Preoperative hydronephrosis is associated with less decline in renal function after radical nephroureterectomy for upper tract urothelial carcinoma

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SINGLA N, HUTCHINSON R, HADDAD A, SAGALOWSKY A, LOTAN Y, MARGULIS V. Preoperative hydronephrosis is associated with less decline in renal function after radical nephroureterectomy for upper tract urothelial carcinoma. *Can J Urol* 2016;23(4):8334-8341.

Introduction: *To compare renal function changes after radical nephroureterectomy (RNU) in patients with upper tract urothelial carcinoma (UTUC) based on the presence of preoperative hydronephrosis.*
Materials and methods: *Clinicopathologic data of 208 patients with UTUC treated surgically from 1998 to 2013 were compiled. Patients with bilateral disease, less than 1 month follow up, missing hydronephrosis data, or who underwent nephron-sparing approaches were excluded. Estimated glomerular filtration rate (eGFR) was calculated preoperatively, at first follow up (within 3 months) and at last follow up using the Modification of Diet in Renal Disease equation. Events were defined as new-onset stage III chronic kidney disease (CKD) or worsening of CKD stage in preexisting CKD. Kaplan-Meier event-free survival was assessed. Cox regression was performed to identify predictors of events.*
Results: *A total of 132 patients were analyzed, including 62 (47.0%) with hydronephrosis. Median follow up was 28.6 months. Patients with hydronephrosis had larger tumors (p = 0.045) and higher pathologic stage (p = 0.010) than those without hydronephrosis. Baseline eGFR was comparable between groups (p = 0.088). Patients without hydronephrosis experienced greater declines in eGFR following surgery (p < 0.001) and higher event rates at first (42.8% versus 24.2%, p = 0.028) and last (54.2% versus 30.6%, p = 0.008) follow up. On Cox regression, hydronephrosis predicted lower event likelihood in the long term (univariate HR 0.54, p = 0.033), while ureteral tumor location predicted lower event likelihood in the short term (HR 0.52, p = 0.030).*
Conclusions: *Patients with hydronephrosis undergoing RNU for UTUC experience less decline in renal function than those without hydronephrosis. Given the prevalence of renal dysfunction in patients with UTUC, our results may help inform preoperative counseling.*

Key Words: upper tract urothelial carcinoma, radical nephroureterectomy, hydronephrosis, renal function

Introduction

Upper tract urothelial carcinoma (UTUC) is uncommon, comprising approximately 5% of all urothelial tumors.[1,2] Radical nephroureterectomy (RNU) remains the current gold standard treatment of UTUC.[3-5] Decline in estimated glomerular filtration rate (eGFR) can be significant following RNU[6-11] and decrease eligibility for platinum-based chemotherapy regimens,[6,10,12] thereby affecting oncologic outcomes. While partial ureterectomy can be an alternative to RNU, the incidence of ureteral tumors amenable to such approaches is limited, and the actuarial utilization of these techniques is lower still.[13] Hence, a better understanding of factors predictive of worse renal function following radical surgery is essential.

The prognostic role of preoperative radiographic hydronephrosis has been investigated extensively in predicting advanced disease and worse oncologic outcomes in UTUC.[14-19] This association may be related to increased retrograde pressure facilitating

Accepted for publication July 2016

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lymphovascular backflow in an already thinned ureteral or renal pelvis wall proximally.[17] The effect of hydronephrosis on eligibility for neoadjuvant chemotherapy remains to be further elucidated especially in light of prospective trials currently recruiting (NCT01261728, NCT02412670). The limited retrospective studies that have considered this issue reveal conflicting findings; some have demonstrated a protective effect[20,21] while another suggests a role as a risk factor.[22] Other factors identified as adverse predictors for renal function after RNU have included advanced age, lower preoperative eGFR, smaller tumor size, and tumor location within the renal pelvis.[10,20,22,23] In the present study we evaluated preoperative clinicopathologic characteristics predictive of renal function outcomes in patients with UTUC treated with RNU. Such information may help inform preoperative counseling by identifying patients who would less likely be able to receive platinum-based adjuvant chemotherapy.

