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Title: Predictors and patterns of non-urothelial recurrence after nephroureterectomy for upper tract urothelial carcinoma (UCAN Collaboration)

Authors: Andrew B. Katims[1,9], Amy L. Tin[2], Melissa Assel[2], Patrick Hensley[3], Roger Li[4], Vitaly Margulis[5,11], Surena Matin[6], Maximilian Pallauf[8,10], Roderick K Clark[7], Jay D. Raman[7], Nirmish Singla[8], Philippe E. Spiess[4], and Jonathan Coleman[1]

Affiliations
[1]Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY.
[2]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY.
[3]Department of Urology, University of Kentucky College of Medicine, Lexington, KY
[4]Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, FL.
[5]Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX.
[6]Department of Urology, University of Texas MD Anderson Cancer Center, Houston, TX.
[7]Department Urology, Penn State Health, Hershey, PA.
[8]Department of Urology, James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD.
[9]Department of Urology, New York Medical College, Valhalla, NY.
[10]Department of Urology, University Hospital Salzburg, Paracelsus Medical University, Salzburg, Austria
[11]South Central Section Representative, *The Journal of Urology*

Corresponding Author: Jonathan Coleman, 353 E 68th St, New York, NY, (347) 971-3925, colemanj@mskcc.org

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Abstract

Purpose: After radical nephroureterectomy for upper tract urothelial carcinoma, 25% of patients experience distant metastasis within 5 years. Non-urothelial recurrence is associated with poor prognosis and survival, with ~80% of patients dying within 2 years. We evaluated predictors, patterns, and timing of recurrences after radical nephroureterectomy and the association between recurrence location and cancer-specific survival.

Materials and Methods: Separate competing risk regression models with each site as the outcome and all other recurrence sites as the competing risk. A Cox proportional hazards model evaluated predictors and the association between cancer-specific survival and recurrence site, adjusting for time from surgery to recurrence. A separate model including multiple sites (yes/no) evaluated the association with cancer-specific survival, also adjusting for recurrence sites.

Results: 2177 patients with upper tract urothelial carcinoma underwent radical nephroureterectomy between 01/2000-02/2021 from 7 institutions, with 454 developing non-urothelial recurrence (survivor median follow-up, 34 (IQR 11, 70) months). Improved cancer-specific survival rates were seen in lung and lymph node metastasis compared to other sites (HR 0.60, 95% CI 0.37, 0.97, p = 0.038; HR 0.65, 95% CI 0.41, 1.02, p = 0.063, respectively). Recurrence to multiple concurrent non-urothelial sites was associated with worse cancer-specific survival rates (HR 1.68, 95% CI 1.30, 2.17, p<0.001). Significant recurrence associations included tumor size, high stage/grade, and tumor location. There was no statistically significant survival differences based on timing of recurrence.

Conclusions: Recurrences were common within 2 years. Lung/lymph node recurrences portended the most favorable cancer-specific survival rates. Understanding the timing and location of recurrence can tailor surveillance strategies.

Introduction

Radical nephroureterectomy (RNU) is the standard treatment for most patients diagnosed with high-grade upper tract urothelial carcinoma (UTUC). Unfortunately, 20-40% of patients will experience intravesical recurrence (IVR), 20-40% will harbor lymph node metastasis, and approximately 25% will experience distant metastasis within the first 5 years.[1, 2] IVR has an unclear effect on cancer-specific survival (CSS) with mixed reports varying from no effect to worse cancer-specific survival if muscle invasive occurs within a 2-year period after RNU.[3] Soft tissue recurrence is associated with worse prognosis and poor CSS, with approximately 80% of patients dying from disease within 2 years of recurrence.[3, 4]

