Predictive Factors of Intravesical Recurrence after Ureteroscopy in Upper Urinary Tract Urothelial Carcinoma Followed by Radical Nephroureterectomy

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ABSTRACT

Objective: To investigate the risk factors of developing intravesical recurrence (IVR) in patients with upper urinary tract urothelial carcinoma (UTUC) who underwent ureterorenoscopy (URS) before radical nephroureterectomy with bladder cuff excision (RNU).

Materials and Methods: This retrospective study collected data from the medical records of patients diagnosed with UTUC between January 2012 and December 2019. All the patients underwent ureteroscopy before radical surgery. Patients previously diagnosed with bladder cancer were excluded. A total of 63 patients were included in the study. Tumour factors, such as multiplicity, location, size, histologic grade, pathologic T-stage, and lymphovascular invasion status, were evaluated. The type of endoscopic procedure and time interval between URS and RNU were analysed to determine the factors affecting IVR.

Results: The associated factors with IVR included multifocal tumours (HR = 4.8 (1.9–11.9)), large size tumours greater than or equal to 4 cm (HR = 3.3 (1.5–7.0)), and time interval greater than or equal to 5 weeks between URS and RNU (HR = 2.6 (1.2–5.5)). Factors including tumour location (kidney or ureter), size, grading, T-stage, and lymphovascular invasion as well as the type of endoscopic procedure were not at high risk for IVR.

Conclusion: The predictive factors of IVR for UTUC patients who underwent URS before RNU included a multiplicity of primary tumours and a tumour size greater than or equal to 4 cm, while a time interval between URS and RNU greater than or equal to 5 weeks increased the risk of IVR.

Keywords: Upper tract urothelial carcinoma; intravesical recurrent; bladder cancer; ureteroscopy; biopsy (Siriraj Med J 2023; 75: 234-240)

INTRODUCTION

Upper urinary tract urothelial carcinoma (UTUC) is an uncommon malignancy accounting for about 5–10% of urothelial carcinomas.[1-3] Radical nephroureterectomy with bladder cuff excision (RNU) is considered as the gold standard procedure for localised UTUC because it provides effective control and improves cancer-specific survival.[4,5]

A unique feature of urothelial carcinoma is the formation of multifocal tumours simultaneously and subsequently. Thus, the development of a tumour on the other side throughout the collecting system is possible in

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patients with primary UTUC.[6-8] The most common site of recurrence is the bladder. The intravesical recurrence (IVR) rate in patients who underwent RNU was found to be as high as 15–50%, while 5–10% of patients with IVR developed muscle invasive disease.[9,10] Thus, IVR is related to the risk of disease progression as well as an increased overall cost of treatment and decreased quality of life resulting from surveillance cystoscopy and bladder tumour surgery.[11]

Due to recent advancements in endoscopic technology, ureterorenoscopy (URS) is now increasingly used for the diagnosis and treatment of UTUC. This procedure is considered minimally invasive and pain-killers are not extensively required.[12] Several previous studies have reported that URS improved the accuracy of definitive diagnosis, staging, and histopathologic grading for UTUC.[13-15] URS has now become the method of choice to evaluate UTUC before performing definite surgery or for treating the disease following kidney sparing surgery.

However, there are many concerns that URS affects the long-term outcome of UTUC. Several studies have reported an association between URS and an increased risk of IVR but did not specify the risk factors involved.[13,16-21] Intravesical chemotherapy has been recommended for patients who underwent URS before RNU to prevent IVR, but this may not be universally suitable.[11,22,23] Therefore, here, the risk factors were evaluated for IVR in UTUC patients who underwent URS before RNU. The results may elucidate the patient choices available for future IVR prevention.

