Surveillance guidelines based on recurrence patterns for upper tract urothelial carcinoma

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Abstract

Introduction: Upper tract urothelial carcinoma (UTUC) accounts for 5% of all urothelial tumours. Due to its rarity, evidence regarding postoperative surveillance is lacking. The objective of this study was to develop a post-radical nephroureterectomy (RNU) surveillance protocol based on recurrence patterns in a large multi-institutional cohort of patients.
Methods: Retrospective clinical and pathological data were collected from 1029 patients undergoing RNU over a 15-year period (1994–2009) at 10 Canadian academic institutions. A multivariable model was used to identify prognostic clinicopathological factors, which were then used to define risk categories. Risk-based surveillance guidelines were proposed based on actual recurrence patterns.
Results: Overall, 555 (49.9%) patients developed recurrence, including 289 (25.9%) in the urothelium and 266 (23.9%) with loco-regional and distant recurrences. Based on multivariable analysis, three risk groups were identified: 1) low-risk patients with pTa-T1, pN0 disease and no adverse histological features (high tumour grade, lymphovascular invasion [LVI], tumour multifocality); 2) intermediate-risk patients with pTa-T1, pN0 disease with one or more of the adverse histological features; and 3) high-risk patients with a ≥pT2 tumour and/or nodal involvement. Low-, intermediate-, and high-risk patients were free of urothelial recurrence at three years in 72%, 66%, and 63%, respectively, and free of regional/distant recurrence in 93%, 87%, and 62%, respectively. The risks of loco-regional and distant recurrences (p<0.0001) and time to death (p<0.0001) were significantly different between the low-, intermediate-, and high-risk patients.

Conclusions: Based on recurrence patterns in large multicentre patient cohort, we have proposed an evidence-based, risk-adapted post-RNU surveillance protocol.

Introduction

Upper tract urothelial carcinoma (UTUC) accounts for only 5% of all urothelial tumours [1]. Advanced UTUC carries a poor prognosis with 5-year cancer specific survival (CSS) rates of less than 50% in patients with pT3 tumours, 35% in pN+ disease, and 5-10% in pT4 tumours. These compare to a rate of more than 80% in organ-confined UTUC [2,3]. Radical nephroureterectomy (RNU) with bladder cuff excision is the gold standard management of non-metastatic UTUC. Post-operative recurrences after RNU are common and can occur at different sites: bladder (30%), locoregional (20%), distant (10-20%) and contralateral upper tract (2-6%).[4-8]

Due to the rarity of UTUC, evidence regarding post-operative surveillance is lacking. Recently, nomograms predicting intravesical, loco-regional, and distant metastatic recurrence based on clinico-pathologic variables have been developed using large retrospective multi-institutional data [3,4,6]. However, the temporal and anatomic patterns of recurrence following RNU have not been defined in these publications.

To date, only the European Association of Urology (EAU) and Canadian Urological Association (CUA) have guidelines on post-operative surveillance of UTUC [1,9,10]. The EAU recommends two surveillance pathways for "invasive" and "non-invasive" tumours (1). The CUA proposes three surveillance protocols based on tumour grade, pathologic T stage, and pathologic node status [10]. Given the emergence of data regarding pathologic prognostic variables and the cost and potential morbidity associated with surveillance, it is prudent to tailor surveillance to patients at differing risk of recurrence. Our objective is to develop a post-RNU surveillance protocol based on recurrence patterns in a large multi-institutional cohort of patients.

Methods

Retrospective clinical and pathologic data were collected from 1029 patients undergoing RNU over a 15-year period (1994–2009) at 10 Canadian academic institutions. Data on patients undergoing renal sparing management was not available.

All patients were treated with open or laparoscopic RNU with or without regional lymph node dissection. The extent of lymphadenectomy was based on the presence of gross lymphadenopathy on preoperative imaging or intraoperative assessment. The indications for neoadjuvant/adjuvant chemotherapy were made on an individual patient basis by the treating urologist and medical oncologist.

Surgical specimens were reviewed by anatomical pathologists at each participating institution. Centralized pathological review was not performed. Tumours were staged according to the American Joint Committee on Cancer TNM classification system and graded according to the World Health Organization/International Society of Urologic Pathology consensus classification [11,12].

Although uniform surveillance was not performed across all institutions, in general patients were evaluated with history, physical examination, blood work, urinary cytology, cystoscopy, chest radiography, and CT urogram every 3-6 months in the first year, every 6-12 months up to 5 years, and annually thereafter. Bone scan and cross sectional chest imaging were performed if clinically indicated.

Two principal outcomes were investigated: urothelial recurrence (in the bladder or contralateral upper tract) and metastatic recurrence. Metastatic recurrence was further stratified by loco-regional (nephrectomy bed or retroperitoneal lymph nodes) and distant (lung, bone, liver, brain, or other). Time to recurrence was calculated as time from RNU to evidence of first recurrence. For multiple recurrences, only the first recurrence was considered.