Large-scale data regarding timing and prognosis of recurrence based on site is sparse. Two SEER based studies have analyzed patients with metastases and found that patients with liver metastasis had the worst overall survival compared to other metastatic locations.[5, 6] Aside from lacking granularity, these studies had a heterogenous cohort and included both patients with *de novo* metastasis as well as those with metachronous metastatic recurrence. A recent study showed that patients who recurred in the liver and bone had the worst overall prognosis, with lymphovascular invasion (LVI) as the only significant predictor.[7] However, this was a small, single institution study and larger, multi-institutional studies are needed to validate and expand upon these findings. Other risk-factors for recurrence include stage, grade, lymph node metastasis, tumor necrosis, and tumor architecture.[8]

Timing of recurrence on survival has mixed data in lower tract urothelial cancer. While some studies have shown that time to recurrence does not impact survival,[9, 10] others suggest that late recurrences have a more indolent course.[11, 12] No studies to our knowledge have evaluated the prognostic effect of early versus late recurrence in UTUC. As such, we aimed to utilize a large, multi-institutional cohort to define patterns, predictors, and timing of non-urothelial recurrence after RNU and associated survival outcomes. The study does not aim to address causal relationships between recurrence location and impact on survival, but rather to aid clinicians in determining appropriate surveillance schedules after surgery.

Methods

Following institutional review board approval, a total of seven institutions identified patients with UTUC who underwent RNU between 01/2000-02/2021. For five of the seven institutions, the included patients were consecutive patients seen at those institutions. For the two remaining institutions, one consisted of patients with complete stage and eGFR follow up and the other consisted of consecutive patients operated on by a single surgeon.

For our primary aim, we sought to define the timing and pattern of non-urothelial recurrences after RNU. We first used Kaplan-Meier methods to report the overall rate of non-urothelial recurrences. We then assessed the cumulative incidence for each of the following extravesical recurrence sites: retroperitoneal (RP) LN, distant LN, renal fossa, lung, bone, abdominal viscera/peritoneal, other (brain, ureteral stump and other atypical soft tissue sites such as peri-vesicular soft tissue and subcutaneous), and multiple concurrent non-urothelial sites. All patients had standard of care follow up through either NCCN or AUA guidelines. [13, 14] Recurrences were defined radiographically and/or through tissue biopsy. A competing risk regression model with each site of interest as the main outcome and the competing risk being all other recurrence sites

was used. Patients who did not have a recurrence were censored at the date of last follow-up, defined as the patient's last clinical encounter. Since IVR is considered a distinct entity from soft tissue metastasis, this outcome was not incorporated into our competing risk model. However, acknowledging that bladder recurrence may cause significant management burden for patients and potential risk for progression and mortality, we also presented the Kaplan-Meier estimated risk of urothelial recurrence.

To validate previously identified predictors of non-urothelial recurrence, we utilized a multivariable Cox regression model which included the following predictors: tumor size (continuous), LVI (no vs yes), stage (categorized as ≤T1N0 vs T2N0 vs T3or4N0 vs N+), grade (low vs high), and primary location (renal/pelvis/calyces vs ureter vs kidney and ureter). Patients missing any of the predictors or with metastasis at the time of radical nephroureterectomy were excluded from this particular analysis.

To evaluate the association between CSS and site of recurrence, we created a Cox proportional hazards regression model with time from recurrence to death of disease as the outcome, the primary predictor of recurrence site and adjusted for time from surgery to recurrence among patients who had a non-urothelial recurrence. Patients with recurrences at multiple concurrent non-urothelial sites were excluded from this analysis, as we addressed this in a subsequent aim. We prespecified that we would additionally ascertain whether the association between recurrence site and CSS differed based on time of recurrence, therefore we also created another model which included the interaction term between recurrence site and time from surgery to recurrence.

