419	100				
Sessile	101	30				
Multifocality			0.271			
No	412	106				
Yes	108	24				
Location			0.110			
Ureter	256	69				
Pelvis	264	61				
Tumor stage			0.000[a]	1.581	1.265-1.976	0.000[a]
Ta	30	4				
T1	150	19				
T2	202	57				
T3	135	48				
T4	3	2				
Node stage			0.519			
N0	52	11				
Nx	458	116				
N+	10	3				
Tumor grade			0.005[a]			0.133
G1	19	0				
G2	310	70				
G3	191	60				
Tumor necrosis			0.137			
No	466	115				
Yes	54	15				

Table III. Continued.

Variables	Patients, n	Recurrence, n	Univariate analysis P-value	Multivariate analysis		
				Hazard ratio	95% CI	P-value
Tumor size, cm			0.306			
≤3	313	76				
>3	207	54				
CIS			0.344			
Absent	504	127				
Present	16	3				
Adjuvant therapy			0.648			
No	485	119				
Yes	30	9				

[a]Statistically significant. CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; CIS, carcinoma *in situ*.

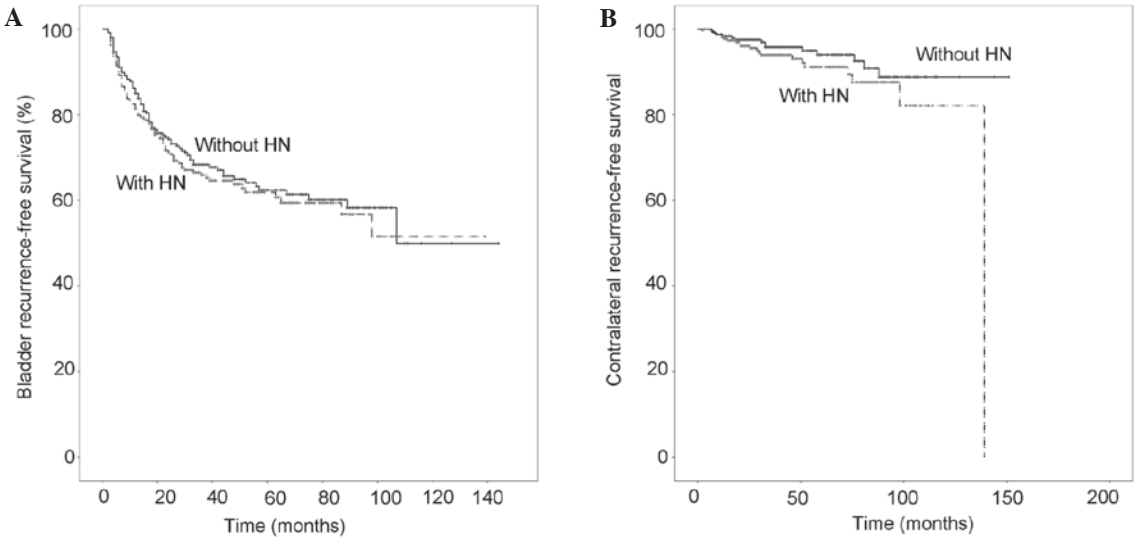

Figure 3. (A) Kaplan-Meier estimated bladder recurrence-free survival curves stratified by the presence of HN (P=0.552). (B) Kaplan-Meier estimated contralateral upper tract urothelial carcinoma-free survival curves stratified by the presence of HN (P=0.164). HN, hydronephrosis.

There were 340 patients with muscle-invasive disease (T stage ≥2), and 191 patients were diagnosed with histological grade 3 disease by final pathology. Preoperative HN was associated with advanced age (P=0.007), sessile tumor architecture (P<0.001), ureteral location (P<0.001), high tumor stage (P<0.001) and higher histological grade (P=0.002). No distribution differences in terms of gender, preoperative kidney function, multifocality, presence of carcinoma *in situ* (CIS) or tumor size were identified.

Survival outcomes and HN. During a median follow-up duration of 54 months (range, 12-151 months), 120 patients (23.1%) died, including 105 patients (20.2%) who succumbed to urothelial cancer. Of these patients, 78 (65.0%) had preoperative HN. The 5-year CSS and OS rates for patients with HN were 86.9 and 86.2%, respectively: Markedly lower than for patients without HN (93.3 and 91.9%, respectively).

Kaplan-Meier estimated CSS and OS curves are shown in Fig. 1A and B. The presence of HN was a significant risk factor for poorer CSS and OS times according to univariate analysis (P=0.004 and P=0.009, respectively). In the multivariate analysis, the presence of HN remained a significant predictive factor for CSS and OS (P=0.001 and P=0.011, respectively). The multivariate analysis also confirmed male gender, advanced age and higher tumor stage as risk factors for reduced survival (Tables II and III).

As higher tumor stage is a well-established predictor of survival (11), the predictive role of HN was analyzed only in the 340 patients with muscle-invasive disease (T≥2) (Table III). Of the 189 patients with HN, there were 68 mortalities, comprising 58 cancer-specific mortalities, during follow-up. By contrast, only 39 mortalities, including 31 cancer-specific mortalities, occurred among the remaining 151 patients without HN. The differences in CSS and OS times between the two groups were

statistically significant (P=0.009 and P=0.012, respectively; Fig. 2A and B).