Clinical characteristics including age, gender, prior history of bladder or UTUC, and history of neo-adjuvant or adjuvant chemotherapy were recorded. Collected pathologic parameters included pT stage, pN status, tumour grade, concomitant carcinoma in-situ (CIS), presence of tumour multifocality, presence of lymphovascular invasion (LVI), and surgical margins status. Univariate and multivariate analysis was performed to identify clinico-pathologic characteristics associated with each of the two principal outcomes (urothelial and metastatic recurrence). A p-value ≤ 0.05 was considered statistically significant.

Based on the prognostic features identified on multivariate analysis, clinico-pathologic risk categories were defined and recurrence patterns in each risk category were analyzed by anatomic site and time from RNU. Surveillance protocols for bladder, contralateral upper tract, and metastases were subsequently proposed based on recurrence patterns.

Results

Baseline characteristics
A total of 1029 patients were included in this study. Table 1 shows the baseline characteristics of patients overall and based on recurrence pattern. The mean follow-up duration was 2.46 +/- 3.06 years.

Recurrence rates
Overall, 555 (49.9%) patients developed recurrence; 25.9% in the urothelium and 23.9% in loco-regional or distant sites. Mean time to urothelial recurrence and locoregional or distant recurrence was 7.03 +/- 0.24 months and 8.06 +/- 0.23 months, respectively. The majority of urothelial recurrences were diagnosed in the first 2 years (91.3%) (Figure 1). The latest documented urothelial recurrence was in the bladder at 150 months post RNU.
A larger proportion of loco-regional and distant recurrences were detected later in follow-up with 50% detected in the first year, 73% within 2 years and 93% within 5 years (Figure 2). The latest loco-regional or distant recurrence was documented at 147 months in the nephrectomy bed. The most common sites of metastasis were lung (26%), nephrectomy bed (26%), liver (21%), bone (18%), and retroperitoneal lymph nodes (8%). Five patients developed brain metastases.

Prognostic factors and risk stratification

Table 2 shows the results of the univariate and multivariate analyses looking at predictors of urothelial recurrence. Advanced age, history of bladder UC, history of adjuvant chemotherapy, ≥pT3 tumours, pN+ status, concomitant CIS, tumour multifocality, positive surgical margins, and presence of LVI were associated with urothelial recurrence on univariate analysis. On multivariate analysis, age, female gender, tumour multifocality, positive surgical margins, and presence of LVI were significant predictors of urothelial recurrence. After adjusting for other adverse pathologic features, pT and pN stage were no longer independent predictors of urothelial recurrence on multivariate analysis. Interestingly, concomitant CIS in the RNU specimen was also not an independent predictor of urothelial recurrence.

On univariate analysis, adjuvant chemotherapy, ≥pT3 pN+, high tumour grade, concomitant CIS, multifocality, positive margins, and LVI were associated with locoregional or distant recurrence. On multivariate analysis female gender, ≥pT3 pN+, high tumour grade, tumour multifocality, and LVI were significant predictors of loco-regional and distant recurrence Table 3.

Given the similar prognostic features predicting both urothelial and locoregional or distant recurrence identified on multivariate analysis, three different risk categories were devised (Table 4).

Temporal and anatomic pattern of recurrence based on risk group

Low, intermediate and high-risk patients had an overall 5-year survival rate was 59%, 47% and 34%, respectively.

Figure 3 shows bladder recurrence stratified by risk group. The proportion of bladder recurrences in low, intermediate, and high-risk patients was 14%, 33%, and 53%, respectively. Low, intermediate and high-risk patients had a 3-year survival for urothelial recurrence of 72%, 66%, and 63%, respectively. Approximately 52% of all bladder recurrences occurred in high and intermediate risk patients in the first year post RNU. Similar trends are seen with recurrences in the contralateral upper tract (Figure 4).

Figures 5a-e show loco-regional/distant recurrence patterns by site. The vast majority of nephrectomy bed (84%) and liver (79%) recurrences occurred in high-risk patients in the first 18 months post RNU (Figures 5a-b). Low, intermediate and high-risk patients had a 3-year survival for regional/distant recurrence of 93%, 87% and 62%. Retroperitoneal nodal metastases occurred almost exclusively in high-risk patients with only 1 recurrence observed in an intermediate-risk patient (Figure 5c). Similarly, lung and bone metastases are rare in low-risk patients (3.3% and 4.4% respectively); with a significant proportion observed in intermediate and high-risk patients in the first 18 months following RNU (54.1% and 64.4% respectively) (Figures 5d-e). Brain metastases occurred only in high-risk patients and all within 18 months of RNU.

Figure 6 represents patterns for abdominal recurrences. This includes recurrences in liver, retroperitoneal nodes, nephrectomy bed, and contralateral upper tract. The rationale for this analysis is that all these sites are amenable to detection by the same imaging modality (CT or

MR of abdomen/pelvis with urogram phase). Overall, approximately 72.5% of all abdominal recurrences occurred in the first 2 years post RNU and almost exclusively in high (79%) and intermediate risk (17%) patients.

