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Urologic Oncology: Seminars and Original Investigations 32 (2014) 981–988

UROLOGIC ONCOLOGY

Original article

Degree of hydronephrosis predicts adverse pathological features and worse oncologic outcomes in patients with high-grade urothelial carcinoma of the upper urinary tract

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Received 28 January 2014; received in revised form 24 February 2014; accepted 24 February 2014

Abstract

Objective: To evaluate degree of hydronephrosis (HN) as a surrogate for adverse pathological features and oncologic outcomes in patients with high-grade (HG) and low-grade (LG) upper tract urothelial carcinomas (UTUCs).

Methods: We retrospectively reviewed 141 patients with localized UTUCs that underwent extirpative surgery at a tertiary referral center. Preoperative imaging was used to evaluate presence and degree of ipsilateral HN. We evaluated degree of HN (none/mild vs. moderate/severe), pathological findings, and oncologic outcomes.

Results: HG UTUC was present in 113 (80%) patients, muscle-invasive disease (≥pT2) in 49 (35%), and non–organ-confined disease (≥pT3) in 41 (29%). At a median follow-up of 34 months, 49 (35%) patients experienced intravesical recurrence, 28 (20%) developed local/systemic recurrence, and 24 (17%) died of UTUC. HN was graded as none/mild in 77 (55%) patients and moderate/severe in 64 (45%). In patients with HG UTUC, but not LG, degree of HN was associated with advanced pathological stage ($P < 0.001$), positive lymph nodes ($P = 0.01$), local/systemic recurrence-free survival (hazard ratio [HR] = 5.5, $P = 0.02$), and cancer-specific survival (HR = 5.2, $P = 0.02$). On multivariable analysis of preoperative factors, degree of HN in patients with HG UTUC was associated with muscle invasion (HR = 9.3; 95% CI: 3.08–28.32; $P < 0.001$), non–organ-confined disease (HR = 4.5; 95% CI: 1.66–12.06; $P = 0.003$), local/systemic recurrence-free survival (HR = 2.5; 95% CI: 1.07–5.64; $P = 0.04$), and cancer-specific survival (HR = 2.6; 95% CI: 1.05–6.22; $P = 0.04$).

Conclusions: Degree of HN can serve as a surrogate for advanced disease and predict worse oncologic outcomes in HG UTUC. Degree of HN was not predictive of intravesical or local/systemic recurrence in LG UTUC.

Keywords: Upper tract urothelial carcinoma; Hydronephrosis; Nephroureterectomy; Outcome; Chemotherapy

1. Introduction

Upper tract urothelial carcinoma (UTUC) is a rare disease and represents 5% to 8% of all urothelial malignancies [1]. The gold standard of treatment for patients with UTUC is radical nephroureterectomy (RNU) [2]. Patients subjected to RNU may be overtreated if they have low-grade (LG) disease or low-stage disease or both and undertreated if they have advanced and non–organ-confined disease. The latter patients may benefit from perioperative chemotherapy; however, it is challenging to identify these patients correctly with preoperative staging [3]. Upper tract tissue sampling and radiographic imaging alone are not reliable in accurately predicting stage, therefore other preoperative surrogates are needed to help identify which

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http://dx.doi.org/10.1016/j.urolonc.2014.02.018
1078-1439/

patients have advanced disease associated with poor prognosis. These patients should be considered for neoadjuvant chemotherapy, as many patients who undergo extirpative surgery do not have sufficient renal reserve to receive platinum-based adjuvant chemotherapy [4]. The theoretical advantages of neoadjuvant compared with adjuvant chemotherapy include eradication of micrometastases, improved patient tolerability before surgery, and ability to deliver higher doses before loss of renal function after surgery [5].

Common preoperative factors used to predict muscle-invasive or non–organ-confined disease include tumor grade, tumor architecture, tumor location, and radiographic imaging [6]. In urothelial carcinoma of the bladder, presence of hydronephrosis (HN) before radical cystectomy is a surrogate for higher pathological stage and worse oncologic outcomes [7]. Presence of HN in UTUC has also been suggested to be associated with advanced pathological stage on final specimen and has been linked to development of cancer metastasis and survival [8–12]. However, confounding studies have identified the contrary [13–15]. All prior HN studies evaluated patients with LG and high-grade (HG) UTUCs as 1 cohort. Furthermore, several of these studies included intravesical recurrence (IVR) in their assessment of local/systemic recurrence. This study uniquely explores the associations of degree of HN and its effects on local/systemic and bladder recurrences separately in LG and HG groups. It is possible that the implications of HN in LG tumors are significantly different from that in HG tumors, and these patients should not undergo neoadjuvant chemotherapy if that is the case.