Pathology confirmed that 178 patients (34.2%) had intravesical recurrence and 35 patients (6.7%) had subsequent contralateral UTUC. Of the patients with HN, 99 experienced intravesical recurrence and 22 contralateral disease during follow-up, and there was no association between the presence of HN and bladder cancer recurrence-free survival time (P=0.552) or the development of contralateral carcinoma-free survival time (P=0.164) (Fig. 3A and B).

Discussion

Preoperative HN can be present in bladder tumors and UTUCs. The incidence of HN in bladder tumors is reported to be 5.3-22.7%, and the presence of HN has been demonstrated to be associated with poor pathological outcomes, tumor recurrence and progression (18-20). The presence of HN is more prevalent in UTUC than in bladder tumors (52.1% in the current study), which may be because urinary obstruction is more likely to occur in the ureter from a small mass.

There have been a number of studies focused on the association between the presence of HN and clinicopathological characteristics and prognosis (17,22-25,27). The majority of these studies have reported a predictive role of HN in poor pathological outcomes, however, there has been no consensus on the association between HN and poor prognosis. Ng *et al* (17) confirmed that HN was independently associated with cancer metastasis and cancer-specific mortality by preoperative multivariable analysis controlling for preoperative clinical features. However, their research was based on only 106 patients and HN was no longer an independent risk factor upon postoperative multivariable analysis. Hwang *et al* (25) reported that preoperative HN predicted poor prognosis in 114 patients; data on architecture, multifocality and preoperative renal function were unavailable. Ito *et al* (22) reported that 67 patients (73.6%) exhibited HN in a retrospective study of 91 cases, and validated the correlation between HN and poor pathological outcomes, whilst a higher HN grade was not associated with disease-specific or metastasis-free survival. Bozzini *et al* (27) conducted a relatively large-scale study with 401 patients, however, HN was present in only 18.4% of patients and the median follow-up period was 26 months. Furthermore, whilst studies by Messer *et al* (23) and Brien *et al* (24) demonstrated that HN was associated with muscle-invasive and non-organ confined disease, these studies were lacking in follow-up data.

The proportions of HN reported in previous studies may differ due to the lack of clear criteria with which to evaluate HN. Based on the current analysis, the presence of HN was associated with a number of poor pathological outcomes, including high tumor stage, high tumor grade and sessile tumor architecture. In addition, a greater number of tumors were located in the ureter in patients with HN, and previous studies have demonstrated that patients with ureteral tumors have a poorer prognosis compared with those with renal pelvis tumors, after adjustment for a number of pathological variables (28,29). A recent study attributed this difference in prognosis to the fact that ureteral tumors are more likely to have HN (30). According to univariate and multivariate survival analyses, the presence of HN was associated with poorer survival, which confirmed the role of HN as an independent risk factor for poor prognosis. Preoperative HN must be carefully evaluated as a significant predictive factor for prognosis as well as higher tumor stage and tumor grade. The present study observed no correlation between HN and bladder recurrence or contralateral UTUC, and no such association has been reported previously (31).

Using conservative surgeries, including segmental ureterectomy or endoscopic management, renal function may be preserved and perioperative complications with RNU avoided (32). Clinical consideration of advanced disease based on the presence of HN could allow physicians to better individually assess treatment options in UTUC; patients with HN may not be suitable candidates for less invasive surgical options. In addition, patients with locally advanced UTUC have significantly higher local recurrence and distant metastasis rates following RNU, compared with patients exhibiting early stage disease (11,33). Such findings call for effective strategies for perioperative systemic therapy to improve survival. The presence of HN also indicates a need for aggressive treatment, including lymphadenectomy and systemic chemotherapy.

Neoadjuvant chemotherapy appears to achieve favorable oncological outcomes in high-risk patients (15,16), while adjuvant chemotherapy confers minimal impact on OS or CSS (34,35). In addition, not all patients are able to receive adjuvant treatment due to comorbidities and impaired renal function following RNU (36). Hoshino *et al* (37) found that patients with no HN or a lower grade of HN have a higher risk of missing the opportunity to undergo adjuvant chemotherapy for impaired renal function following RNU. Thus, if patients without HN are evaluated as high-risk (based on lymph node metastasis or higher biopsy grade) and systemic chemotherapy is considered, neoadjuvant chemotherapy is recommended before renal function becomes impaired.

The limitations of the current study include the retrospective design and data collection, and the lack of re-evaluation of a number of CT films. Therefore, the study cohort may be subject to selection and recall bias. The incidence of UTUC in the Chinese population is markedly higher compared with that of western populations, and the biology may differ (38). Although the mechanisms related to these ethnic differences are still not fully known, dietary exposure to toxins may play a major role (39). In addition, Chinese UTUC patients are more likely to be female, and females are less likely to be of an advanced pathological disease stage compared with males (40,41). Despite its limitations, the present study is currently the largest to report on the predictive role of HN in UTUC patients, and the first study confirming an association between HN and poor prognosis after controlling for other clinical and pathological characteristics in a large sample.

In conclusion, preoperative HN is prevalent in UTUC. The presence of preoperative HN predicted poorer pathological outcomes and was a significant risk factor affecting survival. The evaluation of HN may therefore be informative for decisions concerning surgical strategies, and the presence of HN should raise the possibility of employing an aggressive treatment strategy.

Acknowledgements

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