MATERIALS AND METHODS

This retrospective study reviewed the medical records of UTUC patients who underwent URS before RNU at a university hospital between January 2012 and December 2019. The study was approved by the ethics committee of the institute. (COA no. Si 648/2019) All the patients participated in a surveillance program that included physical and laboratory examination, cystoscopy, and imaging studies. None of the patients received intravesical chemotherapy before the first IVR. Patients who were previously diagnosed with bladder cancer, locally advanced UTUC, or metastatic disease at the first diagnosis and those who had absences in the surveillance program were excluded. Data from the medical records were collected as case record forms and classified as follows:

1. **Patient characteristics,** including gender, age at the first diagnosis, and follow-up interval.
2. **Disease factors** (final pathologic report of the RNU specimen), including:
   i Multiplicity of the tumour (unifocal, multifocal)
   ii Location of the tumour (renal calyx or pelvis, upper ureter, and lower ureter)
   iii Tumour size; cumulative (mm)
   iv Histologic grading
   v Pathologic T-stage
   vi Lymphovascular invasion.
3. **Procedural factors,** including:
   i The endoscopic procedure (URS alone, URS with biopsy, URS with laser ablation, URS immediately followed by RNU)
   ii Time interval between URS and RNU (weeks).
4. **Outcomes,** including the incidence of IVR, time interval between URS and the first IVR, and total number of IVR during surveillance.

The endoscopic procedure was performed utilising semi-rigid or flexible ureteroscopy. Tumour biopsy was performed using a basket or cup biopsy forceps, while laser ablation was performed utilising a holmium:YAG or thulium:YAG laser depending on the surgeon preference.

Radical nephroureterectomy was performed as different approaches, including open surgery (retroperitoneal through flank incision), laparoscopy (transperitoneal and retroperitoneal), and transperitoneal robotic-assisted. Distal ureter and bladder cuff excision for all the nephroureterectomy approaches was performed in one fashion through a low small transverse incision as a similar incision to extract the kidney. All the bladder cuff excisions were performed using an extravesical approach.

The patients' demographics, disease factors, and procedural factors were compared between the IVR and non-IVR patients. The independent t-test (normality) or Mann–Whitney U-test (non-normality) were used to assess quantitative data, while the chi-square test or Fisher's exact test were utilised for qualitative data. All the continuous data are shown herein as the median and interquartile range and an ROC curve was used to determine the appropriate cut-off value that showed a significant relationship with IVR. Factors with a p-value < 0.05 were considered statistically significant. Kaplan–Meier analysis was utilised to calculate the recurrence-free survival, while Cox-regression analysis was employed to predict the factors affecting IVR. Factors with a p-value < 0.05 in the univariate analyses were enrolled into the multivariate analyses.

RESULTS

Out of the 63 patients included in this study, 29 (46.0%) developed IVR during surveillance. The median time to develop the first IVR after the endoscopic procedure was 8.0 (4.5–11.5) months. The median number of total

IVR during the follow-up period was 2.0 (1.0–3.0).

The patient characteristics for both the non-IVR and IVR groups are shown in Table 1. There were no differences in the proportions between the two groups in terms of the gender, age at the first diagnosis, and follow-up interval (from the first diagnosis to the last visit).

Disease factors

Tumour multiplicity showed a significant difference between the non-IVR and IVR groups (p-value = 0.002) (Table 1). Comparing tumour multiplicity, 100% of patients who had multifocal primary tumours developed IVR, while the unifocal tumours did not significantly lead to the development of IVR among the various tumour sites (renal calyx or pelvis, proximal ureter, and distal ureter). Univariate analyses showed an increased risk of IVR for multifocal tumours (HR, 4.8; 95%CI, 1.9–11.9; p-value = 0.001) as well as in the multivariate analyses (HR, 4.3; 95%CI, 1.7–10.9; p-value = 0.002) (Table 2). Kaplan–Meier analysis revealed that the patients with unifocal tumours had a significantly higher rate of recurrence-free survival compared to patients with multifocal tumours (62.4 months vs 9.0 months, p-value < 0.005) (Fig 1).

Utilising the ROC curve to identify an appropriate cut-off value showed that a tumour size of 40 mm or larger had a higher rate of IVR than smaller tumours in both univariate analyses (HR, 3.3; 95%CI, 1.5–7.0; p-value = 0.002) and multivariate analyses (HR, 3.0; 95%CI, 1.4–6.5; p-value = 0.005). Patients with tumours smaller than 40 mm also had a significantly higher rate of recurrence-free survival compared to patients with tumours larger than 40 mm (68.8 months vs. 31.3 months, p-value < 0.001) (Fig 2).