Materials and methods

Following institutional review board approval, clinicopathologic data of 208 consecutive patients undergoing surgical treatment for UTUC between 1998 and 2013 at a single institution were retrospectively compiled. Patient demographics, comorbidities, and disease properties including tumor location, multifocality, pathologic stage, grade, presence of necrosis, tumor architecture (papillary versus sessile), presence of lymphovascular invasion, and mortality data were collected. Patients who underwent a nephron-sparing approach, had bilateral disease, had less than 1 month of follow up, or were missing preoperative hydronephrosis data were excluded. A parallel analysis excluding patients who received chemotherapy was also performed.

The Modification of Diet in Renal Disease (MDRD) equation[24] was used to calculate the eGFR immediately prior to surgery, at first follow up (within 3 months after surgery), and at last follow up. "Events" were defined as either new-onset stage III or greater chronic kidney disease (CKD, eGFR < 60 mL/min/1.73 m^2) or, in patients with preexisting stage III CKD or higher, worsening of CKD stage.

Tumors were staged per the 2002 TNM classification,[25] and grading was assessed per the 1998 consensus classification.[26] Follow up assessments including screening for recurrence and an evaluation for renal function were performed at maximum 4 month intervals within the first postoperative year, semi-annually for the second year, and annually thereafter.

Operative technique was based on surgeon discretion incorporating factors such as tumor location, multifocality, size, likelihood of invasion, and surgeon experience. Performance of lymphadenectomy was based on surgical judgment, with tumor location dictating boundaries of node dissection. Neoadjuvant and adjuvant chemotherapy was administered per clinician discretion, taking into account tumor stage, risk stratification, overall health status, renal function, and patient preference.

Outcomes were measured by time to event across all time points and by first postoperative follow up appointment. Independent-sample Mann-Whitney U and chi-squared tests were used to compare continuous and categorical variables, respectively. Event-free survival was assessed with Kaplan-Meier analysis and compared using log-rank test. Univariate and multivariate Cox regression analyses were performed to identify predictors of new-onset and worsening CKD. All statistical analyses were conducted using SPSS version 22.0 (IBM, Armonk, NY, USA). All reported p values are 2-sided, with statistical significance defined for $p < 0.05$.

Results

A total of 132 patients who underwent RNU for UTUC were included for analysis, with median follow up of 28.6 months (IQR 7.1-51.0). Clinicopathologic characteristics of our cohort are summarized in Table 1. Median age was 68 years, and most (66.7%) were men. Data was further stratified based on the presence (62 patients, 47%) or absence (70 patients, 53%) of preoperative radiographic hydronephrosis ipsilaterally. In comparing these two groups, a greater proportion of patients without hydronephrosis were male (77.1% versus 54.8%, p = 0.009) and diabetic (31.3% versus 13.8%, p = 0.031). Meanwhile, patients with hydronephrosis tended to have larger tumors (median 3.5 cm versus 2.9 cm, p = 0.045) and a greater proportion of advanced (non-organ-confined, ≥ pT3) stage (46.8% versus 24.3%, p = 0.010). No significant differences were noted with regard to age (p = 0.516), race (p = 0.384), comorbid hypertension (p = 0.847), body mass index (BMI, p = 0.261), baseline Eastern Cooperative Oncology Group (ECOG) performance status (p = 0.406), tobacco use (p = 1.000), receipt of neoadjuvant (p = 0.168) or adjuvant (p = 0.330) chemotherapy, tumor grade (p = 0.214), tumor location (renal versus ureteral, p = 0.098), multifocality (p = 0.727), tumor architecture (papillary versus sessile, p = 0.362), or lymphovascular invasion (p = 0.531). Median follow up duration was comparable between the two groups (28.6 months versus 28.9

TABLE 1. **Clinicopathologic data stratified by presence or absence of preoperative ipsilateral hydronephrosis**