Finally, we assessed if having multiple concurrent non-urothelial sites of recurrence was associated with worse CSS compared to only one site of recurrence. We therefore included patients with recurrences at multiple concurrent non-urothelial sites in this analysis and used a Cox proportional hazards regression model with time from recurrence to death from disease as the outcome, the primary predictor was a binary variable defined as whether patients had multiple concurrent sites of recurrence, adjusted for time from surgery to recurrence, and all recurrence sites from the analysis of our secondary aim. All analyses were conducted using R version 4.3.2

Results

We identified 2272 patients, 95 patients were excluded due to incomplete recurrence data (Supplemental Figure 1); therefore, 2177 patients remained for analysis. Table 1 presents baseline characteristics of the study cohort.

Among our cohort, 454 patients developed a non-urothelial recurrence, with a median follow-up among patients who did not develop a non-urothelial recurrence of 34 (IQR 11, 70) months. The Kaplan-Meier estimated risk (and corresponding 95% CI) of having a non-urothelial recurrence at 6-, 12-, and 24-months after RNU is 7.3% (6.1%, 8.4%), 13% (12%, 15%), and 19% (17%, 21%), respectively. Table 2 presents the site of non-urothelial recurrences. Due to the limited number of distant LN recurrences (n=6), this was grouped together with RP LN recurrences and termed "LN" in all subsequent analyses. Figure 1 presents the cumulative incidence for each of the recurrence sites. 686 patients developed urothelial recurrences, and the median follow-up among patient who did not develop a urothelial recurrence was 23 (IQR 6, 56) months.

Supplemental Figure 2 presents the Kaplan-Meier estimated risk of developing a urothelial recurrence: 6-, 12-, and 24-months probabilities are 13% (95% CI 12%, 15%), 25% (95% CI 23%, 27%), and 34% (95% CI 32%, 36%), respectively.

Previously identified predictors were validated in this study (Table 3). These included tumor size (HR 1.05, 95% CI 1.01-1.09, p=0.016), stage (overall p<0.001), and high grade on final pathology (HR 2.06, 95% CI 1.22-3.49, p=0.004). While tumor location (overall p = 0.052) did not meet conventional levels of significance, the upper bound of the CI for tumor location in both the renal pelvis and ureter (HR 1.29, 95% CI 0.97-1.71) did not exclude clinical significance compared to the reference group of tumor in the renal pelvis/calyces.

Table 4 presents the results of our analysis looking into the association between recurrence location and CSS, limited to 333 patients who developed a non-urothelial recurrence to a single site. One additional patient was excluded as his survival status was unknown. There were 196 deaths from disease. The median follow-up among patients with non-urothelial recurrence who did not die from disease was 20 (IQR 4, 48) months. We found evidence of a difference in the risk of CSS based on the site of the non-urothelial recurrence (overall p <0.001). In particular, with "other" sites as the reference group, there was evidence of improved rates of CSS for the recurrence sites of lung and LN, though the latter did not meet conventional levels of significance (HR 0.60, 95% CI 0.37, 0.97, p = 0.038; HR 0.65, 95% CI 0.41, 1.02, p = 0.063, respectively). There was no statistically significant association between recurrence site and CSS based on timing of recurrence (overall p-value for interaction term = 0.3). Therefore, the final model did not include the interaction term. After additionally including patients who developed non-urothelial recurrence to multiple concurrent sites (n=121), we found evidence that recurrence to multiple concurrent non-urothelial sites was associated with worse rates of CSS (HR 1.58, 95% CI 1.05, 2.39, p=0.030).

Discussion

Using a multi-institutional cohort of over 2000 patients, we found a 19% non-urothelial and 34% urothelial recurrence probability 24-months after RNU for UTUC. Recurrences often were detected at multiple sites simultaneously which portended the worst CSS, while recurrences in the lymph nodes or lung alone were associated with more favorable survival outcomes compared to other sites. Interestingly, the timing of recurrence was not statistically associated with survival rates. One previous study assessed site of metastatic recurrence after RNU and its impact on survival.[7] Our results are generally in line with these findings in that those with lymph node and lung metastases had a more indolent course compared to those with multiple sites of recurrence. In this study, as well as in other SEER-based studies, liver, and in one study, bone involvement was a poor prognostic factor.[5, 15] In our cohort, liver (i.e. abdominal viscera) and bone did have an increased risk of cancer specific death, but this did not reach statistical significance. The causal relationship between site specific metastasis and differences in survival outcomes will require additional research.