In contrast to abdominal metastases, a significant proportion of pulmonary and bone metastases occurred in intermediate risk patients. High-risk patients more commonly developed early recurrence at these sites (in the first 24 months post RNU).

Recurrence free survival rates for bladder, contralateral upper tract, and loco-regional/distant sites for each risk category are listed in Table 5.

Finally, we utilized cox regression analysis to determine if there are significantly differences in outcomes by risk category and note that there was no statistically significant difference in urothelial recurrence between the three groups but there was significantly worse loco-regional and distant recurrences (high-risk chi-square 20.4, p<0.0001, intermediate-risk chi-square 3.7, p=0.06) and time to death (high-risk chi-square 28.6, p<0.0001, intermediate-risk chi-square 11.0, p=0.0009) in the intermediate and high-risk patients.

Surveillance recommendation

We propose a surveillance protocol outlined in Table 6. In general, the intensity of surveillance increases with increasing risk of recurrence. Past 5 years in high-risk individuals we recommend yearly follow-up. Time to stop surveillance is at the discretion of clinical judgment.

Discussion

UTUC is a rare disease and data regarding patterns of recurrence in the literature are sparse. Many of the principles of management of UTUC therefore have been extrapolated from bladder cancer. The EUA and CUA have published surveillance guidelines but both are based mostly on small single center retrospective series and do not incorporate potential pathologic prognostic variables [1, 9, 10]. We propose new surveillance guidelines based on a large multi-institutional series of 1029 patients treated with RNU for UTUC.

Predictors for recurrence observed in our dataset are in keeping with other series [3, 4, 6]. Tumour multifocality, positive margins, and LVI were all associated with increased risk of urothelial recurrence. As expected, in addition to these adverse histologic features, high tumour grade, advanced pT stage (pT2-4), and pN+ were associated with locoregional/metastatic recurrence.

Two areas of controversy remain: concomitant CIS and impact of tumour location. Our study and those of the French national collaborative group [3, 13] did not demonstrate concomitant CIS to be prognostic while multiple other studies reported an association with intravesical recurrence and cancer specific survival [4, 6, 14-16]. Rink *et al.* [17] did not find that tumour location was associated with recurrence outcomes while Yafi *et al.* [18] showed that ureteral tumour location and multifocality were both independently associated with worse recurrence-free survival compared to tumours in the renal pelvis. Our analysis supports that tumour multifocality but not tumour location has an adverse prognostic significance [19].

Despite the minor differences in our study and others, several predictors remain strong. Based on these predictors we have been able to create a post RNU risk based surveillance protocol. Furthermore, we included the temporal and anatomic patterns of recurrence in each risk group to guide frequency and timing of diagnostic modalities as well as recurrence risk at different anatomic locations. A salient feature of our proposed protocol is the lack of chest imaging in low risk disease and more judicious use of abdominal imaging in low and intermediate risk patients. Our results also reiterate the importance of the initial surveillance cystoscopy at the 3-month postoperative time-point, given the evident risk of early bladder recurrence, especially in the absence of post-operative intravesical chemotherapy, which was not used in any of our patients [20].

Our analysis confirms the high-risk of intravesical recurrence in intermediate and high-risk patients, and the high-risk of locoregional/metastatic recurrence in high-risk patients, in keeping with existing literature. Surgery alone does not appear to be adequate in patients with high-risk disease and multimodal therapy should be considered. Given the fact that decline in renal function following RNU classically precludes a large proportion of patients from adjuvant chemotherapy [21, 22] and there is new evidence for adjuvant chemotherapy in this population [23], strong consideration should be given to whether or not neoadjuvant/adjuvant chemotherapy may benefit patients with high-risk features. The limitation with this approach is that the definition of "high-risk" is based on post-operative pathologic parameters, although some have attempted to predict high-risk disease based on tumour grade on endoscopic biopsy and endoscopic tumour appearance and location [2].

This analysis is limited by the absence of patients who underwent renal-conserving management including segmental ureterectomy and endoscopy. Additional limitations include the short mean follow-up and the low number of events beyond 2 years, making it difficult to suggest strong recommendations beyond this period. Furthermore, we did not capture whether recurrence was diagnosed on imaging only or in the context of symptomatic presentation. Only the first diagnosed recurrence was considered and metachronous metastases at other anatomic sites were not included in the analysis. Finally, patient management and surveillance was heterogenous across centers, and patients receiving adjuvant chemotherapy were not excluded. The drawback of routine surveillance is the potential for false positive results exposing the patient to unnecessary invasive confirmatory studies. In the context of metastatic UTUC, it is not known whether detecting a systemic recurrence early by surveillance versus detection when symptomatic results in improved chemotherapy outcomes. In bladder cancer survival outcomes are not different for those with asymptomatic vs. symptomatic recurrences [24, 25]. However, this notion should not undermine the importance of surveillance, as some urothelial recurrences are curable.