	Total	**No hydronephrosis**	**Hydronephrosis present**	**p value***
Total patients	132	70	62	--
Median age (IQR), yrs.	68 (59-76)	68 (61-76)	68 (57-75)	0.516
Gender (% male)	66.7	77.1	54.8	0.009*
Race (%)				0.384
Caucasian	73.0	74.6	71.2	
African American	9.9	6.8	13.5	
Hispanic	15.3	15.3	15.4	
Other	1.8	3.4		
Diabetes (%)	23.0	31.3	13.8	0.031*
Hypertension (%)	67.2	68.8	65.5	0.847
Median BMI (IQR)	27.7 (24.7-31.0)	27.1 (24.3-30.4)	27.8 (25.9-31.6)	0.261
ECOG performance status (%)				0.406
0	29.2	32.4	25.8	
1	50.8	48.5	53.2	
2	16.2	17.6	14.5	
3	3.8	1.5	6.5	
History of tobacco use (%)	75.6	75.8	75.4	1.000
Neoadjuvant chemotherapy (%)	11.4	7.1	16.1	0.168
Adjuvant chemotherapy (%)	14.4	11.4	17.7	0.330
Median tumor size (IQR), cm	3.4 (2-5.5)	2.9 (1.9-4.7)	3.5 (2.6-6.3)	0.045*
pT stage (%)				0.028*
pTa	41.7	52.9	29.0	
pTis	3.0	2.9	3.2	
pT1	14.4	17.1	11.3	
pT2	6.1	2.9	9.7	
pT3	31.1	21.4	41.9	
pT4	3.8	2.9	4.8	
Non-organ-confined (> pT3), %	34.8	24.3	46.8	0.010*
High grade (%)	85.6	81.4	90.3	0.214
Location (%)				0.098
Renal pelvis only	33.3	40.0	25.8	
Ureter involved	66.7	60.0	74.2	
Tumor multifocality (%)	47.7	45.7	50.0	0.727
pN stage				0.162
pNx	31.8	35.7	27.4	
pN0	59.8	60.0	59.7	
pN1	8.3	4.3	12.9	
Presence of necrosis (%)	11.0	6.6	15.8	0.144
Architecture (%)				0.362
Papillary	82.6	85.7	79.0	
Sessile	17.4	14.3	21.0	
Lymphovascular invasion (%)	26.5	21.4	32.3	0.172
Overall mortality (%)	25.8	18.6	33.9	0.049*
Cancer-specific mortality (%)	18.9	11.4	27.4	0.026*
Non-cancer-specific mortality (%)	6.8	7.1	6.5	1.000
Median follow up (IQR), mos.	28.6 (7.1-51.0)	28.6 (10.6-51.0)	28.9 (4.0-51.5)	0.531

*independent-samples Mann-Whitney U tests were used to compare continuous variables and Chi-square tests for categorical variables. P values all two-sided with statistical significance defined for $p < 0.05$ (indicated by asterisk)
IQR = interquartile range; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group

months, p = 0.531). In total, 34 (25.8%) patients died, 25 (18.9%) due to disease. Both overall mortality (OM) and cancer-specific mortality (CSM) were higher in patients with preoperative hydronephrosis (OM: 33.9% versus 18.6%, p = 0.049; CSM: 27.4% versus 11.4%, p = 0.026), while non-CSM was comparable between the two groups (p = 0.215).

Median baseline eGFR was comparable between the groups (p = 0.088), with a similar breakdown of baseline CKD stage as shown in Table 2. Patients without hydronephrosis experienced greater declines in median eGFR following RNU when compared to those with hydronephrosis, both at first (-9.9 versus -2.5 mL/min/1.73 m^2, p < 0.001) and last (-11.0 versus

TABLE 2. **Renal function outcomes stratified by presence or absence of preoperative ipsilateral hydronephrosis**

	Total	No hydronephrosis	Hydronephrosis present	p value*
Preoperative				
Median eGFR (IQR)	58.9 (47.1-79.0)	61.0 (49.9-81.7)	56.1 (42.6-75.1)	0.088
CKD stage (%)**				0.377
I or II		48.5	51.4	45.2
IIIA		31.1	32.9	29.0
IIIB		12.1	7.1	17.7
IV		6.1	7.1	4.8
V		2.3	1.4	3.2
1st postoperative follow up				
Median eGFR (IQR)	38.8 (52.1-65.3)	51.4 (39.3-63.4)	52.2 (38.7-67.4)	0.629
CKD stage (%)**				0.807
I or II		36.4	32.9	40.3
IIIA		26.5	28.6	24.2
IIIB		25.0	25.7	24.2
IV		8.3	10.0	6.5
V		3.8	2.9	4.8
Median change in eGFR (IQR)	-6.3 (-17.1 to 0)	-9.9 (-25.1 to -1.6)	-2.5 (-9.5 to +3.8)	< 0.001*
Total events (%)	34.1	42.9	24.2	0.028*
New-onset stage III CKD (%)	16.7	21.4	11.3	0.161
Worsening CKD stage (%)	17.4	21.4	12.9	0.252
Median time to 1st follow up (IQR), mos.	1.9 (0.5-3.2)	2.2 (0.5-3.4)	1.5 (0.4-3.0)	0.400
Last follow up				
Median eGFR (IQR)	51.3 (36.3-67.5)	46.3 (34.1-65.4)	54.1 (39.0-70.8)	0.135
CKD stage (%)**				0.314
I or II	32.6	28.6	37.1	
IIIA	25.0	21.4	29.0	
IIIB	25.8	32.9	17.7	
IV	10.6	10.0	11.3	
V	6.1	7.1	4.8	
Median change in eGFR (IQR)	-7.7 (-23.0 to +0.5)	-11.0 (-29.1 to -4.0)	-1.5 (-11.2 to +7.3)	< 0.001*
Total events (%)	43.2	54.3	30.6	0.008*
New-onset stage III CKD (%)	24.2	27.1	21.0	0.425
Worsening CKD stage (%)	18.9	27.1	9.7	0.014*
Median time to last eGFR (IQR), mos.	23.0 (6.5-42.7)	23.8 (9.8-42.0)	22.7 (3.8-44.5)	0.608