2. Methods

With institutional review board approval, a retrospective review was conducted of patients who underwent RNU or distal ureterectomy for UTUC from July 1998 to July 2013. Patients with metastatic or unresectable UTUC were excluded. Patients undergoing conservative management with endoscopic ablation were also excluded. Patients with a history of bladder cancer were included in this study; however, patients with prior muscle-invasive bladder cancer, prior cystectomy, or cystectomy at time of RNU were excluded. Patients did not receive a postoperative dose of adjuvant mitomycin C as previously described in the One Dose Mitomycin-C trial [16]. Pathological characteristics (primary tumor and nodal stage, tumor grade, location, focality, and architecture [papillary vs. sessile]), lymphovascular invasion, and presence of carcinoma in situ were assessed by a genitourinary pathologist using the 2010 American Joint Committee in Cancer-Union for International Cancer Control staging criteria and the 2004 World Health Organization/International Society of Urological Pathology consensus classification [17].

Patients were required to have available preoperative imaging to assess presence and degree of ipsilateral HN. Imaging conducted within 6 months before surgery was reviewed. Ipsilateral HN was graded by O.M.D. using preoperative computer tomography with or without contrast, intravenous pyelogram, or renal ultrasound imaging. If more than 1 imaging modality was available for a patient, preference was given to computer tomography before intravenous pyelogram and ultrasound. Degree of HN was assigned as follows: none (no calyx or pelvic dilation), mild (pelvic dilatation alone), moderate (mild calyx dilation), or severe (severe calyx dilation or calyx dilation accompanied by renal parenchyma atrophy).

Patients were followed up every 3 to 4 months for the first year, semiannually for the second through fifth year, and then annually thereafter. Follow-up included physical examination, routine blood work, urine cytology, chest radiography, cystoscopy, and upper tract imaging. Further workup was obtained when clinically indicated. Local recurrence was defined as recurrence in the renal fossa or retroperitoneal disease, whereas systemic recurrence was defined as any distant recurrence. IVR was assessed separately from local and systemic recurrence. Death and cause of death were assessed by the treating physician and death certificate or death certificate alone.

2.1. Statistical analysis

The associations between HN and clinical and pathological parameters were assessed using Fisher exact test or chi-square analysis. Kaplan-Meier analysis was used to evaluate oncologic survival data. To identify risk factors for muscle invasion and non–organ-confined disease, preoperative and postoperative parameters were evaluated with univariate (UVA) and multivariate (MVA) binary logistic regression analyses. UVA and MVA Cox regression analyses were conducted to assess intravesical recurrence-free survival (RFS), local/systemic RFS, and cancer-specific survival (CSS). Statistical significance was defined as 2-sided $P < 0.05$. All statistics were conducted using SPSS (Version 19, IBM, Armonk, NY).

3. Results

Clinical and pathological characteristics of the 141 patients who met inclusion criteria are presented in Table 1. Median age at the time of surgery was 70 years (range: 35–92), and 91 patients (64%) were male. A total of 50 patients (35%) had a history of bladder cancer. Perioperative chemotherapy was administered to 23 patients: neoadjuvant chemotherapy ($n = 10$, 7%), adjuvant chemotherapy ($n = 10$, 7%) or both ($n = 3$, 2%). Patients underwent laparoscopic or open RNU ($n = 129$, 91%) according to the surgeon's preference. All distal ureterectomy procedures ($n = 12$, 9%) were conducted as open procedures. Lymph node (LN) dissection was conducted to the surgeon's preference in 46 patients (33%) and did not follow a predefined template.

Table 1
Clinical and pathologic characteristics of 141 patients treated with extirpative surgery for UTUC

	n (%)
Patients	141 (100)
Median age (range)	70 (35–92)
Gender	
Male	91 (64)
Female	50 (36)
History of bladder cancer	
No	91 (65)
Yes	50 (35)
Hydronephrosis	
Absent	38 (27)
Present	103 (73)
Degree of hydronephrosis	
None	38 (27)
Mild	39 (28)
Moderate	37 (26)
Severe	27 (19)
Pathologic tumor grade	
Low	28 (20)
High	113 (80)
Tumor focality	
Unifocal	73 (52)
Multifocal	68 (48)
Location	
Renal pelvis	100 (71)
Ureter	41 (29)
Pathologic T stage	
Tis	6 (4)
Ta	55 (39)
T1	31 (22)
T2	8 (6)
T3	37 (26)
T4	4 (3)
Lymph node status	
pN0	33 (23)
pNx	100 (71)
pN+	8 (6)
Intravesical recurrence	
No	92 (65)
Yes	49 (35)
Local/systemic recurrence	
No	113 (80)
Yes	28 (20)
Dead of disease	
No	117 (83)
Yes	24 (17)

HG cancer was detected in 113 patients (80%), T stage ≥pT2 in 49 patients (35%), and nodal positive disease in 8 patients (6%). Tumors occurred most often in the renal pelvis (n = 100, 71%). No HN was present in 38 (27%) patients, whereas HN was present in 103 patients (73%) and graded as mild (n = 39, 28%), moderate (n = 37, 26%), or severe (n = 27, 19%). Patients were grouped by degree of HN (none/mild vs. moderate/severe) owing to similar rates of disease recurrence and survival within each pairing. Median follow-up for the patients alive at analyses was 34 months (range: 1–149). IVR occurred in 49 (35%) patients, local/systemic recurrence in 28 (20%), and death from disease in 24 (17%).