Conclusion
We identified clinico-pathologic predictors of urothelial and locoregional/metastatic disease recurrence in a large cohort of patients treated with RNU for UTUC. Using the identified

prognostic features, a pathologic based-risk stratification system was developed and transposed into a risk-based post RNU surveillance protocol.

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Figures and Tables

Fig. 1. Urothelial recurrence (bladder, contralateral upper tract, ureteric stump) in six-month intervals post-radical nephroureterectomy (RNU).
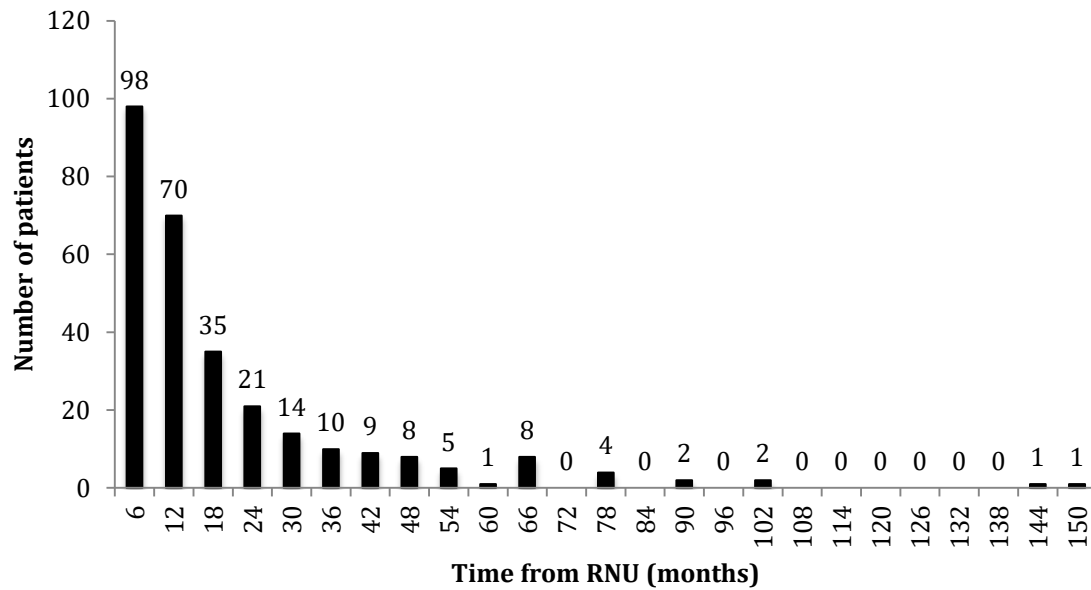
Fig. 2. Loco-regional/distant recurrence in six-month intervals post- radical nephroureterectomy (RNU).
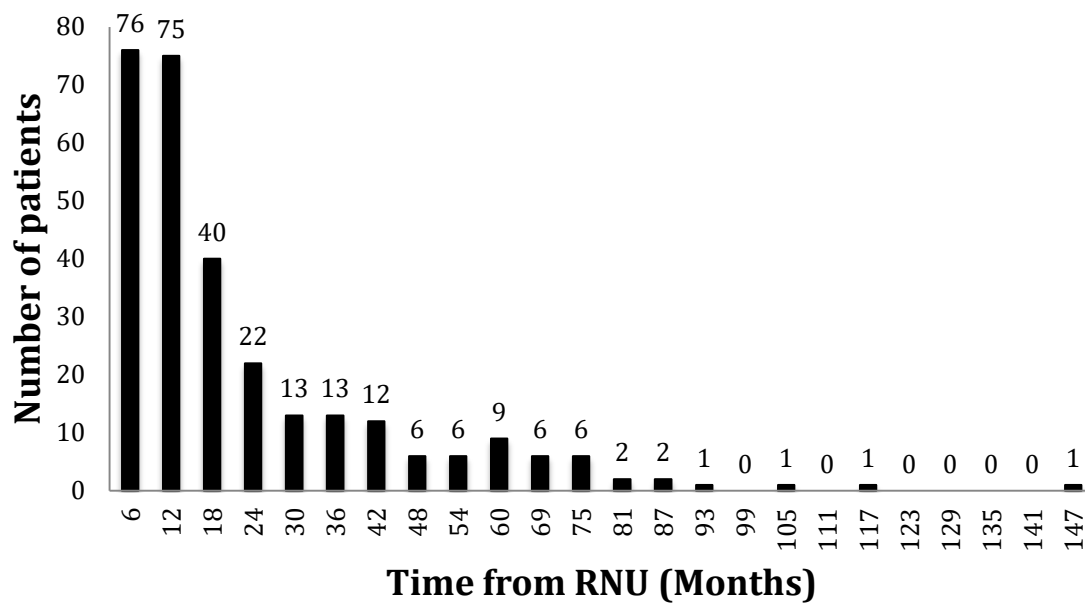
Fig. 3. Bladder recurrence stratified by risk group. RNU: radical nephroureterectomy
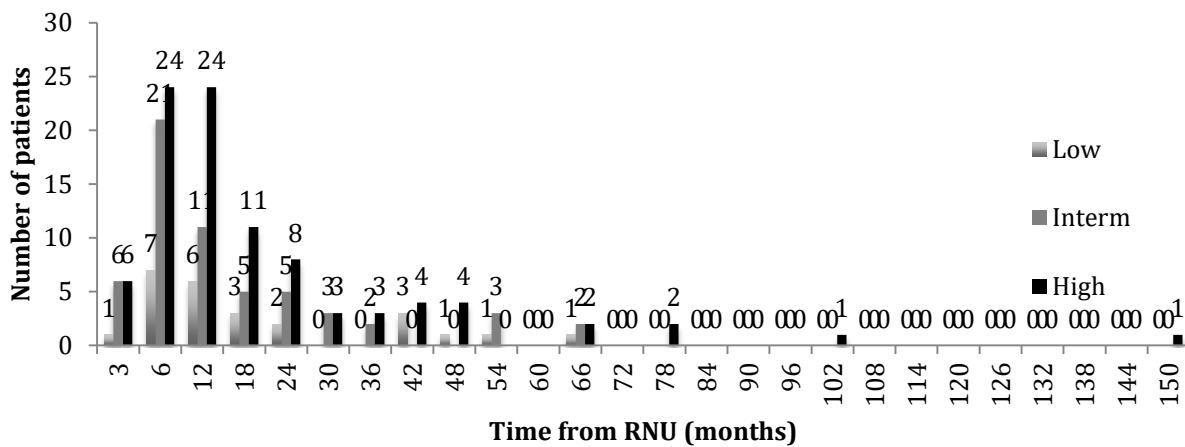
Fig. 4. Contralateral upper tract recurrence stratified by risk group. RNU: radical nephroureterectomy.
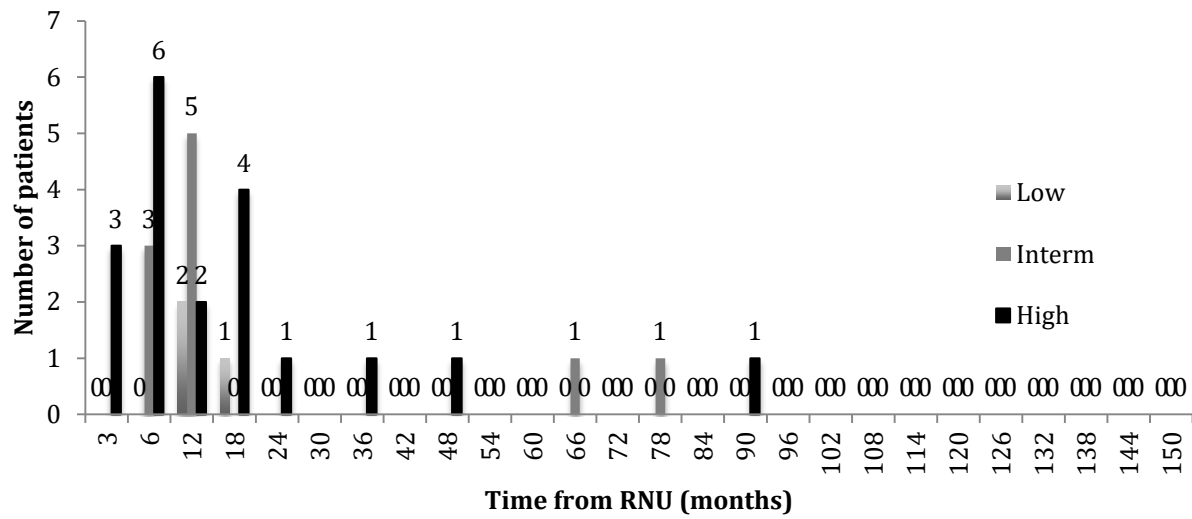
Fig. 5. Nephrectomy bed recurrence stratified by risk group. RNU: radical nephroureterectomy.