*independent-samples Mann-Whitney U tests were used to compare continuous variables and Chi-square tests for categorical variables. P values all two-sided with statistical significance defined for p < 0.05 (indicated by asterisk)
**CKD stages are defined as eGFR > 90 (I), 60-89.9 (II), 45-59.9 (IIIA), 30-44.9 (IIIB), 15-29.9 (IV), and < 15 (V), in mL/min/1.73 m^2
eGFR = estimated glomerular filtration rate; IQR = interquartile range; CKD = chronic kidney disease

TABLE 3. **Univariate and multivariate Cox regression analyses for predictors of worse renal outcomes at first and last postoperative follow up visit**

		First follow up		Last follow up	
	Variable	**HR (CI)***	**p value****	**HR (CI)***	**p value****
Univariate analysis	Male gender	1.50 (0.78-2.87)	0.220	0.94 (0.55-1.61)	0.833
	Age	1.03 (1.00-1.06)	0.030**	1.05 (1.02-1.08)	< 0.001**
	Race				
	Caucasian	Ref.	Ref.	Ref.	Ref.
	African American	0.47 (0.14-1.54)	0.212	0.89 (0.40-2.00)	0.891
	Hispanic	0.36 (0.11-1.17)	0.088	0.45 (0.16-1.25)	0.446
	Other	1.40 (0.19-10.38)	0.740	1.06 (0.25-4.42)	1.000
	Diabetes	0.78 (0.38-1.62)	0.506	1.44 (0.81-2.57)	0.212
	Hypertension	1.09 (0.59-2.02)	0.781	1.25 (0.70-2.23)	0.454
	BMI	0.99 (0.94-1.04)	0.679	1.01 (0.97-1.05)	0.716
	History of tobacco use	0.87 (0.45-1.67)	0.679	1.20 (0.63-2.29)	0.588
	Neoadjuvant chemotherapy use	1.25 (0.56-2.78)	0.585	1.21 (0.52-2.82)	0.667
	Adjuvant chemotherapy use	--	--	0.67 (0.30-1.47)	0.317
	Tumor size	0.97 (0.84-1.11)	0.629	0.95 (0.84-1.07)	0.409
	Multifocality	0.93 (0.53-1.62)	0.785	1.55 (0.93-2.59)	0.093
	Presence of necrosis	1.13 (0.40-3.21)	0.816	0.93 (0.42-2.06)	0.858
	Lymphovascular invasion	1.48 (0.79-2.76)	0.219	1.62 (0.92-2.87)	0.097
	Preoperative hydronephrosis	0.70 (0.38-1.32)	0.274	0.54 (0.31-0.95)	0.033**
	Tumor location in ureter	0.54 (0.30-0.99)	0.045**	0.92 (0.54-1.55)	0.743
	Sessile architecture	0.79 (0.36-1.77)	0.570	0.86 (0.44-1.70)	0.665
	Non-organ-confined disease (> pT3)	1.46 (0.78-2.72)	0.233	1.06 (0.59-1.89)	0.856
	High grade	1.13 (0.55-2.34)	0.733	1.66 (0.86-3.21)	0.132
	pN+	0.42 (0.06-3.11)	0.396	2.12 (0.82-5.46)	0.121
	Baseline eGFR	0.99 (0.97-1.00)	0.087	0.99 (0.98-1.01)	0.295
	Baseline CKD stage III or more	1.08 (0.59-1.96)	0.803	0.88 (0.52-1.48)	0.622
Multivariate analysis	Age	1.04 (1.01-1.07)	0.022**	1.04 (1.02-1.07)	0.001**
	Tumor location in ureter	0.52 (0.28-0.94)	0.030**	--	--
	Preoperative hydronephrosis	--	--	0.63 (0.36-1.11)	0.629

