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The Effect of Diagnostic Ureterorenoscopy on Intravesical Recurrence in Patients Undergoing Nephroureterectomy for Primary Upper Tract Urinary Carcinoma

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Keywords
Upper urinary tract · Urothelial carcinoma · Diagnostic ureterorenoscopy · Radical nephroureterectomy · Intravesical recurrence

Abstract
Objective: The objective of this study is to evaluate the effect of diagnostic ureterorenoscopy (URS) prior to radical nephroureterectomy (RNU) on intravesical recurrence (IVR), in patients with primary upper urinary tract urothelial carcinoma (UTUC). ***Materials and Methods:*** Retrospective analysis of 354 patients, who underwent RNU for UTUC from 10 urology centers between 2005 and 2019, was performed. The primary endpoint was the occurrence of IVR after RNU. Patients were divided into URS prior to RNU (Group 1) and no URS prior to RNU (Group 2). Rates of IVR after RNU were compared, and a Cox proportional hazards model was used to evaluate potential predictors of IVR. ***Results:*** After exclusion, a total of 194 patients were analyzed: Group 1 $n = 95$ (49.0%) and Group 2 $n = 99$ (51.0%). In Group 1, a tumor biopsy and histopathological confirmation during URS were performed in 58 (61.1%). The mean follow-up was 39.17 ± 39.3 (range 12–250) months. In 54 (27.8%) patients, IVR was recorded after RNU, and the median recurrence time within the bladder was 10.0 (3–144) months. IVR rate was 38.9% in Group 1 versus 17.2% in Group 2 ($p = 0.001$). In Group 1, IVR rate was 43.1% in those undergoing intraoperative biopsy versus 32.4% of patients without biopsy during diagnostic URS ($p = 0.29$). Intravesical recurrence-free survival (IRFS) was longer in Group 2 compared to Group 1 (median IRFS was 111 vs. 60 months in Groups 2 and 1, respectively ($p < 0.001$)). Univariate analysis revealed that IRFS was significantly associated with URS prior to RNU (HR: 2.9, 95% CI 1.65–5.41; $p < 0.001$). In multivariate analysis, URS prior to RNU (HR: 3.5, 95% CI 1.74–7.16; $p < 0.001$) was found to be an independent prognostic factor for IRFS. ***Conclusion:*** Diagnostic URS was associated with the poor IRFS following

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RNU for primary UTUC. The decision for a diagnostic URS with or without tumor biopsy should be reserved for cases where this information might influence further treatment decisions.

Introduction

Upper urinary tract urothelial carcinoma (UTUC) is a rare malignancy that accounts for 5–10% of all urothelial tumors, and the estimated incidence of UTUC is approximately 1–2 cases per 100,000 individuals [1, 2]. Current guidelines recommend performing urinary cytology, cystoscopy, and imaging of the upper urinary tract as the standardized initial assessments for UTUC and diagnostic ureterorenoscopy (URS), with or without tumor biopsy should be performed, especially in patients where additional information will effect treatment decisions [3].

Radical nephroureterectomy (RNU) with bladder cuff excision is the gold standard treatment for localized UTUC [4]. Intravesical recurrence (IVR) after RNU for UTUC occurs in 22–47% of patients [5–7]. Male gender, the previous bladder cancer diagnosis, smoking, preoperative CKD, positive preoperative urinary cytology, ureteral location, multifocality, invasive pathological tumor (pT) stage, necrosis, laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins are identified as important predictors of bladder recurrence after RNU [8]. Identifying risk factors for IVR after RNU is a major challenge for UTUC patients.

URS combined with tumor biopsy provides direct visualization of the entire collecting system, which can increase the detection rate of UTUC lesions [9, 10]. It has been reported that URS prior to RNU did not affect IVR or cancer-specific survival in patients with UTUC [11]. However, recent studies suggest a higher rate of IVR after RNU in patients who had prior URS [12, 13]. Theoretically, IVR may occur due to pyelolymphatic, pyelotubular, and pyelovenous backflow of irrigation during URS [14, 15], or it may occur via backflow of malignant urothelial cells and tumor seeding during URS [11, 16, 17]. The aim of this study was to evaluate the effect of URS prior to RNU on IVR in patients with primary UTUC.

Materials and Methods

Data from 354 patients, who underwent RNU for UTUC in 10 urology centers between 2005 and 2019, were analyzed retrospectively. Preoperative cystoscopy was performed routinely in all patients to diagnose a potential synchronous bladder tumor. Patients with concurrent presence of bladder urothelial carcinoma (UC) and a history of the previous diagnosis with UC or non-UC histopathology were excluded. Patients, who received intravesical chemotherapy after RNU, were also excluded.

