Site of Metastatic Recurrence Impacts Prognosis in Patients with Upper Tract Urothelial Carcinoma

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Introduction

- Upper tract urothelial carcinoma (UTUC) comprises 5% to 10% of all urothelial malignancies.
- The standard treatment is radical nephroureterectomy (RNU) with bladder cuff excision and lymph node dissection.
- Given that most tumors are invasive at time of diagnosis, metastatic recurrences have been estimated to occur in more than 25% of patients at 5 years .
- Patients who experience metastatic disease recurrence following RNU are known to have poor prognosis, with 80% dying within 2 years.
- The influence of the specific site of metastatic recurrence on prognosis, however, is not well documented in the literature.
- A better understanding of the timing and site of systemic metastatic recurrences may help in the development of individualized treatment plans for UTUC patients following RNU and in the exploration of the genetic associations of UTUC recurrence.

Objectives

To investigate the impact of site of metastatic recurrence on prognosis in patients with UTUC

Materials and Methods

- We performed a retrospective analysis of patients with biopsy-proven UTUC who underwent RNU at our institution from 2003 to 2018 without receiving any neoadjuvant or adjuvant chemotherapy.
- Patients with metastatic disease at presentation or with multiple synchronous primary tumors were excluded.
- Recurrences in the bladder or the contralateral upper tract were **not** considered as metastatic recurrences.
- Competing-risks survival analysis was performed to estimate the cumulative incidence of metastatic disease recurrence in our cohort from time of surgery, treating death as a competing-risk event.
- Univariable and multivariable competing-risks regression analyses were used to evaluate predictors of metastatic disease recurrence.
- In the subset of patients who developed metastatic recurrence, the Kaplan-Meier method and the log-rank test were used to estimate and compare recurrence site-specific survival probabilities following recurrence.
- Cox regression analysis was performed to assess site-specific prognosis and evaluate the association of the time to cancer-specific death outcome with primary site of recurrence.

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Results

- A total of 248 patients were identified.
- Median age at RNU was 71, and most patients in the cohort (76.2%) had high-grade disease (Table 1).
- Overall, 50 (20.2%) patients developed metastatic disease recurrence over a median follow-up of 27.5 months (IQR 7.5-60.5 months).
- The 1-year and 2-year cumulative incidences of metastatic recurrence were 11.2% and 18.8%, respectively (Figure 1).

Table 1. Clinicopathologic characteristics of the study cohort.

Characteristic	N (%)
Number of Patients	248
Median Age [IQR] (years)	71 [63-77]
Sex	
Male	171 (69)
Female	77 (31)
Race	
White	222 (89.5)
Nonwhite	26 (10.5)
Charlson Comorbidity Index	
0	22 (8.9)
1-2	162 (65.3)
≥3	64 (25.8)
Preoperative Symptoms	
No	89 (35.9)
Yes	159 (64.1)
History of Bladder Cancer	
No	169 (68.2)
Yes	79 (31.8)
Tumor Location	
Ureter	31 (12.5)
Renal Pelvis	182 (73.4)
Both	35 (14.1)
Tumor Architecture	
Papillary	153 (61.7)
Sessile	95 (38.3)
Pathologic Stage Classification	
T0, Tis, Ta, T1	145 (58.5)
T2-4	103 (41.5)
Pathologic Nodal Classification	
N0/NX	230 (92.7)
N1-3	18 (7.3)
Tumor Grade	
Low	59 (23.8)
High	189 (76.2)
Median Pathologic Tumor Size [IQR] (cm)	3.2 [2-4.7]
Lymphovascular Invasion	
Absent	175 (70.6)
Present	45 (18.2)
Indeterminate	28 (11.3)
Multifocality	
No	221 (89.1)
Yes	27 (10.9)
Surgical Margin	
Negative	220 (88.7)
Positive	28 (11.3)

Figure 1. Cumulative incidence plot of metastatic upper tract urothelial carcinoma recurrence over time.

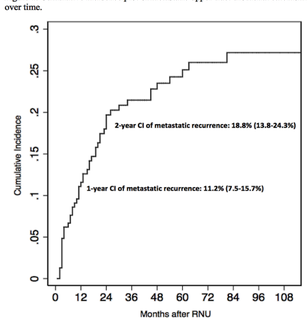


Table 2. Univariable (crude) and multivariable (adjusted) competing-risks regression analyses for evaluating the risk of metastatic recurrence in patients with upper tract urothelial carcinoma.

Variable		Crude SHR (95% CI)	p-value	Adjusted SHR (95% CI)	p-value
Preoperative Symptoms	No	REF	-	REF	-
	Yes	2.14 (1.12-4.08)	0.022	1.95 (0.97-3.92)	0.061
Pathologic Stage	pT0, Tis, Ta, T1	REF	-	REF	-
	pT2-4	1.96 (1.13-3.40)	0.017	1.10 (0.42-1.66)	0.61
Nodal Involvement	pN0/NX	REF	-	REF	-
	pN1-3	3.23 (1.37-7.62)	0.007	2.02 (0.79-5.14)	0.14
Tumor Grade	Low	REF	-	REF	-
	High	8.37 (2.04-30.4)	0.003	6.14 (1.46-25.9)	**0.013**
Lymphovascular Invasion	Absent	REF	-	REF	-
	Present	3.64 (2.03-6.55)	<0.001	2.59 (1.21-5.55)	**0.014**
Multifocality	No	REF	-	REF	-
	Yes	1.97 (1.00-3.86)	0.049	1.50 (0.70-3.19)	0.29

SHR = subhazard ratio; 95% CI = 95% confidence interval; REF = reference

- In univariable analyses, presence of preoperative symptoms, pT2 or greater stage disease, nodal involvement, high tumor grade, LVI, and multifocality were significantly associated with increased risk of metastatic recurrence (Table 2).
- Only high grade and LVI remained significantly predictive of metastatic recurrence in multivariable analyses.