*HR = hazard ratio; CI = confidence interval (95%); BMI = body mass index; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease
**statistical significance defined for p < 0.05 (indicated by asterisk)

-1.5 mL/min/1.73 m^2, p < 0.001) follow up. This trend was concordantly reflected by higher event rates at first (42.8% versus 24.2%, p = 0.028) and last (54.2% versus 30.6%, p = 0.008) follow up in patients without hydronephrosis as well. The significant differences in event rates were upheld both at first (43.1% versus 20.0%, p = 0.020) and last (55.2% versus 33.3%, p = .030) follow up after excluding patients that received any chemotherapy from the analysis as well.

Kaplan-Meier log-rank analysis demonstrated improved event-free survival in patients with preoperative hydronephrosis across all time points (p = 0.030), albeit event-free survival was comparable between the two groups at first follow up (p = 0.268), as shown in Figure 1. On multivariate Cox regression analysis, older age was an independent predictor of events at first follow up (hazard ratio, HR [95% CI] = 1.04 [1.01-1.07], p = 0.022), while tumor location in the ureter was associated with lower likelihood for the development of events (HR [95% CI] = 0.52 [0.28-0.94], p = 0.030) as shown in Table 3. The presence of hydronephrosis was also associated with a lower likelihood of experiencing an event at last follow up (HR = 0.54 [0.31-0.95], p = 0.033) on univariate analysis, while older age remained predictive of events on multivariate analysis (HR = 1.04 [1.02-1.07], p = 0.001). Receipt of neoadjuvant or adjuvant chemotherapy was not found to be significantly predictive of events at first or last

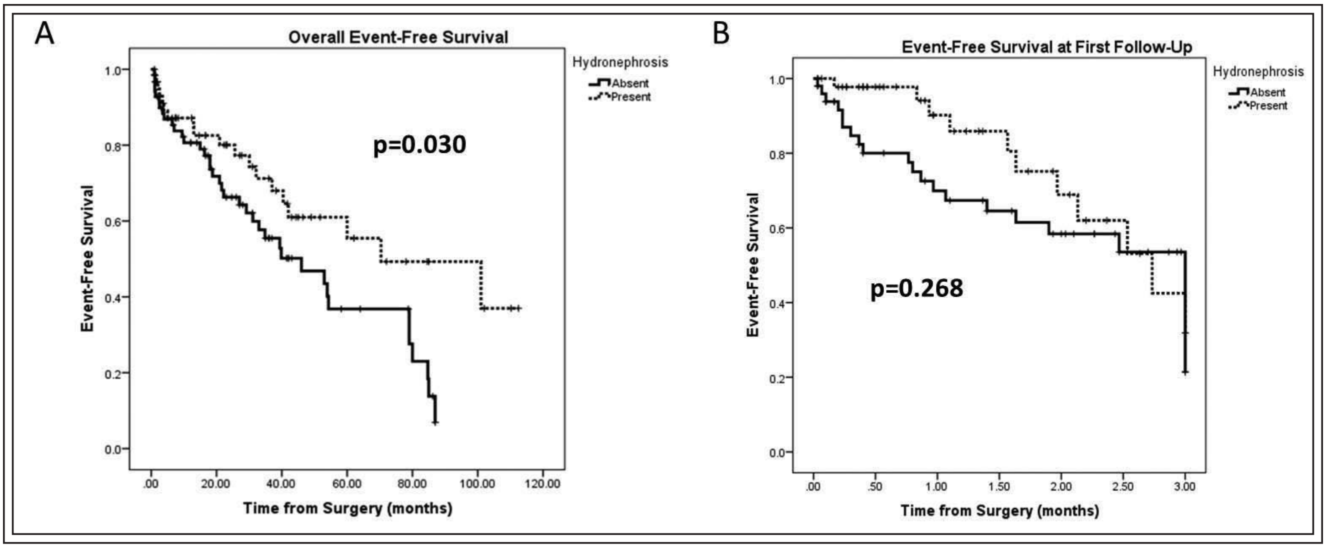

Figure 1. Kaplan-Meier log-rank analysis demonstrating **(A)** improved event-free survival following RNU in patients with preoperative hydronephrosis versus those without hydronephrosis across all time points (p = 0.030) and **(B)** comparable event-free survival between the two groups at first postoperative follow up visit (p = 0.268).