Data items included demographic characteristics, intraoperative and postoperative parameters, and pathological and oncologic findings while follow-up medical records were retrospectively evaluated. All patients underwent standard open, laparoscopic, or robotic RNU with bladder cuff resection, which was performed using an extravesical technique. Lymphadenectomy was performed in cases where lymph node (pN) involvement was suspected, but it was not routinely applied to cross the whole patient cohort.

The presence of ureteral dilatation and hydronephrosis (HN) was diagnosed with an upper tract imaging modality, either ultrasound, computed tomography, or MRI based on each surgeon's routine practice. URS, with or without tumor biopsy, was performed in suspicious cases where definitive diagnosis could not be made with imaging modalities or in some cases was performed based on the individual surgeon's clinical judgment. Rigid and/or flexible URS was used, depending on the location of the tumor.

Pathological specimens were evaluated at each institution's pathology department using tumor-node-metastasis classification for staging and the 2004 WHO classification for grading. Patient follow-up was performed based on the European Association of Urology (EAU) guidelines recommendations [3].

The primary endpoint of this study was the occurrence of IVR after RNU. Patients were divided into 2 groups: URS prior to RNU (Group 1) versus no URS prior to RNU (Group 2). The diagnosis of IVR was defined by cystoscopic diagnosis followed by pathological confirmation. The IVR rates following RNU were compared between the groups. Whether tumor biopsy was performed during the URS procedure or not was also analyzed. The time from diagnostic URS to RNU was calculated to evaluate the effect of concurrent or delayed RNU on IVR.

The secondary endpoint of this study was the identification of potential risk factors for IVR. Demographic patient details including age, gender, BMI, and concurrent diabetes mellitus (DM) and hypertension were evaluated. Factors related to the disease such as laterality, location, preoperative HN, preoperative ureteral dilatation, RNU approach, pT stage and pN stage, tumor grade, surgical margin status, presence of carcinoma in situ, neoadjuvant and adjuvant chemotherapy, follow-up duration, and the presence of local recurrence or metastatic disease were also analyzed. A Cox proportional hazards model was used to evaluate the potential predictors for IVR.

Statistical Analysis

All analyses were performed using the Statistical Package for Social Sciences program, Version 20.0 (IBM Inc., Armonk, NY, USA). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum, as appropriate. χ^2 test was used to compare categorical variables between the groups. For comparison of continuous variables between 2 groups, the Student's *t* test was used. For univariate analysis, intravesical recurrence-free survival (IRFS) was calculated by the Kaplan-Meier method, and log-rank test was performed. Cox regression analysis was performed to determine significant prog-

nostic factors. In univariate analysis, variables significant at the $p < 0.2$ level and variables considered clinically important were entered in Cox regression analysis. The statistical level of significance for all tests was considered to be 0.05.

Results

Patient Characteristics

After exclusion, 194 patients were included in the study. The mean age of patients was 66.3 ± 9.8 years (range 39–90 years), and 154 (79.4%) were male and 40 (20.6%) were females. The follow-up period ranged from 12 to 250 months, with a mean of 39.17 ± 39.3 months. Open RNU was performed in 87 (45.2%) patients, 95 (48.9%) patients underwent laparoscopic RNU, and 12 (6.2%) patients underwent robotic RNU.

Group 1 included 95 (49.0%) patients who had URS prior to RNU, and Group 2 included 99 (51.0%) patients who had RNU without prior URS. In Group 1, a tumor biopsy during URS was performed for pathological confirmation in 58 (61.1%) patients. Demographic and clinical characteristics of these groups are presented in Table 1. There was no significant difference between the 2 groups with regard to age, gender, diabetes mellitus, hypertension, BMI, laterality, preoperative ureteral dilatation, pT, pN, tumor grade, positive surgical margins, concurrent carcinoma in situ, follow-up duration, or neoadjuvant chemotherapy. Additionally, local recurrence, metastasis, and adjuvant chemotherapy rates have similar distribution between the 2 groups ($p > 0.05$). Preoperative HN was significantly more common in Group 1 ($p = 0.022$) while in Group 2 75% of the tumors had a pelvicalyceal location which was significantly more common than in Group 1 ($p = 0.001$).