Histologic grading, pathologic T-stage, and presenting with LVI did not affect the IVR (p-value = 0.72, 0.38, and 0.65, respectively).

Procedural factors

The time interval between URS and RNU demonstrated a significant difference between the non-IVR and IVR patients (p-value = 0.03). Utilising the ROC curve, a cut-off value of 5 weeks showed an association with IVR (p-value = 0.01). A time interval of 5 weeks or longer was related to an increased risk of IVR in the univariate analyses (HR, 2.6; 95%CI, 1.2–5.5; p-value = 0.01); however, the multivariate analyses did not show a significant association. Patients who underwent RNU less than 5 weeks after the first endoscopic intervention had a higher rate of recurrence-free survival (69.3 months vs. 35.7 months, p-value < 0.01) (Fig 3).

No difference in developing IVR was shown among the various types of initial endoscopic procedures (p-value = 0.36).

DISCUSSION

Although preoperative URS has been associated with an increased risk of IVR, this endoscopic procedure remains popular in the diagnosis and treatment of UTUC. Preoperative URS is crucial, especially in cases of controversial radiographic findings or in those considering kidney sparing surgery.[24] A previous study reported that 3% of patients who had suspected UTUC and who underwent RNU had benign pathologic findings. The suggestion to perform preoperative ureteroscopy undoubtedly improves precise decision-making before radical surgery.[25]

Many studies have demonstrated that IVR after endoscopic management of UTUC does not affect the long-term outcome and cancer-specific mortality. Gurbuz et al. reported that UTUC patients without preoperative URS had a similar 5-year survival rate compared with UTUC patients who received preoperative URS (77% vs. 73%, p-value = 0.4).[26] Sankin et al. reported a similar result, whereby patients with preoperative URS had a significantly higher IVR compared with patients without preoperative URS, but there were no significant differences in cancer-free survival and metastatic-free survival.[20] Therefore, IVR remains a factor to be considered when opting for URS.

Our results revealed that a multiplicity of tumours was a risk factor in developing IVR. Patients with multifocal tumours had 100% IVR and also a significantly lower recurrence-free survival rate compared with those suffering from unifocal tumours. Sung et al. also reported that multifocal tumours were a predictive factor of IVR after RNU[21], while Kang et al. reported a 3-fold greater risk of IVR in patients with multifocal tumours and recommended that these high-risk patients should be closely followed up.[6] There was no difference in risk of IVR among various tumour locations, including intrarenal, and proximal and distal ureter, which had unifocal tumours.

This study reported a correlation between the tumour size and an increased risk of IVR. Patients who had a tumour size of 40 mm or larger were at a 3-fold greater risk of developing IVR (p-value = 0.005). Shibing et al. reported that a tumour size larger than 3 cm was an adverse prognostic factor for cancer-specific survival, recurrence-free survival, and overall survival in UTUC patients who had undergone RNU with or without URS.[27]

Other previous studies reported that delaying radical surgery according to preoperative URS was associated with an increased risk of IVR. Lee et al. noted that UTUC

TABLE 1. Patient characteristics among the IVR and non-IVR groups.