We also looked at associated factors for non-urothelial recurrence. Previous studies have shown that LVI, pre-operative hydronephrosis, tumor multifocality, architecture (i.e. papillary vs sessile), size, and pathological stage are associated with disease recurrence.[2, 7] In our study, we found that while large tumor size, high grade, and multifocality in both the renal pelvis and

ureter were associated with recurrence, increasing stage had the most significant association with non-urothelial recurrence. To this point, after accounting for stage, LVI no longer remained significantly associated with recurrence. Further, when stratifying by receipt of neoadjuvant or adjuvant chemotherapy, final pathologic stage remained had the most significant association with recurrence.

The AUA recommends a risk stratified surveillance approach after RNU.[14] For those with >T2 disease, patients are recommended for cross-sectional imaging of the abdomen and pelvis every three to six months for the first two years, every six months for the second two years, and annually thereafter to year five. Further, imaging of the chest should be performed every 6 to 12 months for the first five years, though there is scant evidence to support timing of follow up. Our results are generally in line with these recommendations in that most recurrences occur rapidly, within the first 24 months and included multiple sites, particularly the retroperitoneal lymph nodes and lungs, highlighting the importance of incorporating these sites in a surveillance strategy.

Our study is not without limitations. Due to the multi-institutional and retrospective nature, several factors were not standardized across institutions. For example, all patients underwent surveillance per standard of care after RNU, but there was inter-institutional variation which would affect the reporting of timing. Additionally, it was at the discretion of each institution to specifically report the nodal stage "Nx" rather than "unknown" or "missing." Further, recurrences were defined as identified from imaging modalities and not always biopsy proven. Finally, conventional salvage treatments provided were not standardized and evolved over the study interval which could have affected survival outcomes.

Conclusion

In our study period, recurrences were most common in the first two years after RNU for UTUC, and when located outside of the bladder are often the cause of death for patients. Surveillance strategies after RNU should be most intensive in the first 24 months after surgery, with imaging intervals extended to every 6 months thereafter. Bladder recurrences were also common within the first two years indicating the need for cystoscopic surveillance as part of a follow up protocol. We did not find evidence of differences in CSS based on time of recurrence. Future research should focus on biologic differences between site of recurrence which could account for differences in survival and impact therapeutic decisions.

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Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Abbreviations

Abbreviation	Meaning
RNU	Radical nephroureterectomy
UTUC	Upper tract urothelial cancer
IVR	Intravesical recurrence
CSS	Cancer specific survival
LVI	Lymphovascular invasion
RP	Retroperitoneal
LN	Lymph node
NCCN	National Comprehensive Cancer Network
AUA	American Urological Association

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Table 1a. Patient characteristics. Data are presented as N (%) or median (IQR).

	N	N = 2,177
Male	2,177	1,448 (67%)
Race	2,148	
White		1,985 (92%)
Black		60 (2.8%)
Other		103 (4.8%)
BMI	1,904	28 (25, 32)
Smoking Status	2,154	
Never		704 (33%)
Former		1,089 (51%)
Current		361 (17%)
Diabetes	1,824	382 (21%)
Hypertension	1,819	1,150 (63%)
Institution	2,177	
1		167 (7.7%)
2		169 (7.8%)
3		216 (9.9%)
4		653 (30%)
5		389 (18%)
6		230 (11%)
7		353 (16%)

Abbreviations: BMI, body mass index.