Degree of HN was associated with T stage ≥pT2 and positive LN status in patients with HG (Table 2) but not LG tumors (data not shown). Degree of HN was also predictive

Table 2
Pathological characteristics and outcomes for patients with high-grade tumors stratified by degree of hydronephrosis (none/mild vs. moderate/severe)

	High-grade tumor, *n* (%)	Degree of hydronephrosis, *n* (%)		*P* value
		None/mild	Moderate/severe	
Number of patients	113 (100)	58 (51)	55 (49)	–
Gender				
Male	73 (65)	42 (72)	31 (56)	0.08
Female	40 (35)	16 (28)	24 (44)	
Location				
Renal pelvis	75 (65)	43 (74)	32 (58)	0.07
Ureter	38 (65)	15 (26)	23 (42)	
Tumor architecture				
Papillary	65 (58)	34 (59)	31 (56)	0.81
Sessile	48 (42)	24 (41)	24 (44)	
Pathological T stage				
<pT2	64 (57)	43 (74)	21 (38)	**<0.001**
≥pT2	49 (43)	15 (25)	34 (62)	
Lymph node status				
pN0	28 (25)	9 (16)	19 (34)	**0.01**
pNx	77 (68)	47 (81)	30 (55)	
pN+	8 (7)	2 (3)	6 (11)	
CIS				
Absent	77 (68)	43 (74)	34 (62)	0.16
Present	36 (32)	15 (26)	21 (38)	
LVI				
Absent	79 (70)	44 (76)	35 (64)	0.16
Present	34 (30)	14 (24)	20 (36)	
Intravesical recurrence				
No	73 (65)	40 (69)	33 (60)	0.38[a]
Yes	40 (35)	18 (31)	22 (40)	
Local/systemic recurrence				
No	86 (76)	50 (86)	36 (65)	**0.02**[a]
Yes	27 (24)	8 (14)	19 (35)	
Dead of disease				
No	89 (79)	51 (88)	38 (69)	**0.02**[a]
Yes	24 (21)	7 (12)	17 (31)	

CIS = carcinoma in situ; LVI = lymphovascular invasion.
[a] *P* value calculated using log-rank analysis. Bold values are statistically significant.

of local/systemic RFS (hazard ratio [HR] = 5.5, $P = 0.02$) and CSS (HR = 5.2, $P = 0.022$) in patients with HG, but not LG tumors in log-rank analyses (Fig.). Degree of HN was not predictive of IVR in either tumor grade. Degree of HN in HG tumors was predictive of muscle-invasive disease on UVA (odds ratio [OR] = 4.6; 95% CI:

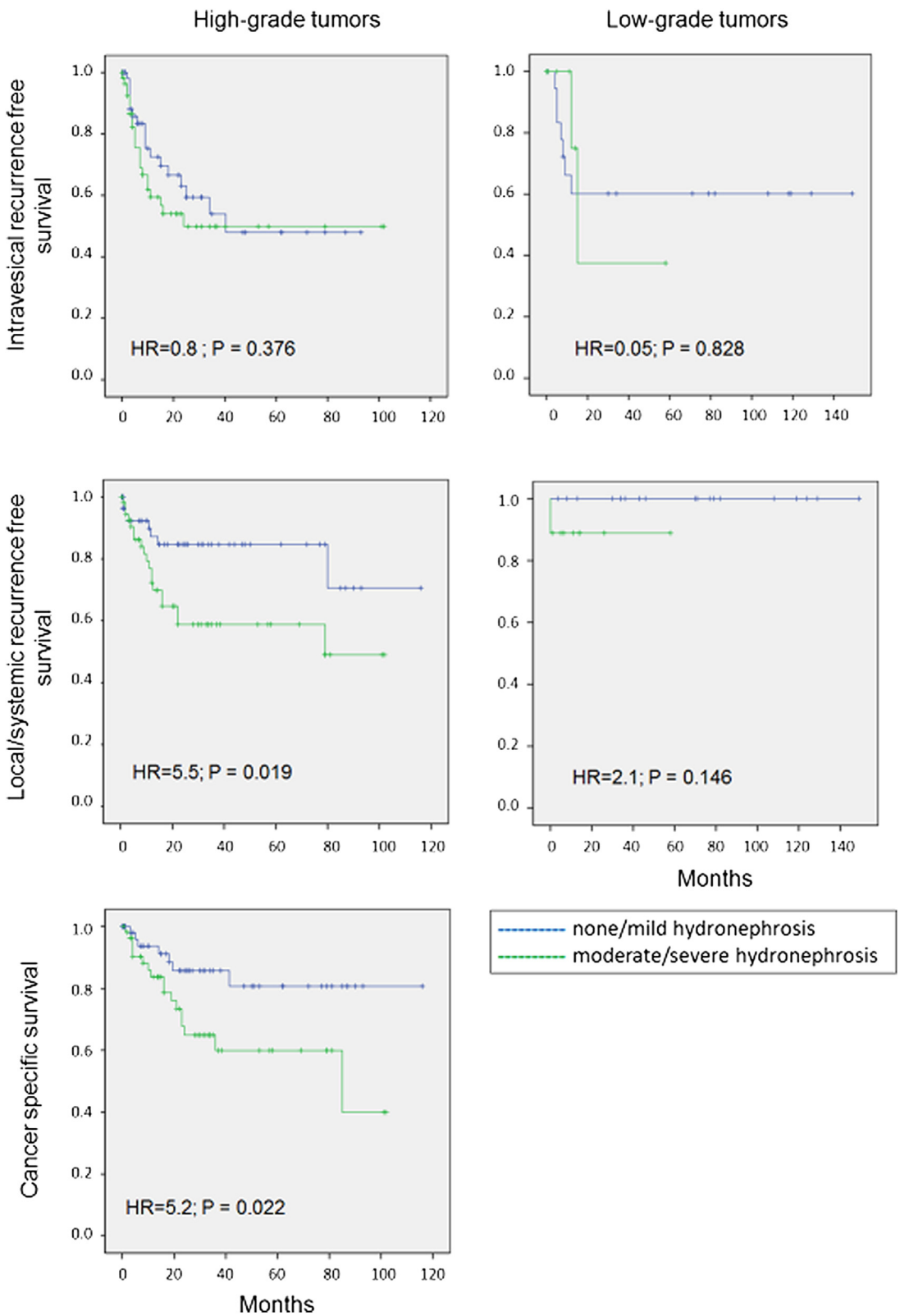

Fig. Kaplan-Meier log-rank analyses for intravesical recurrence-free survival, local/systemic recurrence-free survival and cancer-specific survival in 28 patients with low-grade tumors and 113 patients with high-grade tumors treated with extirpative surgery for UTUC stratified by the degree of preoperative hydronephrosis. (Color version of figure is available online.)

2.08–10.34; $P < 0.001$) and MVA (HR = 9.3; 95% CI: 3.08–28.32; $P < 0.001$) when adjusting for age, sex, tumor location, and tumor architecture (Table 3). Degree of HN in HG tumors was also predictive of non–organ-confined disease on UVA (OR = 3.0; 95% CI: 1.36–6.75; $P = 0.007$) and MVA (HR = 4.5; 95% CI: 1.66–12.06; $P = 0.003$) when adjusting for age, sex, tumor location and tumor architecture. Tumor architecture (papillary vs. sessile) was the only other variable predictive of muscle invasion and non–organ-confined disease on both UVA and MVA.

Degree of HN, T stage ≥pT2, and lymphovascular invasion were predictive of both local/systemic RFS and CSS on UVA in patients with HG tumors (Table 4). Degree of HN remained predictive of local/systemic RFS (HR = 2.5; 95% CI: 1.07–5.64; $P = 0.04$) and CSS (HR = 2.6; 95% CI: 1.05–6.22; $P = 0.04$) when pre-RNU parameters were assessed on MVA. Degree of HN lost predictive ability when T stage and additional post-RNU parameters were assessed on MVA. T stage ≥pT2 was predictive of both local/systemic RFS (HR = 5.5; 95% CI: 1.80–17.06; $P = 0.003$) and CSS (HR = 5.3; 95% CI: 1.55–17.96; $P = 0.01$) on MVA in the post-RNU parameter model. Degree of HN and T stage were not predictive of IVR-free survival. Only ureteral tumor location was predictive of IVR-free survival on UVA (HR = 1.9; 95% CI: 1.10–3.44; $P = 0.02$) and MVA with pre-RNU parameters (HR = 1.9; 95% CI: 1.02–3.42; $P = 0.04$), but not on MVA with post-RNU parameters.