Characteristic	*Non-IVR group*	*IVR group*	*P-value*
Patient demographics			
Gender ***n*** (%)			0.06
Male	15 (42.9%)	19 (67.9%)	
Female	20 (57.1%)	9 (32.1%)	
Age at the 1st diagnosis (year), median [IQR]	68 [61-76]	71 [64-79]	0.35
Follow-up interval (month), median [IQR]	45 [33-67]	48 [29-72]	0.98
Disease factors			
Multiplicity of the tumour ***n*** (%)			**0.002**
Unifocal tumour	35 (100.0%)	21(75.0%)	
Multifocal tumour	0 (0.0%)	7 (25.0%)	
Location of unifocal tumour ***n*** (%)			0.33
Renal calyx or pelvis	23 (65.7%)	10 (47.6%)	
Upper ureter	6 (17.1%)	4 (19.1%)	
Lower ureter	6 (17.1%)	7 (33.3%)	
Size of the tumour (mm), median [IQR]	28 [18-34]	34 [25-48]	**0.04**
Histologic grade ***n*** (%)			0.72
Low grade	6 (17.1%)	3 (10.7%)	
High grade	29 (82.9%)	25 (89.3%)	
Pathologic T-stage ***n*** (%)			0.38
T1 or lower	22 (62.9%)	14 (50.0%)	
T2	6 (17.1%)	9 (32.1%)	
T3 or higher	7 (20.0%)	5 (17.9%)	
LVI ***n*** (%)			0.65
Not present	33 (94.3%)	25 (89.3%)	
Present	2 (5.7%)	3 (10.7%)	
Procedural factors			
Initial endoscopic procedure ***n*** (%)			0.36
URS alone	5 (14.3%)	2 (7.1%)	
URS with biopsy	12 (37.1%)	17 (57.1%)	
URS with laser ablation	3 (8.6%)	3 (10.7%)	
URS followed by immediate-RNU	14 (40.0%)	7 (25.0%)	
Time interval between URS and RNU (week), median [IQR]	2 [1-7]	6 [2-10]	**0.03**

Abbreviations: IVR = intravesical recurrence; LVI = lymphovascular invasion; URS = ureteroreno-scopy; RNU = radical nephroureterectomy with bladder cuff excision.

TABLE 2. Univariate and multivariate analyses of the factors associated with intravesical recurrence.

Characteristic	*Univariate analyses*		*Multivariate analyses*	
	HR (95% CI)	*P-value*	*HR (95% CI)*	*P-value*
Location of tumour				
Unifocal tumour	1	-	1	-
Multifocal tumour	4.8 (1.9-11.9)	0.001	4.3 (1.7-10.9)	**0.002**
Size of tumour				
< 40 mm	1	-	1	-
≥ 40 mm	3.3 (1.5-7.0)	0.002	3.0 (1.4-6.5)	**0.005**
Time interval between URS and RNU+BCE				
< 5 weeks	1	-	1	-
≥ 5 weeks	2.6 (1.2-5.5)	0.01	1.7 (0.7-3.9)	0.19