Fig. 6. Liver metastasis stratified by risk group. RNU: radical nephroureterectomy.

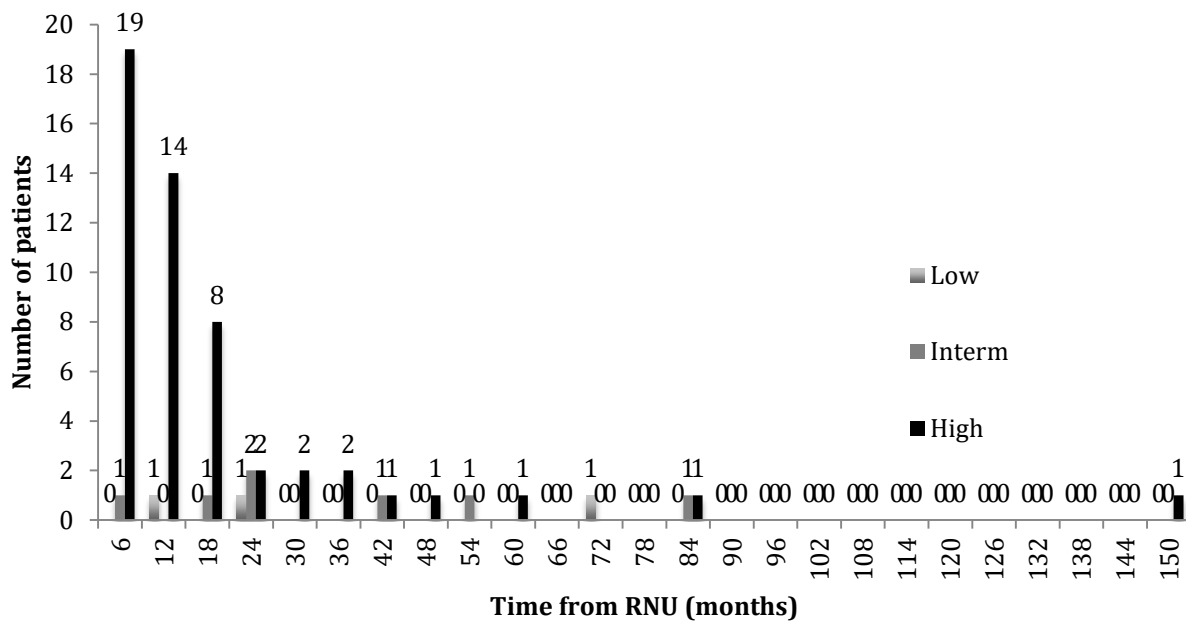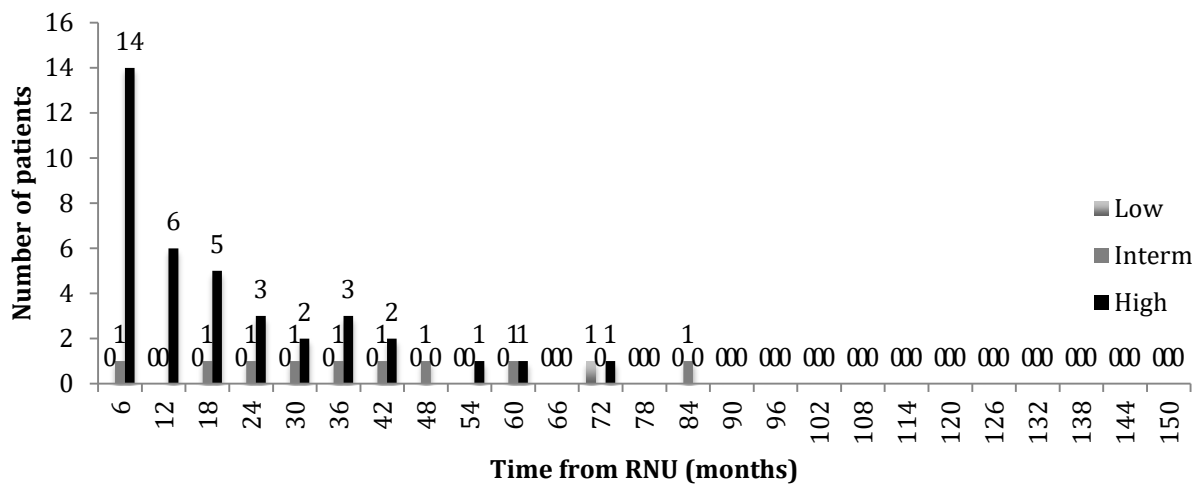| Table 1. Baseline clinical and pathologic characteristics				
	All patients	**No recurrence**	**Urothelial recurrence**	**Loco-regional/distant recurrence**
Median age, years (range)	71.59 (62.82, 77.40)	71.55 (62.25, 77.60)	72.45 (63.96, 78.10)	70.25 (62.80, 76.70)
Gender				
Male	707 (64%)	355 (64%)	180 (63%)	172 (65%)
Female	405 (36%)	203 (36%)	108 (37%)	94 (35%)
Prior bladder UC				
Yes	303 (28%)	128 (23%)	95 (33%)	81 (31%)
No	791 (72%)	419 (77%)	191 (67%)	181 (69%)
Prior UTUC				
Yes	88 (9%)	43 (9%)	29 (10%)	16 (7%)
No	878 (91%)	421 (91%)	252 (90%)	205 (93%)
Tumour location				
Renal pelvis	565 (52.3%)	329 (60.4%)	119 (42.6%)	117 (45.5%)
Ureter	274 (25.4%)	136 (25%)	72 (25.8%)	66 (25.7%)
Both	242 (22.4%)	80 (14.7%)	88 (31.5%)	74 (28.8%)
Distal ureter management				
Extravesical only	346 (38.8%)	167 (37.1%)	108 (40.8%)	71 (39.9%)
Extra and open intravesical combined	440 (49.3%)	233 (51.8%)	124 (46.8%)	83 (46.6%)
Extravesical and endoscopic intravesical combined	107 (12.0%)	50 (11.1%)	33 (12.5%)	24 (13.5%)
Neoadjuvant chemotherapy				
Yes	40 (4.1%)	11 (2.3%)	16 (5.6%)	13 (5.9%)
No	933 (95.9%)	457 (97.6%)	268 (94.4%)	208 (94.1%)
Adjuvant chemotherapy				
Yes	133 (12%)	24 (4%)	51 (18%)	58 (22%)
No	968 (88%)	529 (96%)	236 (82%)	203 (78%)
Pathological tumour stage				
pT0	7 (0.7%)	3 (0.6%)	2 (0.7%)	2 (0.8%)
pTa	244 (23.6%)	167 (31.6%)	55 (21%)	22 (9.1%)
pTis	42 (4.1%)	18 (3.4%)	14 (5.3%)	10 (4.1%)
pT1	236 (22.8%)	120 (22.7%)	77 (29.4%)	39 (16.1%)
pT2	174 (16.8%)	84 (15.9%)	45 (17.2%)	45 (18.6%)
pT3	271 (26.2%)	118 (22.3%)	60 (22.9%)	93 (38.4%)
pT4	59 (5.7%)	19 (3.6%)	9 (3.4%)	31 (12.8%)