4. Discussion

UTUC, compared with bladder cancer, potentially poses greater risk for early lymphatic and vascular dissemination owing to the thin muscle layer of the ureter and renal pelvis [18]. Patients with HG and high-stage disease treated with neoadjuvant chemotherapy may experience tumor downstaging, and in rare cases, even complete response, which may translate into increased CSS [19,20]. Cisplatin-based chemotherapy requires an epidermal growth factor receptor of 50 to 60 ml/min/1.73 m^2. Up to 26% to 30% of patients initially eligible for neoadjuvant chemotherapy are ineligible for adjuvant chemotherapy owing to loss of renal function after surgery [4,21]. Therefore, preoperative diagnosis of advanced disease, and thereby poor prognosis, is of utmost importance so that patients may receive neoadjuvant chemotherapy before renal function decreases below the threshold of platinum tolerability. Tumor stage is the most significant prognostic factor for oncologic outcome in patients with UTUC. Unfortunately, accurately predicting tumor stage before extirpative surgery is challenging owing to the limitations of modern cross-sectional imaging and tissue sampling with small-caliber instrumentation [22,23]. Predicting tumor stage requires a multifactorial approach possibly incorporating readily available preoperative characteristics such as HN.

Less than half of the patients from this study were contributed to the multi-institutional UTUC Collaboration database, which ceased collection in 2008. Although the UTUC Collaboration has assessed HN previously, this is the first study, to our knowledge, to evaluate oncologic outcomes in patients stratified by both tumor grade and degree of HN. Prior studies have evaluated HN in cohorts composed of both HG and LG tumors. Several studies individually identified that HN was associated with worse oncologic outcomes (metastasis-free survival, CSS, and overall survival), whereas other studies identified no such associations (Table 5) [8,11–13,15]. Furthermore, the relationship between HN and muscle-invasive disease also varied in several studies [9,10,14]. Presence of HN (37%–89%) and HG tumors (44%–80%) is well distributed among most of the studies. HN was present in only 18% of patients evaluated by Bozzini et al., and the distribution of

Table 3
Univariate and multivariate binary logistic regression analyses of preoperative parameters to assess muscle-invasive and non–organ-confined UTUC in 113 patients with high-grade UTUCs

	Muscle-invasive UTUC			Non–organ-confined UTUC		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Univariate						
Age at surgery	1.0	0.97–1.03	0.9	1.0	0.98–1.04	0.5
Gender (female vs. male)	1.1	0.51–2.41	0.8	1.1	0.49–2.41	0.8
Degree of hydronephrosis (none/mild vs. moderate/severe)	**4.6**	**2.08–10.34**	**<0.001**	**3.0**	**1.36–6.75**	**0.007**
Tumor location (renal pelvis vs. ureter)	1.1	0.49–2.38	0.8	0.9	0.39–1.98	0.7
Tumor architecture (papillary vs. sessile)	**9.1**	**3.47–18.92**	**<0.001**	**8.2**	**3.42–19.59**	**<0.001**
Multivariate						
Age at surgery	1.0	0.95–1.03	0.6	1.0	0.96–1.05	0.9
Gender (female vs. male)	0.7	0.26–1.88	0.5	0.8	0.29–2.03	0.6
Degree of hydronephrosis (none/mild vs. moderate/severe)	**9.3**	**3.08–28.32**	**<0.001**	**4.5**	**1.66–12.06**	**0.003**
Tumor location (renal pelvis vs. ureter)	0.80	0.30–2.12	0.6	0.7	0.26–1.80	0.4
Tumor architecture (papillary vs. sessile)	**13.8**	**4.71–40.72**	**<0.001**	**10.1**	**3.85–26.39**	**<0.001**

Bold values are statistically significant.

Table 4
Univariate and multivariate Cox Regression analyses to assess intravesical recurrence-free survival in 141 patients with high- and low-grade UTUCs and local/systemic recurrence-free survival and cancer-specific survival in 113 patients with high-grade UTUCs