follow up on univariate analysis in our cohort as shown (of note, adjuvant chemotherapy was not assessed on Cox regression for events at first follow up, given the timing of administration). Exclusion of these patients from analysis did not significantly affect our results.

Discussion

Considerable interest has been generated in elucidating the role for chemotherapy in patients with localized UTUC. In contemporary studies, only 37% to 49% of patients with UTUC are eligible to receive platinum-based chemotherapy preoperatively owing to poor baseline renal function,[7,10] which is lowered further by loss of renal function following RNU.[6-11] The ability to predict renal deterioration from surgery based on preoperative factors may facilitate preoperative counseling of patients and help characterize the appropriate timing of chemotherapy administration. Herein we investigated characteristics predictive of renal function preservation or deterioration after RNU and found that patients with ipsilateral hydronephrosis preoperatively experienced less decline in renal function and higher event-free survival compared to those without hydronephrosis.

The oncologic role of hydronephrosis in UTUC has been studied previously and correlates with more advanced disease characteristics and a worse prognosis compared to patients without hydronephrosis.[14-19] Both Brien et al and Chung et al reported hydronephrosis to be an independent predictor for both muscle-invasive and non-organ-confined disease in separate UTUC cohorts,[14,17] while Chung et al also found hydronephrosis severity to be negatively predictive of recurrence-free survival and cancer-specific survival in high grade disease.[17] Higher mortality rates were similarly predicted by hydronephrosis in studies by Ng et al and Cho et al.[16,19] In a Chinese cohort of patients, Chen et al reported that ipsilateral hydronephrosis was predictive for muscle-invasive UTUC and higher histologic grade.[15] The mechanisms for worse oncologic prognosis in UTUC patients with hydronephrosis are likely multifactorial including larger tumors and increased retrograde pressure from obstruction which may facilitate lymphovascular backflow and resultant seeding of cancer cells.[17] While the direct effect of hydronephrosis on oncologic outcomes in UTUC was not the focus of our study, we observed more advanced tumor stage, larger tumor size, and increased OM and CSM rates in patients with hydronephrosis, supporting the association of hydronephrosis with worse disease parameters and clinical outcomes.

Prior studies on UTUC and hydronephrosis did not evaluate whether hydronephrosis affected eligibility for and subsequent receipt of chemotherapy. In retrospective series there appears to be a benefit for both overall and cancer-specific survival from use of adjuvant chemotherapy,[27] yet prospective data is still pending.[28] At the same time, platinum-related nephrotoxicity may significantly reduce overall survival in patients with postoperative renal dysfunction.[6,29] Hydronephrosis may imply a poorly functioning affected kidney, and its presence may help inform the decision to pursue and timing of systemic chemotherapy in eligible patients.

We currently lack prospective randomized data concerning the oncologic benefits of neoadjuvant chemotherapy in UTUC. As we await the results of prospective neoadjuvant trials that are currently recruiting (NCT01261728, NCT02412670), the optimal timing of chemotherapy presently remains unclear. Identifying predictors for and degree of renal function loss following RNU may help determine which patients would be eligible for upfront surgery followed by adjuvant chemotherapy versus those who would be more likely to derive benefit from preoperative chemotherapy due to decreased likelihood of chemotherapy eligibility following surgery. In this regard, patients with ipsilateral hydronephrosis may represent a cohort in which upfront surgery can be offered based on a decreased degree of postoperative renal function loss, while the threshold to administer neoadjuvant chemotherapy may be lower in eligible patients without hydronephrosis—pending, of course, much-needed prospective data for neoadjuvant chemotherapy in UTUC.