Table 1b. Treatment and disease characteristics. Data are presented as N (%) or median (IQR). For stage on RNU, N+ includes N1, N2, or N3; grouping of N0 therefore included N0 and NX or patients where no nodal stage was specified

	N	N = 2,177
Neoadjuvant chemotherapy	2,171	443 (20%)
Adjuvant chemotherapy	2,146	219 (10%)
Tumor Size on RNU (cm)	1,945	3.0 (2.0, 4.5)
Lymphovascular Invasion	2,078	615 (30%)
Stage on RNU	2,169	
T0N0		79 (3.6%)
≤T1N0		1,105 (51%)
T2N0		221 (10%)
T3N0		463 (21%)
T4N0		55 (2.5%)
N+		209 (9.6%)
M+		37 (1.7%)
Grade on RNU	2,083	1,627 (78%)
Tumor Location on RNU	2,112	
Renal Pelvis/Calyces		1,157 (55%)
Only Ureter		494 (23%)
Kidney/Ureter		461 (22%)

Abbreviations: RNU, radical nephroureterectomy.

Table 2. Frequency of non-urothelial recurrence site, patients with more than one recurrence site are grouped in "Multiple non-urothelial recurrences."

	N = 454
Recurrence Site	
Abdominal Viscera/Peritoneal	64
Bone	37
Distant Lymph Nodes	6
Lung	72
Renal Fossa	8
Retroperitoneal Lymph Nodes	98
Other	48
Multiple non-urothelial recurrences	121

Table 3. Association between predictors and non-urothelial recurrence on multivariable Cox regression (N=1,809). For stage on RNU, N+ includes N1, N2, or N3; grouping of N0 therefore included N0 and NX or patients where no nodal stage was specified

Characteristic	HR	95% CI	p-value
Tumor Size on RNU (cm)	1.05	1.01, 1.09	0.016
Lymphovascular Invasion	1.00	0.78, 1.28	>0.9
Stage on RNU			<0.001
≤T1N0	—	—	
T2N0	3.19	1.96, 5.21	
T3or4N0	6.26	4.32, 9.05	
N+	12.7	8.47, 19.0	
Grade on RNU	2.06	1.22, 3.49	0.004
Tumor Location on RNU			0.052
Renal Pelvis/Calyces	—	—	
Only Ureter	0.85	0.62, 1.16	
Kidney/Ureter	1.29	0.97, 1.71	

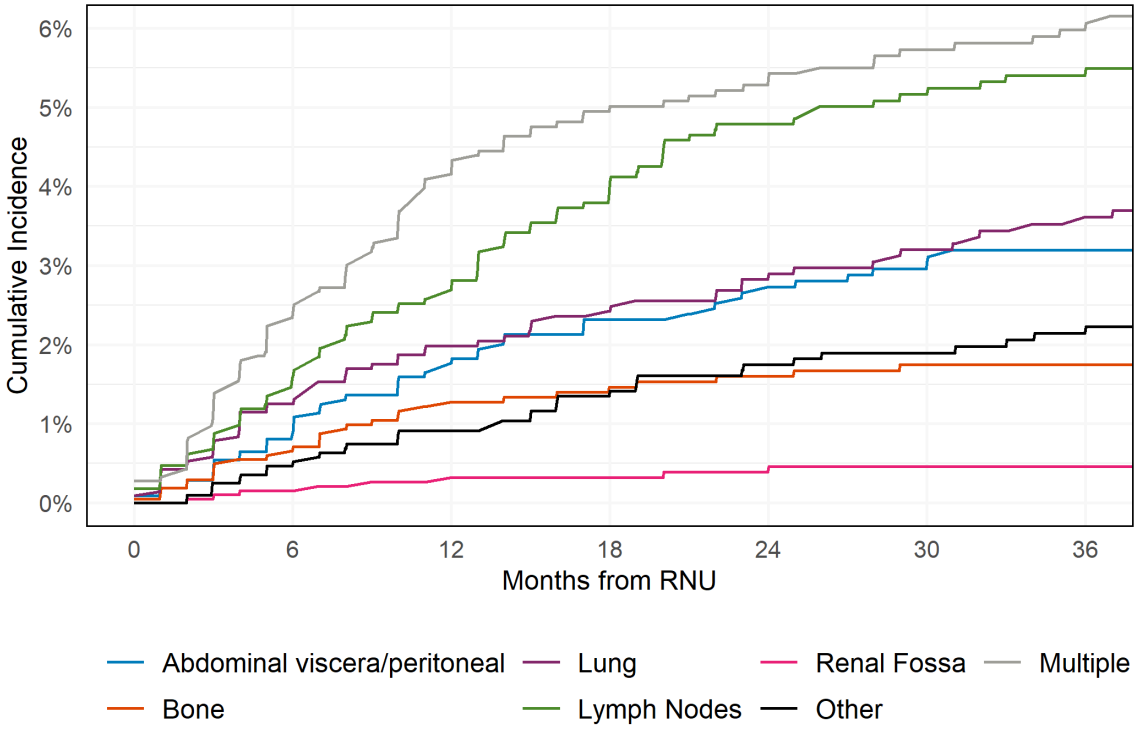
Abbreviations: CI, confidence interval; HR = hazard ratio.