	Intravesical recurrence-free survival			Local/systemic recurrence-free survival			Cancer-specific survival		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Univariate analysis									
Degree of hydronephrosis (none/mild vs. moderate/severe)	1.3	0.74–2.27	0.37	**2.6**	**1.13–5.92**	**0.03**	**2.7**	**1.11–6.49**	**0.03**
Tumor location (renal pelvis vs. ureter)	**1.9**	1.10–3.44	**0.02**	1.5	0.70–3.27	0.29	1.9	0.88–4.41	0.10
Tumor architecture (papillary vs. sessile)	0.8	0.44–1.45	0.50	1.9	0.89–4.12	0.10	1.8	0.81–4.12	0.15
CIS (absent vs. present)	0.7	0.35–1.32	0.25	1.0	0.43–2.26	0.97	1.2	0.49–2.74	0.72
Grade (low vs. high)	1.3	0.63–2.70	0.47	–	–	–	–	–	–
Pathological T stage (<pT2 vs. ≥pT2)	0.9	0.47–1.59	0.65	**6.1**	**2.43–15.34**	**<0.001**	**6.1**	**2.28–6.53**	**<0.001**
Lymph node status (pN0 vs. pN+)	0.3	0.06–1.07	0.06	1.1	0.30–4.28	0.86	1.4	0.35–5.66	0.63
LVI (absent vs. present)	0.5	0.25–1.21	0.14	**2.9**	**1.36–6.36**	**0.01**	**3.2**	**1.44–7.26**	**0.004**
Multivariate analysis for known parameters pre-RNU procedure									
Degree of hydronephrosis (none/mild vs. moderate/severe)	1.1	0.62–2.02	0.70	**2.5**	**1.07–5.64**	**0.04**	**2.6**	**1.05–6.22**	**0.04**
Tumor location (renal pelvis vs. ureter)	**1.9**	**1.02–3.42**	**0.04**	1.5	0.67–3.19	0.35	2.0	0.87–4.50	0.11
Tumor architecture (papillary vs. sessile)	0.7	0.39–1.37	0.33	2.0	0.94–4.45	0.07	2.0	0.88–4.58	0.10
Grade (low vs. high)	1.2	0.55–2.63	0.65	–	–	–	–	–	–
Multivariate analysis for known parameters post-RNU procedure									
Degree of hydronephrosis (none/mild vs. moderate/severe)	1.3	0.66–2.44	0.48	1.1	0.46–2.83	0.79	1.3	0.50–3.23	0.61
Tumor location (renal pelvis vs. ureter)	1.7	0.89–3.15	0.11	1.9	0.82–4.37	0.13	**2.6**	**1.12–.24**	**0.03**
Tumor architecture (papillary vs. sessile)	1.1	0.52–2.23	0.84	0.9	0.35–2.23	0.80	0.7	0.25–1.93	0.49
Grade (low vs. high)	1.3	0.58–2.87	0.52	–	–	–	–	–	–
Pathological T stage (<pT2 vs. ≥pT2)	0.9	0.40–2.11	0.85	**5.5**	**1.80–17.06**	**0.003**	**5.3**	**1.55–17.96**	**0.01**
LVI (absent vs. present)	0.6	0.20–1.62	0.29	1.36	0.52–3.57	0.54	19	0.64–5.57	0.25

CIS = carcinoma in situ; LVI = lymphovascular invasion. Bold values are statistically significant.

tumor grade was unknown in the Ito et al. cohort. In our study, 20% of patients had LG disease, and analyzing all grades together can result in dilution of the effect of HN as this was not a significant predictor for these patients. In other studies, inclusion of patients with LG disease may have influenced the contrary findings.

In an effort to clarify these contradictory findings, we hypothesized that degree of HN was a relevant prognostic feature only in patients with HG urothelial cancer. The first evidence supporting our hypothesis was that the degree of HN was associated with advanced T stage ($P < 0.001$), LN status ($P = 0.01$), local/systemic RFS ($P = 0.02$), and CSS ($P = 0.02$) in patients with HG urothelial cancer. In MVA, the degree of HN was predictive of muscle invasion (OR = 9.3; 95% CI: 3.8–28.32; $P < 0.001$) and non–organ-confined disease (OR = 4.5; 95% CI: 1.66–12.06; $P = 0.003$), after adjusting for age, sex, tumor location, and tumor architecture, identifying HN as an effective preoperative surrogate of tumor stage. Degree of HN in patients with HG tumors was also predictive of CSS (HR = 2.6; 95% CI: 1.05–6.22; $P = 0.04$) when used in a preoperative model (in which it was used as a surrogate of stage and invasiveness of disease); however, HN lost predictive ability when evaluated with postoperative parameters such as T stage, which can readily be explained owing to the close relationship of presence of HN and T stage in patients with HG tumors. Ng et al. [8] evaluated HN in similar models and also identified HN to be predictive of CSS in preoperative but not postoperative models owing to the inclusion of T stage. In our study, HN was predictive of local/systemic RFS (HR = 2.5; 95% CI: 1.07–5.64; $P = 0.04$), but not IVR-free survival, which was evaluated separately. Ng. et al. failed to identify HN as a preoperative predictor of RFS, possibly because IVR was included in their recurrence analysis.

The mechanisms behind the associations between HN, HG tumors, and worse oncologic outcomes are unknown. We speculate that HN may cause outward expansion and longitudinal thinning of the already narrow ureter or renal pelvis wall, which may facilitate the seeding of cancer cells to regional or distant organs. HN may also cause increased outward centrifugal pressure causing reverse flow in lymphatics and vasculature, which may result in increased cancer seeding. Retrograde lymphatic flow has been postulated as a method for developing metastatic disease in other organ systems [24]. As LG disease is less poorly differentiated and less aggressive than HG disease, the expanding pressure of HN may be less likely to result in the spread of disease in patients with LG disease.