Intravesical Recurrence following Radical Nephroureterectomy

IVR after RNU was recorded in 54 (27.8%) of all patients, and the median (range) recurrence time within the bladder was 10.0 (3–144) months. IVR was significantly more likely in Group 1 compared with Group 2 (38.9 vs. 17.2%; $p = 0.001$). Within Group 1, IVR was recorded in 43.1% (25/58) of patients with an intraoperative biopsy versus 32.4% (12/37) without a biopsy during diagnostic URS ($p = 0.29$). Although the recurrence rate was higher in the biopsy subgroup, the difference was not statistically significant but there is trend toward significance which may become significant with larger group sizes.

Table 1. Demographic and clinical characteristics of groups; Group 1 underwent URS while Group 2 did not

	URS		*p* value
	+ (*n* = 95)	– (*n* = 99)	
Gender *n* (%)			
Male	74 (77.9)	80 (80.8)	0.746
Female	21 (22.1)	19 (19.2)	
DM, *n* (%)			
+	16 (17.2)	16 (17.2)	0.999
–	77 (82.8)	77 (82.8)	
HT, *n* (%)			
+	42 (45.2)	34 (36.2)	0.211
–	51 (54.8)	60 (63.8)	
BMI,[a] kg/m^2	26.8±4.2	25.4±3.4	0.055
Laterality, *n* (%)			
Right	40 (42.1)	52 (52.5)	0.146
Left	55 (57.9)	47 (47.5)	
Preoperative hydronephrosis, *n* (%)			
+	55 (57.9)	41 (41.4)	0.022*
–	40 (42.1)	58 (58.6)	
Preoperative ureteral dilatation, *n* (%)			
+	38 (40.0)	33 (33.3)	0.335
–	57 (60.0)	66 (66.7)	
Location, *n* (%)			
Pelvicalyceal	46 (48.4)	74 (74.7)	0.001*
Ureter	35 (36.8)	17 (17.2)	
Both	14 (14.7)	8 (8.1)	
Surgical approach, *n* (%)			
Open	41 (43.2)	46 (46.5)	0.041*
Laparoscopic	52 (54.7)	43 (43.4)	
Robotic	2 (2.1)	10 (10.1)	
pT stage, *n* (%)			
Ta and T1	33 (34.7)	34 (34.3)	0.596
T2	15 (15.8)	11 (11.1)	
T3 and T4	47 (49.5)	54 (54.5)	
pN stage, *n* (%)			
N0	69 (72.6)	78 (78.8)	0.234
N1	1 (1.1)	4 (4.0)	
N2	5 (5.3)	5 (5.1)	
N*X*	20 (21.1)	12 (12.1)	
Grade, *n* (%)			
Low grade	27 (28.4)	33 (33.3)	0.559
High grade	68 (71.6)	66 (66.7)	
Concurrent CIS, *n* (%)			
–	87 (91.6)	93 (93.9)	0.721
+	8 (8.4)	6 (6.1)	
Positive surgical margins, *n* (%)			
–	84 (88.4)	92 (92.9)	0.404
+	11 (11.6)	7 (7.1)	
Follow-up duration,[a] months	36.4±36.3	41.8±41.9	0.340
Intravesical recurrence, *n* (%)			
+	37 (38.9)	17 (17.2)	0.001*
–	58 (61.1)	82 (82.8)	
Neoadjuvant chemotherapy, *n* (%)			
No	87 (91.6)	96 (97.0)	0.189
Yes	8 (8.4)	3 (3.0)	
Adjuvant chemotherapy, *n* (%)			
No	83 (87.4)	80 (80.8)	0.293
Yes	12 (12.6)	19 (19.2)	
Local recurrence, *n* (%)			
No	93 (97.9)	93 (93.9)	0.280
Yes	2 (2.1)	6 (6.1)	
Metastasis, *n* (%)			
No	83 (87.4)	86 (86.9)	0.999
Yes	12 (12.6)	13 (13.1)	

URS, ureterorenoscopy; CIS, carcinoma in situ; DM, diabetes mellitus; HT, hypertension; pT, pathological tumor; pN, lymph node; SD, standard deviation. [a] Data are expressed as mean ± SD. * $p < 0.05$

Table 2. Univariate and multivariate analyses of potential prognostic factors for IRFS

