Original Article

Intravesical recurrence in upper tract urothelial carcinoma patients after radical nephroureterectomy in Rajavithi Hospital

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Keywords:
Upper tract urothelial carcinoma, intravesical recurrence, nephroureterectomy, predictive factors

Abstract

Objective: Upper tract urothelial carcinoma (UTUC) is a malignant disease which is challenging to manage. The modalities for diagnosis and accurate clinical staging are limited, radical nephroureterectomy (RNU) with bladder cuff excision being the gold standard for treatment of UTUC. Subsequent intravesical recurrence (IVR) following RNU is a common problem. This study investigated the risk factors that affect IVR in Rajavithi Hospital. The objective of this study is to investigate whether the risk factors affect intravesical recurrence in UTUC patients after RNU.

Materials and Methods: This retrospective study evaluated 94 patients who had undergone RNU in Rajavithi Hospital for UTUC between November 2006 and February 2021; 69 patients were included in the analysis. Data was analyzed to investigate risk factors that impact IVR and IVR-free survival using Kaplan-Meier and Cox proportional regression methods.

Results: Out of 69 patients, at a mean follow up of 24 months, IVR occurred in 27 patients (39.1%). The overall postoperative 5-year IVR-free survival was 51.3%. Multivariate analysis indicated significant risk factors were high- grade tumor (adjusted HR = 3.47, 95%CI: 1.12-10.76, p = 0.031), ureterorenoscopy (URS) (adjusted HR = 3.45, 95%CI: 1.35-8.81, p = 0.01) and tumor multifocality (adjusted HR = 2.75, 95%CI: 1.02-7.38, p = 0.045). Postoperative 5-year IVR-free survival was significantly different for high-grade tumor compared with low-grade tumor (36.6% vs 82%, p = 0.006) and multiple tumors compared with a solitary tumor (18.4% vs 68.8%, p = 0.003) but there was no significant difference in URS compared with no URS (46.3% VS 51.6, p = 0.158).

Conclusion: The risk factors that affect intravesical recurrence in UTUC patients after Radical nephroureterectomy are high-grade tumor, tumor multifocality, and URS.

Insight Urol 2023;44(1):14-20. doi: doi: 10.52786/isu.a.67

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Manuscript received: April 9, 2023

Revision received: May 8, 2023

Accepted after revision: May 28, 2023

Introduction

Upper tract urothelial carcinoma (UTUC) is a malignant disease, accounting for approximately 5-10% of urothelial neoplasms and 10% of renal tumors.[1] Radical nephroureterectomy (RNU) with bladder cuff excision is the standard treatment for localized UTUC.[2] In comparison with bladder carcinoma, the prognosis of UTUC is relatively poor even though there are various treatment modalities. However, intravesical recurrence (IVR) after RNU is a common problem in patients with UTUC, this event can occur in 27% to 49% of patients, and the prognostic impact of IVR on oncologic outcomes remains unclear.[3,4] Previous studies have reported that environmental and clinicopathological factors, such as gender, tumor multifocality, pT stage and surgical approach, and diagnostic ureteroscopy could affect IVR after RNU.[1,5-8] Due to the relatively high occurrence rate of IVR, European Association of Urology (EAU) guidelines recommend that follow-up cystoscopy should be performed to detect IVR in patients who undergo RNU.[9] For this reason, identifying the risk factors that predict IVR of UTUC after RNU is essential to minimize the need for invasive examinations and facilitate the selection of patients who may benefit from early surgical intervention. Future studies should be performed to find a novel way to reduce the potential risk of IVR after RNU, for example the use of chemoprophylaxis.

Some clinicopathologic prognostic factors of IVR have been validated, but no consensus has been reached for variables that will consistently predict which patients will develop IVR.[10-12] The aim of this study is to identify the prognostic impact of IVR on oncologic outcomes and to identify the clinicopathologic factors that predict IVR in patients treated with RNU for UTUC.

This study was carried out at Rajavithi Hospital with the aim of investigating the risk factors that affect IVR.