We acknowledge that our study has certain limitations. Our cohort represents a single institution, retrospective study. Patients are not equally distributed between LG and HG diseases. Most of these patients did not undergo lymphadenectomy, and not all patients underwent RNU, but

Table 5
Literature review of studies evaluating (A) cancer-specific survival and (B) muscle invasion and non–organ-confined disease in patients with hydronephrosis and UTUCs

Study	Year of publication	Type of study	Number of patients	Method for evaluating hydronephrosis	Presence of hydronephrosis (%)	Patients with high-grade tumors (%)	Patients with tumor stage ≥ pT2 (%)	Method of analysis	Predictive value of hydronephrosis: HR/OR (95% CI), *P* value (as applicable)
(A)									
Chung et al. [current series]	2013	Retrospective, single institution	141	None/mild vs. moderate/severe on CT, IVP, and US	73	80	37	MVA	CSS: 5.2 (72.9–95.1), 0.022
Bozzini et al. [13]	2013	Retrospective, multi-institution	401	Absence vs. presence on CT and MRI	18	53	46	MVA	CSS: NS $P = 0.66$
Zhang et al. [11]	2013	Retrospective, single institution	217	Absence vs. presence on CT, MRI, IVP, and US	51	64	62	MVA	CSS: 5.3 (3.2–8.8), 0.001
Ito et al. [15]	2011	Retrospective, single institution	91	Grade 0/1 vs. 3/4 on CT and MRI	74	N/A	N/A	UVA	CSS: NS $P = 0.1696$
Ng et al. [8]	2011	Retrospective, multi-institution	106	Absence vs. presence on CT	37	44	33	MVA	CSS preoperative model: 12.1 (N/A), 0.03 CSS postoperative model: NS $P = 0.19$
Cho et. al [12]	2007	Retrospective, single institution	104	Grade 0/1/2 vs. 3/4 on CT, IVP, and US	89	80	65	UVA	CSS: $P = 0.022$
(B)									
Chung et al. [current series]	2013	Retrospective, single institution	141	None/mild vs. moderate/severe on CT, IVP, and US	73	80	37	MVA	MI: 5.0 (2.16–11.46), 0.001 NOC: 3.3 (1.42–7.52), 0.005
Messer et al. [10]	2013	Retrospective, multi-institution	408	Absence vs. presence on CT, MRI, IVP, and US	55	73	47	MVA	MI: 7.4 (4.6–11.8), <0.001 NOC: 5.5 (3.4–8.9), <0.001
Favaretto et al. [14]	2012	Retrospective, single institution	274	Absence vs. presence on CT and MRI	51	70	48	MVA	MI: NS $P = 0.065$ NOC: NS $P = 0.4$
Brien et al. [9]	2010	Retrospective, multi institution	172	Absence vs. presence on CT, MRI, and IVP	54	43	56	MVA	MI: 12.0 (5.1–28.2), <0.001 NOC: 5.1 (2.3–11.5), <0.001

CT = computed tomography; IVP = intravenous pyelogram; MI = muscle invasion; MRI = magnetic resonance imaging; NOC = non–organ-confined disease; OS = overall survival; US = ultrasound.

this is characteristic of a real-world population. We were unable to assess all disease risk factors on MVA owing to our cohort size and number of events. Although interobserver variability exists among radiologists and pathologists, we had 1 member of our team grade HN. Despite these limitations, we identified that patients with HG disease and moderate/severe HN are at greatest risk for advanced disease and worse oncologic outcomes. Validation of these findings in a larger cohort of patients with HG UTUC may be valuable.

5. Conclusion

In our study, degree of HN is independently associated with features of advanced disease, and it predicted worse oncologic outcomes in patients with HG UTUC. Degree of HN was not predictive of intravesical or local/systemic recurrence in a small cohort of patients with LG UTUC. Because preoperative imaging is a routinely available diagnostic tool, HN may serve as a surrogate parameter for advanced disease and may be used to help counsel patients with HG tumors toward neoadjuvant chemotherapy and radical surgical treatment.