Parameters	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	0.9 (0.96–1.01)	0.378	0.9 (0.94–1.00)	0.066
Gender (male)	1.2 (0.63–2.30)	0.568	1.3 (0.70–2.68)	0.352
URS(+)	2.9 (1.65–5.41)	**<0.001**	3.5 (1.74–7.16)	**<0.001**
Location	–	0.356	–	0.969
Ureter	Ref		Ref	
Pelvicalyceal	0.6 (0.37–1.20)	0.676	1.0 (0.54–2.13)	0.828
Both	1.0 (0.38–2.78)	0.947	0.9 (0.31–3.04)	0.980
CIS(+)	1.6 (0.68–3.89)	0.268	1.2 (0.47–3.16)	0.673
Positive surgical margins	1.4 (0.36–6.17)	0.578	–	
Preoperative hydronephrosis (+)	1.3 (0.78–2.36)	0.276	1.0 (0.56–1.96)	0.862
pT stage	–	0.117	–	0.316
Ta and T1	Ref		Ref	
T2	2.0 (0.90–4.61)	0.084	1.9 (0.80–4.49)	0.141
T3 and T4	0.9 (0.49–1.65)	0.745	1.0 (0.56–2.07)	0.805
Surgical approach	–	0.992	–	–
Open	Ref		Ref	
Laparoscopic	0.9 (0.56–1.68)	0.921	–	–
Robotic	1.0 (0.24–4.46)	0.954	–	–
Grade(HG)	1.1 (0.62–2.07)	0.682	–	–

Bold values indicate statistical significance. pT, pathological tumor; URS, ureterorenoscopy; CIS, carcinoma in situ.

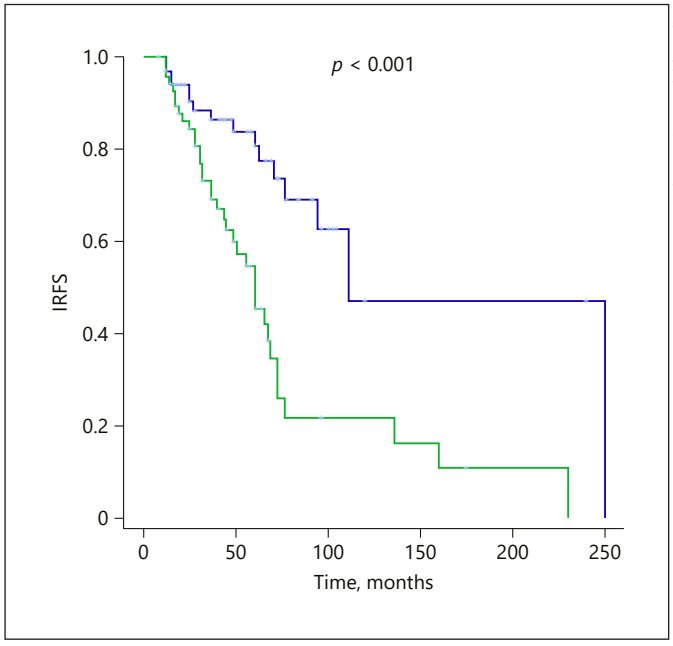

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Fig. 1. The median IRFS in URS+ (Group 1, green line) and URS– (Group 2, blue line) were 60 versus 111 months, respectively ($p < 0.001$). IRFS, intravesical recurrence-free survival; URS, ureterorenoscopy.

The median time from URS to RNU was 30 (0–120) days, although in 16 patients a diagnostic URS was performed during the same session, immediately prior to the RNU. The duration from URS to RNU was not associated with IVR ($p = 0.625$).

IRFS following RNU was longer in patients without prior URS compared to patients with prior URS. The median IRFS in Groups 1 and 2 was 60 versus 111 months, respectively ($p < 0.001$) (Fig. 1).

A Cox proportional hazards model was used to evaluate the potential predictors, and the results are shown in Table 2. Univariate analysis revealed that IRFS was significantly associated with URS prior to RNU (HR: 2.9, 95% CI 1.65–5.41; $p < 0.001$). In multivariate analysis, prior URS to RNU (HR: 3.5, 95% CI 1.74–7.16; $p < 0.001$) was found to be the only independent prognostic factor for IRFS of those investigated (Table 2).

Discussion

The pathogenesis of IVR after RNU for UTUC could theoretically result from either implantation of a single transformed cell after descendant intraluminal seeding or

a pan-urothelial field defect [18–20]. Recently, studies to support a mixed monoclonal and oligoclonal origin of metachronous multifocal UC have suggested that both mechanisms might be involved in the development of IVR following the previous UTUC [21–23]. It has also been suggested that ureteroscope manipulation or tumor dissemination, due to backflow irrigation, may theoretically increase the risk of tumor implantation. This was supported by anecdotal reports suggesting tumor seeding as a consequence of ureteroscopy [15, 24]. However, the literature is inconclusive as to whether URS prior to RNU increases the risk of IVR, and there is no consensus to date. The aim of this study was to address this question, and our results have shown that URS prior to RNU was significantly associated with increased IVR in patients with primary UTUC. However, tumor biopsy during URS did not increase IVR compared to URS without biopsy. Our results also indicate that URS prior to RNU was not associated with a higher rate of local recurrence and metastatic disease. Finally, URS had no effect on the use of neoadjuvant or adjuvant chemotherapy.