Pathological node status				
pNx	269 (29%)	130 (28%)	66 (28%)	73 (31%)
pN0	562 (61%)	306 (67%)	153 (65%)	103 (44%)
pN+	96 (10%)	23 (5%)	16 (7%)	57 (24%)
Pathological tumour grade				
High	749 (69%)	360 (66%)	180 (64%)	209 (83%)
Low	333 (31%)	186 (34%)	103 (36%)	44 (17%)
Surgical margin status				
Positive	117 (11%)	30 (6%)	39 (14%)	48 (20%)
Negative	927 (89%)	496 (94%)	234 (86%)	197 (80%)
Concomitant CIS				
Present	249 (26%)	80 (17%)	92 (33%)	77 (37%)
Absent	698 (74%)	378 (83%)	190 (67%)	130 (63%)
Tumour multifocality				
Positive	275 (29%)	88 (19%)	99 (35%)	88 (41%)
Negative	681 (71%)	372 (81%)	181 (65%)	128 (59%)
Lymphovascular invasion				
Positive	195 (23%)	57 (14%)	60 (23%)	78 (40%)
Negative	664 (77%)	348 (86%)	199 (77%)	117 (60%)

CIS: carcinoma in situ; UC: urothelial carcinoma; UTUC: upper tract urothelial carcinoma.

Table 2. Predictors of urothelial recurrence on univariate and multivariate analysis

	Univariate analysis				Multivaraite analysis		
	HR	**95% CI**	**p**		**HR**	**95% CI**	**p**
Parameter							
Female gender	1.131	0.883 - 1.449	0.3309	Female gender	**1.479**	**1.056 - 2.071**	**0.0228**
Age	**1.018**	**1.005 - 1.030**	**0.0050**	Age	**1.017**	**1.000 - 1.034**	**0.0481**
Prior bladder UC	**1.319**	**1.016 - 1.711**	**0.0373**	Prior bladder UC	1.305	0.904 - 1.886	0.1556
Prior UTUC	1.154	0.763 - 1.745	0.4984	Prior UTUC	0.863	0.477 - 1.560	0.6249
Adjuvant chemotherapy	**3.121**	**2.265 - 4.300**	**<0.0001**	Adjuvant chemotherapy	1.496	0.836 - 2.678	0.1753
$\geq$pT2	0.2562	1.226 - 0.862	0.2562	$\geq$pT2	1.147	0.731 – 1.800	0.5496
$\geq$pT3	**1.410**	**1.043 - 1.905**	**0.0256**	$\geq$pT3	0.945	0.617 – 1.448	0.7964
pN+	**1.751**	**1.027 - 2.983**	**0.0395**	pN+	1.354	0.701 - 2.614	0.3665
pNx	0.822	0.609 - 1.110	0.2017	pNx	1.309	0.900 – 1.905	0.1595
High tumour grade	1.061	0.824 - 1.366	0.6447	High tumour grade	0.969	0.688 - 1.366	0.8592
+ CIS	**1.713**	**1.318 - 2.226**	**<0.0001**	+ CIS	0.902	0.606 - 1.341	0.6095
+Multifocality	**1.831**	**1.416 - 2.367**	**<0.0001**	+Multifocality	**1.925**	**1.367 - 2.710**	**0.0002**
+ Margins	**2.481**	**1.742 - 3.533**	**<0.0001**	+ Margins	**1.624**	**1.032 - 2.557**	**0.0361**
+ LVI	**1.870**	**1.391 - 2.516**	**<0.0001**	+ LVI	**1.811**	**1.187 - 2.763**	**0.0058**

CI: confidence interval; CIS: carcinoma in situ; HR: hazard ratio; LVI: lymphovascular invasion; UC: urothelial carcinoma; UTUC: upper tract urothelial carcinoma.