References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
[2] Roupret M, Babjuk M, Comperat E, et al. European guidelines on upper tract urothelial carcinomas: 2013 update. Eur Urol 2013;63:1059–71.
[3] Lughezzani G, Burger M, Margulis V, et al. Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. Eur Urol 2012;62:100–14.
[4] Lane BR, Smith AK, Larson BT, et al. Chronic kidney disease after nephroureterectomy for upper tract urothelial carcinoma and implications for the administration of perioperative chemotherapy. Cancer 2010;116:2967–73.
[5] Audenet F, Yates DR, Cussenot O, Roupret M. The role of chemotherapy in the treatment of urothelial cell carcinoma of the upper urinary tract (UUT-UCC). Urol Oncol 2013;31:407–13.
[6] Margulis V, Youssef RF, Karakiewicz PI, et al. Preoperative multivariable prognostic model for prediction of nonorgan confined urothelial carcinoma of the upper urinary tract. J Urol 2010;184:453–8.
[7] Stimson CJ, Cookson MS, Barocas DA, et al. Preoperative hydronephrosis predicts extravesical and node positive disease in patients undergoing cystectomy for bladder cancer. J Urol 2010;183:1732–7.
[8] Ng CK, Shariat SF, Lucas SM, et al. Does the presence of hydronephrosis on preoperative axial CT imaging predict worse outcomes for patients undergoing nephroureterectomy for upper-tract urothelial carcinoma? Urol Oncol 2011;29:27–32.
[9] Brien JC, Shariat SF, Herman MP, et al. Preoperative hydronephrosis, ureteroscopic biopsy grade and urinary cytology can improve prediction of advanced upper tract urothelial carcinoma. J Urol 2010;184:69–73.
[10] Messer JC, Terrell JD, Herman MP, et al. Multi-institutional validation of the ability of preoperative hydronephrosis to predict advanced pathologic tumor stage in upper-tract urothelial carcinoma. Urol Oncol 2013;31:904–8.
[11] Zhang X, Zhu Z, Zhong S, Xu T, Shen Z. Ureteral tumours showing a worse prognosis than renal pelvis tumours may be attributed to ureteral tumours more likely to have hydronephrosis and less likely to have haematuria. World J Urol 2013;31:155–60.
[12] Cho KS, Hong SJ, Cho NH, Choi YD. Grade of hydronephrosis and tumor diameter as preoperative prognostic factors in ureteral transitional cell carcinoma. Urology 2007;70:662–6.
[13] Bozzini G, Nison L, Colin P, et al. Influence of preoperative hydronephrosis on the outcome of urothelial carcinoma of the upper urinary tract after nephroureterectomy: the results from a multi-institutional French cohort. World J Urol 2013;31:83–91.
[14] Favaretto RL, Shariat SF, Savage C, et al. Combining imaging and ureteroscopy variables in a preoperative multivariable model for prediction of muscle-invasive and non–organ confined disease in patients with upper tract urothelial carcinoma. BJU Int 2012;109:77–82.
[15] Ito Y, Kikuchi E, Tanaka N, et al. Preoperative hydronephrosis grade independently predicts worse pathological outcomes in patients undergoing nephroureterectomy for upper tract urothelial carcinoma. J Urol 2011;185:1621–6.
[16] O'Brien T, Ray E, Singh R, Coker B, Beard R, British Association of Urological Surgeons Section of Oncology: Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C Trial). Eur Urol 2011;60:703–10.
[17] Miyamoto H, Miller JS, Fajardo DA, Lee TK, Netto GJ, Epstein JI. Non-invasive papillary urothelial neoplasms: the 2004 WHO/ISUP classification system. Pathol Int 2010;60:1–8.
[18] Cummings KB. Nephroureterectomy: rationale in the management of transitional cell carcinoma of the upper urinary tract. Urol Clin North Am 1980;7:569–78.
[19] Matin SF, Margulis V, Kamat A, et al. Incidence of downstaging and complete remission after neoadjuvant chemotherapy for high-risk upper tract transitional cell carcinoma. Cancer 2010;116:3127–34.
[20] Youssef RF, Shariat SF, Lotan Y, et al. Upper urinary tract urothelial carcinoma with loco-regional nodal metastases: insights from the Upper Tract Urothelial Carcinoma Collaboration. BJU Int 2011;108:1286–91.
[21] Kaag MG, O'Malley RL, O'Malley P, et al. Changes in renal function following nephroureterectomy may affect the use of perioperative chemotherapy. Eur Urol 2010;58:581–7.
[22] Scolieri MJ, Paik ML, Brown SL, Resnick MI. Limitations of computed tomography in the preoperative staging of upper tract urothelial carcinoma. Urology 2000;56:930–4.
[23] Guarnizo E, Pavlovich CP, Seiba M, Carlson DL, Vaughan ED Jr, Sosa RE. Ureteroscopic biopsy of upper tract urothelial carcinoma: improved diagnostic accuracy and histopathological considerations using a multi-biopsy approach. J Urol 2000;163:52–5.
[24] Chang TC, Changchien CC, Tseng CW, et al. Retrograde lymphatic spread: a likely route for metastatic ovarian cancers of gastrointestinal origin. Gynecol Oncol 1997;66:372–7.