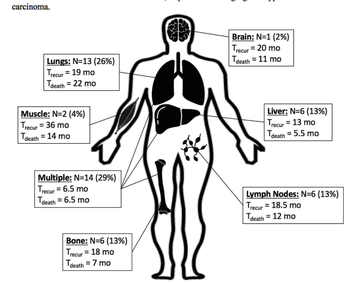
- Of the 50 patients who developed metastatic recurrence, 48 (96%) had initial high-grade disease, and only 2 (4%) had low-grade disease. Initial pathology was reviewed for these 2 patients and confirmed to be low-grade.
- Primary sites of metastatic UTUC recurrence in the 48 patients with high-grade disease and site-specific median times to recurrence are shown below (Table 3, Figure 2).
- Of the 14 patients with metastatic recurrence at multiple sites, 9 had liver and/or bone involvement.
- For the 2 patients with low-grade disease, one had a metastatic recurrence in the lungs 45 months after RNU, and the other had a recurrence in the bone 4 months after RNU.

Table 3. Time to recurrence, time to death after recurrence, and survival probabilities after recurrence for each primary site of metastatic recurrence in patients with high-grade upper tract urothelial carcinoma.

Recurrence Site	Before Recurrence	After Recurrence		
	Median Time to Recurrence [IQR] (months)	Median Time to Cancer-Specific Death [IQR] (months)	6-month Survival Probability	1-year Survival Probability
Lymph Nodes	18.5 [8-30]	12 [9.5-19]	100%	66.7%
Lungs	19 [3-24]	22 [17.5-34.5]	100%	80%
Liver	13 [9-23]	5.5 [1-9]	50%	16.7%
Bone	18 [4-24]	7 [5-9]	57.1%	19.1%
Other*	20 [12-60]	12.5 [11-14]	100%	66.7%
Multiple Sites	6.5 [3-13]	6.5 [2-11]	50%	14.3%

IQR = interquartile range
*Includes brain and muscle

Figure 2. Distribution of metastatic recurrences by primary site, along with site-specific median time to recurrence and median time to death, in patients with high-grade upper tract urothelial carcinoma.



T_recur: median time to recurrence; T_death: median time to cancer-specific death after developing recurrence

- Of the 48 patients with high-grade disease who developed metastatic recurrence, 39 (81%) died due to UTUC over a median follow-up of 10 months (IQR 5-19.5 months).
- Overall median time to cancer-specific death after recurrence was 10 months (IQR 4-15 months).
- Metastatic recurrences in the liver, bone, and multiple sites were significantly associated with worse prognosis compared to other sites (Table 3, Figure 3, Figure 4).
- 21 (44%) patients received systemic chemotherapy (19, 90%) or immunotherapy (2, 10%); significance persisted after adjusting for treatment with salvage therapy.
- Of the 2 patients with low-grade disease who recurred systemically, the patient who recurred in the bone died due to UTUC 14 months after recurrence.

Figure 3. Kaplan-Meier plot of cancer-specific survival after recurrence by primary site of recurrence in patients with high-grade upper tract urothelial carcinoma.

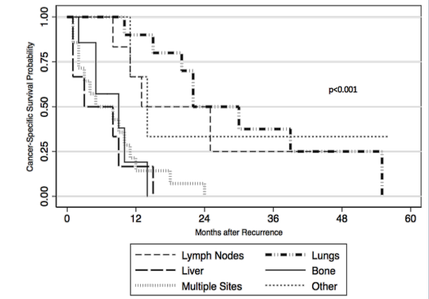
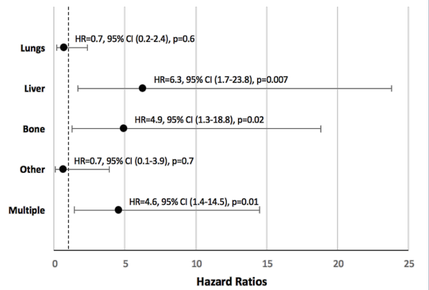


Figure 4. Forest plot showing hazard ratios of cancer-specific mortality for different primary sites of metastatic recurrence compared to lymph nodes in patients with high-grade upper tract urothelial carcinoma.



Limitations

- Retrospective design limitations
- Did not control the systemic salvage therapies that patients received
- Relatively small sample size
- Lack of patients with metastatic recurrence in the brain so could not properly assess its impact on prognosis

Conclusion

- Approximately 20% of patients with high-grade UTUC who undergo RNU will recur systemically.
- LVI is a predictor of metastatic recurrence in this population and may inform decisions regarding perioperative, adjuvant chemotherapy.
- Hepatic and osseous recurrences of UTUC have a relatively quicker onset and less favorable prognosis.
- Pulmonary and lymphatic recurrences of UTUC have a relatively slower onset and insidious prognosis.
- Our findings may benefit efforts to develop recurrence site-specific treatment plans. They also serve as hypothesis-generating data and suggest the importance of initiating studies to further our understanding of the genetic associations of recurrence in UTUC.