Table 4. Association between site of non-urothelial recurrence and time from non-urothelial recurrence to cancer specific survival, adjusted for time from surgery to non-urothelial recurrence.

	Hazard Ratio	95% CI	p-value
Recurrence Site			<0.001
Other Site	Ref.	Ref.	
Lymph Node	0.65	0.41, 1.02	
Renal Fossa	0.95	0.36, 2.46	
Lung	0.60	0.37, 0.97	
Bone	1.46	0.87, 2.45	
Abdominal viscera/peritoneal	1.25	0.79, 1.98	

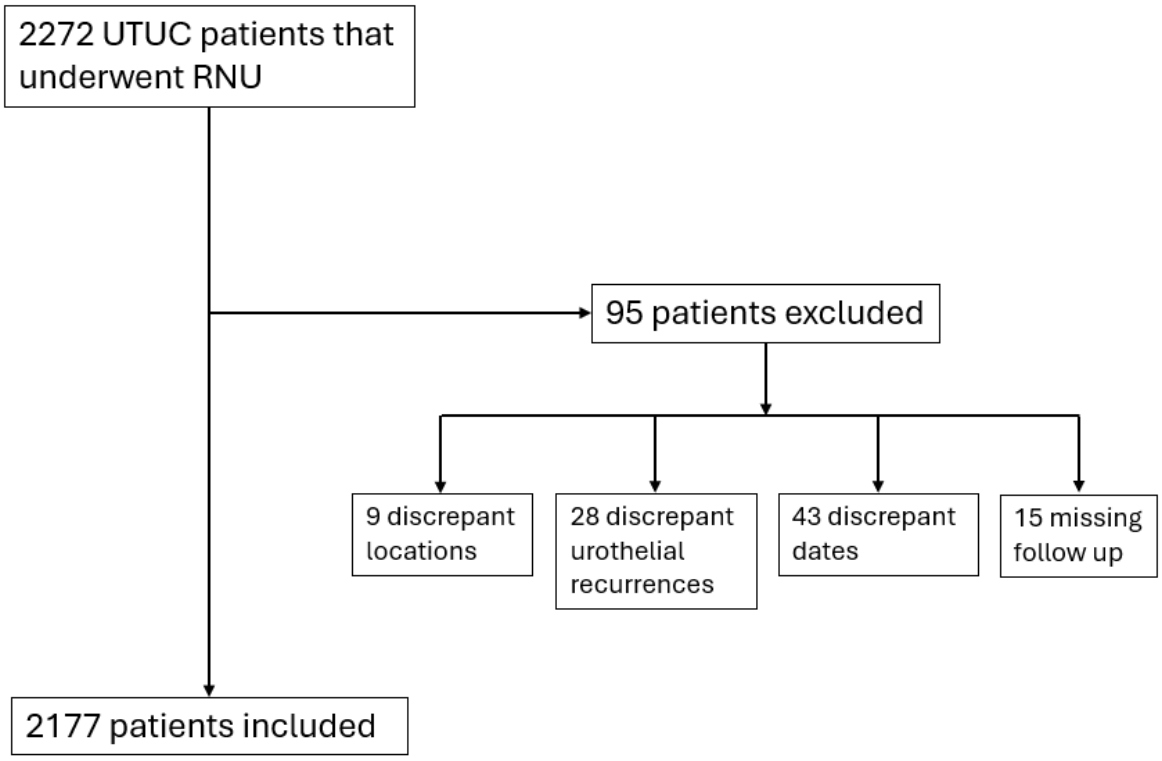
Abbreviations: CI, confidence interval.