Materials and Methods

Patients and inclusion criteria

Ninety-four patients underwent RNU with bladder cuff resection in Rajavithi Hospital between November 2006 and February 2021. All patients underwent routine preoperative cystoscopy before RNU to identify the possibility of synchronous bladder cancer.

Exclusion criteria

Out of the 94 patients, 25 were excluded as a result of synchronous bladder cancer, prior history of bladder cancer, status post cystectomy, no pathologic diagnosis for urothelial carcinoma or positive margin, or incomplete data (Figure 1).

Methods

A total of 69 patients were included in the study cohort. Clinical data on demographic characteristics and follow-up medical records were retrospectively collected after obtaining ethical board review approval from Rajavithi Hospital (study number: 64209).

All patients underwent standard open or laparoscopic RNU with bladder cuff resection, performed using the extravesical technique, where the ureter was dissected through the detrusor hiatus for complete resection of the intraluminal portion of the ureter. The bladder cuff was completely removed, and the bladder was closed using a continuous absorbable suture.

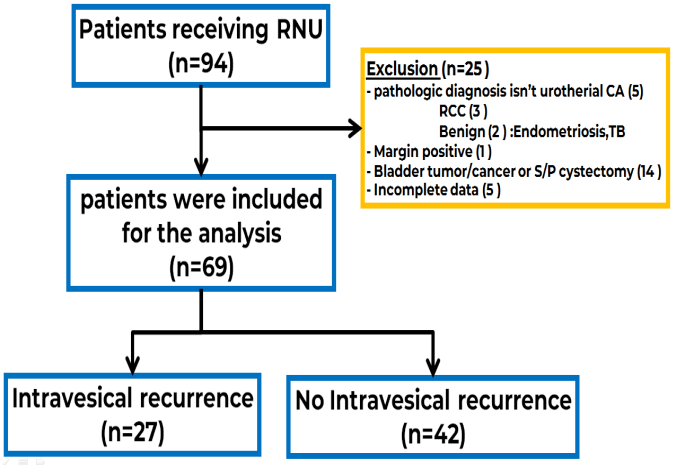

Figure 1. Flow chart of the study

Early ligation of the distal ureter was not routinely performed, and lymphadenectomy was not performed, with the exception of patients with suspiciously enlarged lymph nodes.

None of the 69 patients underwent neoadjuvant chemotherapy.

Diagnostic ureterorenoscopy (URS) was performed before RNU, but only for patients with equivocal diagnostic cases. Patients in whom preoperative URS was not deemed necessary had relatively definite tumor lesions on the radiologic image.

Pathologic evaluation

Tumors were staged according to the Tumor Node Metastasis classification and graded in accordance with the 2004 World Health Organization classification. Tumor location was defined as the renal pelvis, ureter, or both. Tumor multifocality was defined as pathologic confirmation of the synchronous presence of tumors in any location in the renal pelvis and ureter. Concomitant carcinoma in situ (CIS) was defined as the presence of CIS at any location in the renal pelvis and ureter.

Follow-up

All patients underwent cystoscopy every three months for the first two years, every six months for the next two years, and annually after that to check for the recurrence or occurrence of bladder tumors

Abdomen and chest CT and bone scans were performed when clinically indicated. IVR was defined as pathologic confirmation of bladder cancer through cystoscopic biopsy or transurethral resection. IVR excluded any tumor relapse outside the bladder.

Statistical analyses

The clinicopathologic factors affecting IVR were compared using the Chi-square test and Fisher exact test for categorical data and the Student t-test for continuous variables.

The probability of intravesical recurrence-free survival was estimated using the Kaplan-Meier method, and log-rank test values were used to assess the level of statistical difference.

The prognostic effects of clinicopathologic variables on IVR were estimated using univariate and multivariate Cox proportional hazards regression models.

Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to assess the strength of the individual variables. Statistical analysis was performed with Stata v.17, and statistical significance was defined as a $p < 0.05$.