CUAJ – Original Research
Locke et al
Risk-adapted post-RNU surveillance protocol

Table 3. Predictors of loco-regional/distant recurrence on univariate and multivariate analysis							
	Univariate analysis				Multivariate analysis		
	HR	95% CI	p		HR	95% CI	p
Parameter							
Female gender	1.054	0.806 - 1.379	0.6986	Female gender	**2.084**	**1.381 - 3.146**	**0.0005**
Age	1.007	0.994 - 1.020	0.3192	Age	1.007	0.987 - 1.027	0.5145
Prior bladder UC	1.194	0.900 - 1.583	0.2191	Prior bladder UC	1.374	0.896 - 2.107	0.1454
Prior UTUC	0.951	0.561 - 1.613	0.8525	Prior UTUC	1.012	0.474 - 2.162	0.9758
Adjuvant chemotherapy	**3.367**	**2.440 - 4.646**	**<0.0001**	Adjuvant chemotherapy	1.560	0.908 - 2.681	0.1075
≥pT2	**2.080**	**1.371 - 3.154**	**0.0006**	≥pT2	**2.709**	**1.544 - 4.755**	**0.0005**
≥pT3	**4.094**	**2.963 - 5.657**	**<0.0001**	≥pT3	**2.494**	**1.472 - 4.226**	**0.0007**
pN+	**5.165**	**3.582 - 7.449**	**<0.0001**	pN+	**3.114**	**1.827 - 5.308**	**<0.0001**
pNx	1.349	0.982 - 1.853	0.0646	pNx	1.226	0.763 - 1.969	0.4005
High tumour grade	**2.471**	**1.747 - 3.494**	**<0.0001**	High tumour grade	**1.787**	**1.089 - 2.934**	**0.0217**
+ CIS	**1.938**	**1.430 - 2.627**	**<0.0001**	+ CIS	1.030	0.669 - 1.586	0.8936
+Multifocality	**1.939**	**1.445 - 2.603**	**<0.0001**	+Multifocality	**1.634**	**1.087 - 2.456**	**0.0183**
+ Margins	**2.979**	**2.122 - 4.182**	**<0.0001**	+ Margins	**1.270**	**0.779 - 2.072**	**0.3378**
+ LVI	**3.307**	**2.421 - 4.517**	**<0.0001**	+ LVI	**1.620**	**1.031 - 2.544**	**0.0363**

CI: confidence interval; CIS: carcinoma in situ; HR: hazard ratio; LVI: lymphovascular invasion; UC: urothelial carcinoma; UTUC: upper tract urothelial carcinoma.

Table 4. Histopathological risk groups for urothelial and loco-regional/distant recurrence

Risk category	pT stage	pN status	Grade	LVI	Multifocality
Low	pTa-T1	pN0	Low	No	No
Intermediate*	pTa-T1	pN0	High	Yes	Yes
High	≥ pT2	pN +	Any	Any	Any

*Includes any one of grade high, LVI yes, or multifocality yes. LVI: lymphovascular invasion

Table 5. Urothelial and loco-regional/distant recurrence free survival stratified by risk group

	Low	Intermediate	High
Bladder recurrence free survival			
6 months	43 (43%)	104 (42%)	159 (48%)
12 months	33 (33%)	84 (34%)	110 (32%)
24 months	22 (22%)	55 (22%)	62 (18%)
60 months	1 (1%)	2 (1%)	0 (0%)
Upper tract recurrence free survival			
6 months	30 (42%)	80 (41%)	110 (46%)
12 months	24 (33%)	66 (34%)	82 (34%)
24 months	17 (24%)	47 (24%)	49 (20%)
60 months	1 (1%)	2 (1%)	0 (0%)
Local/nodal/distant recurrence free survival		136 (44%)	
6 months	50 (46%)	106 (34%)	255 (50%)
12 months	35 (32%)	67 22%)	165 (33%)
24 months	23 (21%)	2 (0%)	85 (17%)
60 months	1 (1%)		0 (0%)

Table 6. Surveillance protocol											
Month followup	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**36**	**48**	**60**
History, physical, investigations											
Low		x		x		x		x	x	x	x
Intermediate	x	x	x	x		x		x	x	x	x
High	x	x	x	x	x	x	x	x	x	x	x
Chest radiography											
Low											
Intermediate				x				x	x	x	x
High		x		x		x		x	x	x	x
Cystoscopy and cytology											
Low		x		x				x	x	x	x
Intermediate	x	x		x				x	x	x	x
High	x	x	x	x		x		x	x	x	x
Abdominal imaging											
Low				x					x		x
Intermediate		x		x				x	x	x	x
High	x	x		x		x		x	x	x	x