Figure 1. Cumulative incidence of each non-urothelial site.

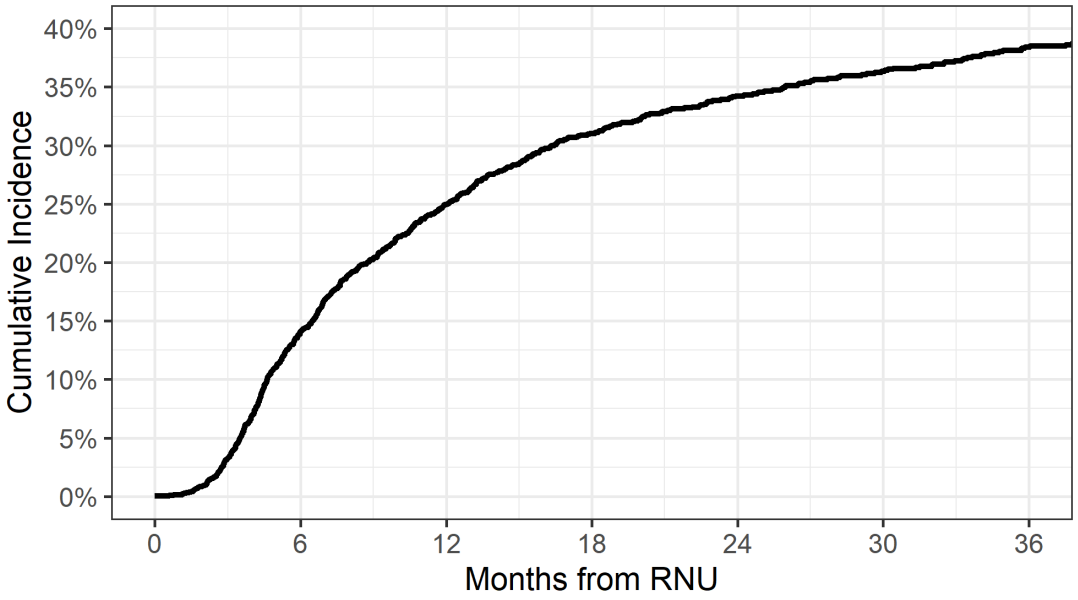


	Months from RNU						
	0	**6**	**12**	**18**	**24**	**30**	**36**
Numbers at Risk	2177	1694	1466	1283	1138	999	899
Number of Events							
Abdominal viscera/peritoneal	2	18	34	42	48	53	54
Bone	1	14	24	27	29	31	31
Lung	2	25	38	45	52	56	61
Lymph Nodes	4	32	53	73	84	90	93
Renal Fossa	0	3	6	6	8	8	8
Other	0	10	17	25	30	32	36
Multiple	6	48	81	92	98	102	106

Supplemental Figure 1. Flow diagram of patient selection



Supplemental Figure 2. Cumulative incidence of urothelial recurrence. Time to urothelial recurrence has been shifted randomly to account for deidentification during data collection.



At Risk	2177	1527	1204	972	829	709	617
Events	1	265	451	543	586	611	633