Results

The median follow-up for the whole cohort was 24 months (interquartile range, 3-120 months). 27 (39.1%) patients experienced IVR within 6.4 months (interquartile range, 1.5-12.5 months) of the median interval between RNU and the first IVR.

Table 1 shows patient characteristics. The average age of patients was 65 years, 40 (58%) were male, 53 (76.8%) had underlying diseases, and 36 (52.2%) were smokers. Tumor classification factors were as follows: high T stage 35 (52.2%), N0 60 (87%), M0 67 (97.1%) and high-grade tumor 50 (72.5%). The locations of the primary tumor were 40 (58%) on the right side and 40 (58%) on the renal pelvis. The tumor was almost restricted to a solitary mass 50 (72.5%) and no CIS 60 (87%). Patients who underwent URS numbered[21] (30.4%), and the most frequent surgical method for RNU was the open technique 56 (81.2%).

Univariate Cox analysis showed that only M1 stage (HR, 11.67;95% CI, 1.28-106.2; p = 0.029), high grade tumor (HR, 4.04;95% CI, 1.38-11.84; p = 0.011), tumor multifocality HR, 3.06;95% CI, 1.43-6.55; p = .0.004) increase the probability of IVR (Table 2).

Then, we continued the analysis with multivariate Cox analysis to eliminate confounding factors and the outcome also showed that high grade tumor (HRadj, 3.47;95% CI, 1.12-10.76; p = 0.031), URS (HRadj, 3.45;95% CI, 1.35-8.81; p = 0.010), and tumor multifocality (HRadj, 2.75;95% CI, 1.02-7.38; p = 0.045) were independent significant factors for poor prognosis for IVR (Table 2).

In the multivariate analysis table, we only show factors that were found to be significant in both the multivariate and the univariate analysis, as these factors were further analyzed in the multivariate analysis.

The overall 5-year intravesical recurrent survival was 51.3%. The 5-year intravesical recurrent survival was 36.6% for high-grade tumors compared with 82% for low-grade tumors (p = 0.006), and 18.4% for multiple tumors compared with

Table 1. Patient characteristics

Characteristics	Total (n = 69)	
ECOG		(%)
0	24	(34.8)
1	35	(50.7)
2	10	(14.5)
Urine cytology		
No	51	(73.9)
Yes	18	(26.1)
Result of Urine cytology, (n = 18)		
No cancer	11	(61.1)
Cancer	7	(38.9)
URS	21	(30.4)
Location of Tumor		
Side		
Right	40	(58.0)
Left	29	(42.0)
Location of Primary Tumor		
Renal pelvis	40	(58.0)
Ureter proximal	13	(18.8)
Ureter distal	16	(23.2)
Multifocal		
Solitary	50	(72.5)
Multiple	19	(27.5)
CIS		
No	60	(87.0)
Yes	9	(13.0)
Surgical Method		
Open	56	(81.2)
Laparoscopic	13	(18.8)

Characteristics	Total (n = 69)	
		(%)
No. of patients	69	(100.0)
Age (years)	65.62 ± 13.15	
Sex		
Female	29	(42.0)
Male	40	(58.0)
Underlying diseases	53	(76.8)
Diabetes mellitus	20	(29.0)
Hypertension	40	(58.0)
Chronic kidney disease	14	(20.3)
Other	9	(13.0)
Smoking	36	(52.2)
T Stage		
T1	7	(10.1)
T2	27	(39.1)
≥T3	35	(50.7)
N Stage		
0	60	(87.0)
1	5	(7.2)
2	4	(5.8)
M Stage		
0	67	(97.1)
1	2	(2.9)
Grade		
Low	19	(27.5)
High	50	(72.5)

CIS = carcinoma in situ, URS = ureterorenoscopy, ECOG = Eastern Cooperative Oncology Group

68.8% for solitary tumors (p = 0.003). However, patients who underwent URS (compared with no URS) did not show statistically significant differences in 5-year intravesical recurrent survival (46.3% VS 51.6, p = 0.158) (Figure 2).