Prior studies addressing renal function outcomes after RNU have revealed conflicting results with respect to the role of hydronephrosis, though the literature remains limited.[20-22] In a retrospective study on 138 patients with UTUC treated with RNU, Rodriguez Faba et al found that preoperative hydronephrosis was actually predictive of impaired renal function for postoperative eGFR ≤ 60 mL/min on linear regression (OR 10.34, p = 0.027),[22] which was contrary to our findings. In another retrospective study on 155 UTUC patients, however, Hoshino et al reported findings concordant with our results.[21] They found that absence of severe hydronephrosis was predictive of worse renal function following RNU on logistic regression (OR 7.40, p = 0.013). In their study, evaluation of postoperative renal function was limited to serum creatinine values between 8 days to 3 months following RNU in order to best reflect the direct effect of RNU on renal function. Similarly, in a large Chinese cohort Fang et al reported hydronephrosis to be associated with a lower likelihood of postoperative eGFR decline to ≤ 60 mL/min/1.73 m^2 on logistic regression (OR 0.801, p<0.001) and hence increased eligibility for adjuvant chemotherapy.[20] In their study, however, renal function assessment was performed early in the postoperative period (ranging from 3 days to 1 month after surgery), which introduces the possibility of post-procedural assessments of renal function that may not represent true postoperative baseline. They also found that neither postoperative renal function nor use of adjuvant chemotherapy was associated with worse survival outcomes, though only 11 patients (1.8%) received chemotherapy.

Changes in renal function related directly to operative intervention may best be reflected by eGFR at first follow up, which would help minimize the effect of perioperative confounders.[20] At the same time, however, there may be additional utility in assessing long term changes in renal function within these patients for prognostic purposes. In our cohort, the effect of preoperative hydronephrosis on predicting change in renal function appeared to be significant in the longer term. While medical renal disease may confound event rates across a longer timeframe, we did not find race, diabetes, hypertension, BMI, or a history of smoking to affect long term renal function. Older age appears to be a well-documented predictor of renal insufficiency after RNU in keeping with our findings.[10,20,21,23]

A plausible explanation for the observed effect of hydronephrosis on postoperative renal function change may be a process whereby the ipsilateral kidney already has some degree of renal compromise to do obstruction. We did not routinely obtain split renal function studies before offering surgical intervention in keeping with standard clinical practice. However, we observed that ipsilateral renal parenchyma appeared thinner on preoperative imaging in hydronephrotic kidneys. The contralateral kidney may already be accounting for the majority of renal function, and as a result, removal of the less functional kidney may be less detrimental. In contrast, removing a kidney in a patient without hydronephrosis may result in removing more functional nephrons at the time of surgery. Our observation that ureteral (rather than renal pelvic) tumors predict a lower likelihood of short term renal function decline on multivariate analysis also supports this notion, as the smaller lumen of the ureter is more susceptible to obstruction. In addition to ureteral location, Fang et al also found larger tumor size and tumor multifocality to be associated with less postoperative renal function decline, further supporting this hypothesis.[20]

There are limitations to our study including its retrospective nature, sample size, and single institution cohort. It is possible that selection bias played a role, as many patients with isolated ureteral tumors may have had hydronephrosis but would have been excluded from analysis if they underwent nephron-sparing approaches such as partial ureterectomy. Preoperative renal scintigraphy and quantitative measures of renal cortical thickness were also not obtained but would certainly provide useful functional and anatomic information in evaluating our hypothesis and allow for additional subanalysis on hydronephrosis severity. Only a limited number of patients received chemotherapy as well, which would limit our ability to analyze survival outcomes from improved adjuvant chemotherapy eligibility. Nonetheless, our study is strengthened by its ability to capture longitudinal changes in eGFR across various time points and similar baseline eGFR between patients with and without hydronephrosis, enabling a fairer comparison between the two groups.

Conclusion

Patients with hydronephrosis undergoing RNU for UTUC experience less decline in postoperative renal function when compared to those without hydronephrosis. Our results may facilitate preoperative counseling for patients with UTUC and help optimize timing of chemotherapy regimens based on an individualized approach to predicting eGFR after radical surgery. The clinical significance of our results can be used by the clinician when planning therapy for UTUC and can further inform the decision to pursue and timing of systemic chemotherapy. □