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

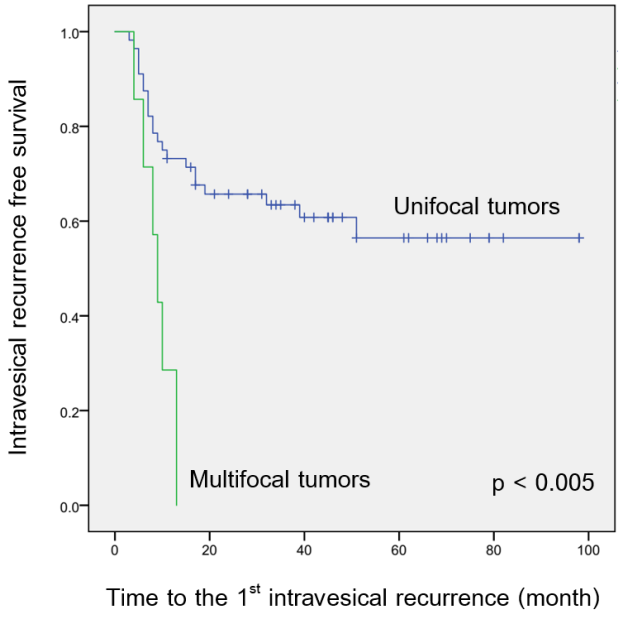

Fig 1. Intravesical free survival according to the location of the tumour

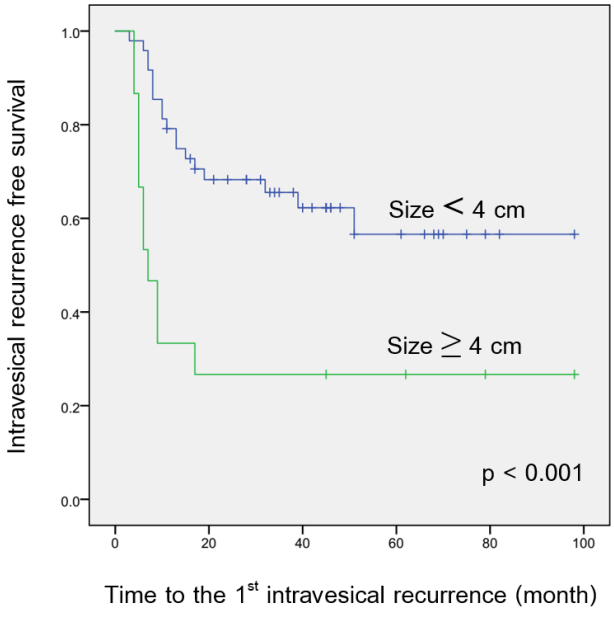

Fig 2. Intravesical free survival according to the size of the tumour

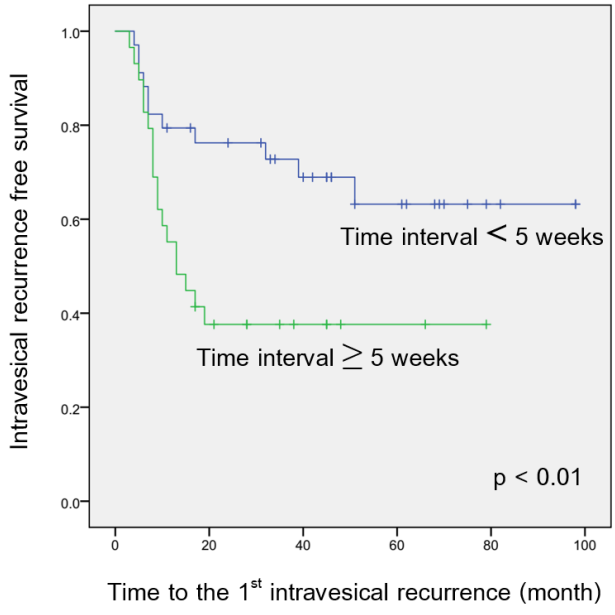

Fig 3. Intravesical free survival according to the time interval between URS and RNU

patients who underwent a 2-session approach (separate sessions of URS and RNU) had a significant risk of IVR compared with patients who followed a 1-session approach (URS and RNU in the same session) or without diagnostic URS (HR, 3.6; 95%CI, 1.0–12.6; p-value = 0.04).[28] However, they did not demonstrate an appropriate time interval between diagnostic URS and RNU that could reduce the risk of IVR. This study showed a significant association between delayed RNU and the risk of IVR at 5 weeks from the ROC curve. Univariate analyses showed that patients who had a time interval between URS and RNU of 5 weeks or longer were at a high risk of IVR (HR, 2.6; 95%CI, 1.2–5.5; p-value = 0.01); however, multivariate analyses did not show a significant association.

An investigation of the role of post-operative intravesical therapy for preventing IVR after RNU using the ODMIT-C trial demonstrated that post-operative single-dose intravesical Mitomycin-C (MMC) following RNU appeared to reduce the relative risk of IVR in the subsequent year by approximately 40%.[11] Wu et al. also reported a significantly lower IVR rate in patients who received either intravesical MMC or doxorubicin after RNU compared with those who did not.[10] These studies reported the efficacy of intravesical chemotherapy in patients who underwent RNU regardless of URS before radical surgery. According to the risk factors identified in this study, the administration of intravesical chemotherapy should be considered for patients who underwent URS before RNU and who had multifocal tumours, a tumour size greater than 40 mm, and a time interval between preoperative URS and RNU of more than 5 weeks. However, further study is required to verify these findings.

There are several limitations of this study to note, including the small number of patients. UTUC is an uncommon cancer and not every patient underwent URS before RNU and other inclusion criteria as aforementioned. This retrospective study also had inherent bias from the different techniques used for the surgical procedure, which depended on the surgeon preference.

CONCLUSION

In this study, the risk factors of developing IVR in UTUC patients who underwent URS before RNU were evaluated as being a multiplicity of primary tumours and a tumour size greater than or equal to 4 cm. A time interval between preoperative URS and RNU of greater than or equal to five weeks was associated with an increased risk of IVR in the univariate analyses.

Potential Conflicts of Interest

The authors declare they have no conflicts of interest.

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