Discussion

This study found that 39.1% of patients with UTUC experienced IVR within a median interval of 6.4 months between RNU and the first IVR, which is in agreement with previous studies (27-49%).[3,4] However, the occurrence of IVR following RNU did not affect CSS and OS when IVR was detected early and the decision for surgical intervention was made based on scheduled cystoscopic follow-up.[13] Currently; two major hypotheses explain the pathogenesis of IVR after RNU for UTUC:[14,15]

1. Pan urothelial field-effect theory: preoperative carcinogen exposure in the entire urothelium accounts for independent tumor development following RNU

2. Intraluminal seeding and implantation of a single transformed cell theory: the bladder is continuously exposed to cancer cells dropping from the upper urinary tract before and during RNU.

The risk factors described in the previous studies are age, gender, tumor multiplicity, TNM stage, grade, tumor location, hydronephrosis, tumor size, previous/concomitant bladder tumors, carcinoma in situ, surgical mode, distal ureter management and URS before RNU.[13,16-24] Among these factors, a history of a prior bladder tumor is the most frequently reported, we excluded the patients with previous/concomitant bladder cancer because the incidence of IVR in those patients is related to localized disease instead of UTUC.

However, our study found that presence of a high grade tumor, tumor multifocality, and URS were independent risk factors for increased probability of IVR. We grouped large tumor size and hydronephrosis as the high stage group. In terms of 5-year intravesical recurrence-free survival, only high-grade tumors and multiple tumors showed a decrease, but URS did not. We chose to perform URS procedures only in patients with equivocal diagnostic cases from imaging, not for all patients. Patients who did not receive preoperative URS had relatively definite tumor lesions on the radiologic image, which could have affected the results, although the pathologic outcomes were not significantly different. Therefore, the lack of significance in 5-year recurrence free survival between the two groups in the study

Table 2. Univariate and multivariate Cox regression analyses predicting intravesical recurrence

Factors	Univariate analysis			Multivariate analysis		
	HR	95%CI	P-value	HRadj	95%CI	P-value
Age ≥ 65 years old	1.53	(0.67-3.50)	0.317			
Male sex	1.25	(0.58-2.71)	0.572			
Underlying diseases	1.79	(0.67-4.76)	0.246			
Smoker	1.83	(0.81-4.13)	0.144			
T stage						
T1	1.00	Reference				
T2	1.65	(0.45-5.99)	0.446			
≥ T3	1.38	(0.37-5.13)	0.628			
N stage						
0	1.00	Reference				
1	2.30	(0.28-18.6)	0.436			
2	0.65	(0.08-5.02)	0.680			
M stage						
0	1.00	Reference		1.00	Reference	
1	11.67	(1.28-106.2)	0.029	3.67	(0.36-36.98)	0.269
Tumor grade						
Low	1.00	Reference		1.00	Reference	
High	4.04	(1.38-11.84)	0.011	3.47	(1.12-10.76)	0.031
ECOG						
0-1 (low)	1.00	Reference				
2-3 (high)	2.10	(0.84-5.24)	0.113			
Urine cytology	1.83	(0.80-4.17)	0.152			
Result of urine cytology, (n = 18)						
No cancer	1.00	Reference				
Cancer	0.52	(0.13-2.11)	0.362			
URS	1.72	(0.80-3.70)	0.163	3.15	(1.35-8.81)	0.010
Result of ureteroscopy, (n = 17)						
No cancer	1.00	Reference				
Cancer	0.04	(0.01-0.25)	0.001			
Left side	1.08	(0.49-2.39)	0.841			
Location of primary tumor						
Renal pelvis	1.00	Reference				
Ureter	1.25	(0.59-2.67)	0.562			
Tumor multifocality	3.06	(1.43-6.55)	0.004	2.75	(1.02-7.38)	0.045
CIS present	2.98	(1.32-6.72)	0.009	2.08	(0.75-5.78)	0.161
Surgical Method						
Open	1.00	Reference				
Laparoscopic	2.23	(0.96-5.20)	0.062			
Duration from URS to RNU > 1 month	2.19	(0.58-8.21)	0.245			

may be attributed to the fact that the URS group exhibited a comparatively lower TNM stage than the non-URS group.