References

1. Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. *J Urol* 2000;164(5): 1523-1525.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65(1):5-29.
3. Margulis V, Shariat SF, Matin SF et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. *Cancer* 2009;115(6):1224-1233.
4. Raman JD, Messer J, Sielatycki JA et al. Incidence and survival of patients with carcinoma of the ureter and renal pelvis in the USA, 1973-2005. *BJU Int* 2011;107(7):1059-1064.
5. Roupret M, Babjuk M, Comperat E et al. European Association of Urology guidelines on upper urinary tract urothelial cell carcinoma: 2015 update. *Eur Urol* 2015;68(5):868-879.
6. 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(4):581-587.
7. Raman JD, Lin YK, Kaag M et al. High rates of advanced disease, complications, and decline of renal function after radical nephroureterectomy. *Urol Oncol* 2014;32(1):47 e9-e14.
8. Silberstein JL, Power NE, Savage C et al. Renal function and oncologic outcomes of parenchymal sparing ureteral resection versus radical nephroureterectomy for upper tract urothelial carcinoma. *J Urol* 2012;187(2):429-434.
9. Singla N, Gayed BA, Bagrodia A et al. Multi-institutional analysis of renal function outcomes following radical nephroureterectomy and partial ureterectomy for upper tract urothelial carcinoma. *Urol Oncol* 2015;33(6):268 e1-e7.
10. Xylinas E, Rink M, Margulis V et al. Impact of renal function on eligibility for chemotherapy and survival in patients who have undergone radical nephro-ureterectomy. *BJU Int* 2013;112(4):453-461.
11. Zigeuner R, Pummer K. Urothelial carcinoma of the upper urinary tract: surgical approach and prognostic factors. *Eur Urol* 2008;53(4):720-731.
12. Dash A, Galsky MD, Vickers AJ et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer* 2006; 107(3):506-513.
13. Lughezzani G, Jeldres C, Isbarn H et al. Nephroureterectomy and segmental ureterectomy in the treatment of invasive upper tract urothelial carcinoma: a population-based study of 2299 patients. *Eur J Cancer* 2009;45(18):3291-3297
14. 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(1):69-73.
15. Chen XP, Xiong GY, Li XS et al. Predictive factors for worse pathological outcomes of upper tract urothelial carcinoma: experience from a nationwide high-volume centre in China. *BJU Int* 2013;112(7):917-924.
16. Cho KS, Hong SJ, Cho NH et al. Grade of hydronephrosis and tumor diameter as preoperative prognostic factors in ureteral transitional cell carcinoma. *Urology* 2007;70(4):662-666.
17. Chung PH, Krabbe LM, Darwish OM et al. Degree of hydronephrosis predicts adverse pathological features and worse oncologic outcomes in patients with high-grade urothelial carcinoma of the upper urinary tract. *Urol Oncol* 2014;32(7):981-988.
18. 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(6):904-908.
19. 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(1):27-32.
20. Fang D, Zhang Q, Li X et al. Nomogram predicting renal insufficiency after nephroureterectomy for upper tract urothelial carcinoma in the Chinese population: exclusion of ineligible candidates for adjuvant chemotherapy. *Biomed Res Int* 2014;2014:529186.
21. Hoshino K, Kikuchi E, Tanaka N et al. Preoperative hydronephrosis: independent predictor for changes in renal function following nephroureterectomy. *Jpn J Clin Oncol* 2012;42(3):202-207.
22. Rodriguez Faba O, Palou J, Breda A et al. Predictive factors for impaired renal function following nephroureterectomy in upper urinary tract urothelial cell carcinoma. *Urol Int* 2014;92(2):169-173.
23. Meyer JP, Delves GH, Sullivan ME et al. The effect of nephroureterectomy on glomerular filtration rate. *BJU Int* 2006;98(4):845-848.
24. Levey AS, Bosch JP, Lewis JB et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130(6):461-470.
25. AJCC: American Joint Committee on Cancer. Cancer Staging Manual, 7th ed. New York, NY: Springer, 2010.
26. Epstein JI, Amin MB, Reuter VR et al. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. *Am J Surg Pathol* 1998;22(12):1435-1448.
27. Leow JJ, Martin-Doyle W, Fay AP et al. A systematic review and meta-analysis of adjuvant and neoadjuvant chemotherapy for upper tract urothelial carcinoma. *Eur Urol* 2014;66(3):529-541.
28. Birtle AJ, Lewis R, Johnson M et al. Time to define an international standard of postoperative care for resected upper urinary tract transitional cell carcinoma (TCC) - opening of the peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (POUT) Trial. *BJU Int* 2012;110(7):919-921.
29. 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(12):2967-2973.