High grade tumor and tumor multifocality are non-modifiable factors. The inclusion of the URS procedure is the only modifiable factor that doctors need to decide upon, whether to do it or not, based on the benefit for diagnosis and risk of IVR, specifically the potential for intraluminal seeding as a consequence of ureteroscope manipulation and irrigation, retrograde flow, increased urine flow rate and intraluminal pressure which may lead to the shedding of tumor cells.[25]

Current evidence suggests that adjuvant intravesical chemotherapy after RNU decreased IVR risk.[26-28] The agents used are mitomycin-c, gemcitabine, or pirarubicin.[29] However, our study does not analyze the effect of adjuvant intravesical chemotherapy on IVR because of the small sample size and incomplete data.

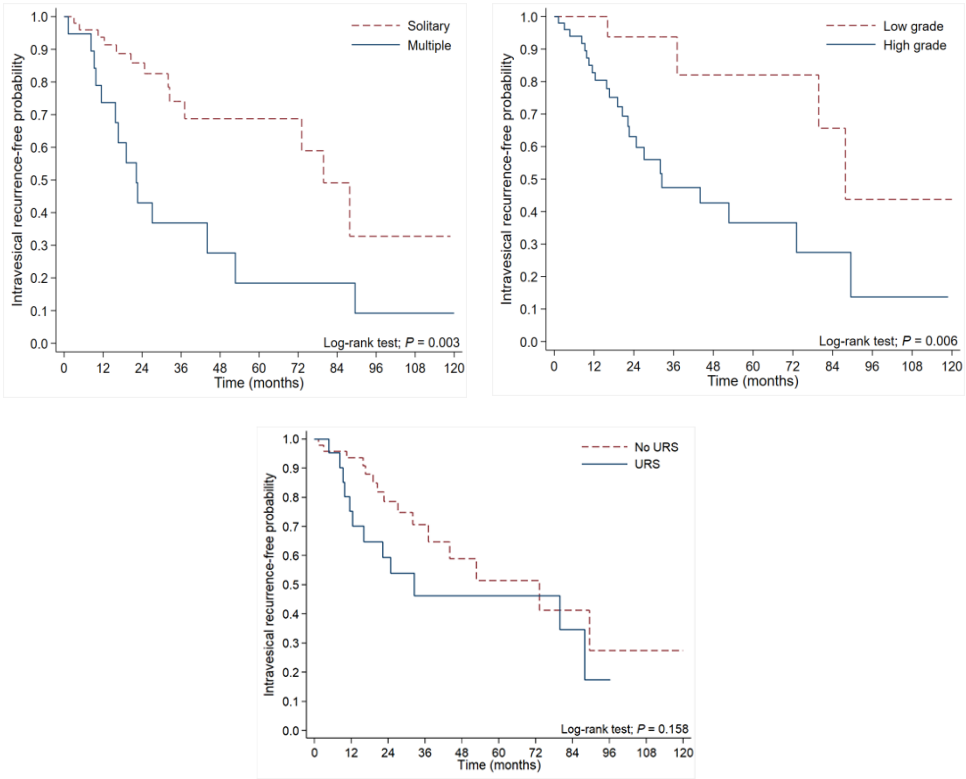

Figure 2. Kaplan-Meier Curves of the 5-year Intravesical Recurrence-free Period Stratified by Tumor Grade, Tumor Multifocality, and URS

The limitations of this study are its retrospective design, small patient population, and a relatively short period of follow-up (median follow-up = 2 years).

Other limitations could be the presence of microscopic, concurrent bladder cancer. Although we excluded patients with a previous history of bladder cancer, there could be some portion of cancer cells in the bladder of some patients.

Conclusions

Our results suggest that the factors that increase IVR risk in UTUC patients after radical nephroureterectomy are high-grade tumor, tumor multifocality, and URS. To reduce IVR, risk-based follow-up and preventive methods should be considered for patients with these risk factors.

Conflict of Interest

The authors declare no conflicts of interest.

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