Ishikawa et al. [11] reported on 208 cases, where URS prior to RNU was performed only in 55 (26.5%) patients. They reported the 2-year IRFS rate was 60.0% in the URS group and 58.7% in the non-URS group ($p = 0.97$) and concluded that URS does not affect IVR in patients undergoing RNU [11]. A large collaborative database study by Nilson et al. [25] included 512 patients, where IVR was seen in 148 patients. In the patient group with URS 46 (27.5%) had IVR whereas 97 (28.36%) patients who did not undergo URS exhibited IVR, and these proportions did not differ between the 2 groups ($p > 0.05$). They concluded that URS is not an independent risk factor for IVR. In another cohort study, the authors found that URS prior to RNU was not associated with a higher risk of IRFS even in patients without a history of bladder cancer [26]. Yoo et al. [27] investigated whether biopsy during URS for UTUC before RNU affected IVR. Patients were stratified according to tumor location and the impact of URS-biopsy (URS-Bx) on IVR. They found 5-year IRFS was not significantly different according to URS-Bx in the overall patient group. However, they concluded URS-Bx was a significant risk factor for IVR in patients with renal pelvic tumor. In contrast, in our study tumor location did not affect IVR rate.

In contrast, there are studies which have confirmed the negative impact of URS on IRFS. Sung et al. [28] evaluated 630 patients retrospectively, of whom 44.7% had URS prior to RNU. They found the 5-year IRFS rates were 42.6 and 63.6% in patients with and without URS, respectively, and this was significantly different ($p < 0.001$) [28]. A meta-analysis, including 8 eligible studies, containing 3,975 patients, demonstrated that URS was associated with poorer IRFS (HR = 1.51, 95% CI 1.29–1.77; $p < 0.001$) irrespective of prior bladder tumor [29]. In a further meta-analysis, including 2,372 patients in total, a statistically significant association between performance of URS prior to RNU and IVR was found in patients undergoing RNU (HR 1.56, 95% CI 1.33–1.88; $p < 0.001$) [30]. These results are in line with our study results; we, therefore, caution that especial care should be taken for UTUC patients at risk of IVR. Intravesical chemotherapy following URS may prevent IVR and prevent the need for additional surgical interventions. Randomized control trials are needed to assess the effects of post-URS intravesical chemotherapy on IVR rates.

Sung et al. [28] evaluated whether manipulation, such as tumor biopsy and balloon dilation, were performed or not during URS. They reported the IVR rate was higher in patients with manipulation during URS compared to patients receiving no manipulation during URS although, the difference was not significant. We found similar results and concluded that there is trend toward significance with increasing number of cases.

Another potential criticism of performing URS prior to RNU is the delay in providing definitive treatment. These patients could be exposed to increased risk of intraluminal tumor seeding, either through increased risk following manipulation or through a longer duration between presentation and definitive treatment (or both). For this reason, in patients in our cohort who had IVR, the time delay to radical surgery was included in analysis. However, we did not find any differences between the concurrent and delayed RNU groups in terms of IVR incidence. Lee et al. [31] in their study stratified into 3 groups depending on the timing of URS: the no URS group; a second group with concurrent URS; and a third group with delay to URS, in the latter the median delay was 5 days. They reported that delay of RNU after URS significantly increased the risk for IVR. Sankin et al. [32] also reported the same relationship between time delay and risk for IVR. In contrast, Sung et al. [28] reported that the duration from URS to RNU was not associated with IVR, in line with our findings.

Limitations of the Study

The present study is limited by its retrospective nature. Patients were included from 10 different centers, which, thus, included variation of practice, such as there being no definitive standard criteria for performing URS prior to RNU. Another limitation was that our data lacked the

data regarding the uni- or multilocality of the tumors. Thus, it was not possible to comment on manipulations other than any tumor biopsy which may have been performed. Finally, single-center pathological review was not performed which will, therefore, include interobserver differences which are common in reporting tumor grade and stage.

Conclusions

Diagnostic URS was associated with the poor IRFS following RNU for primary UTUC. The decision for a diagnostic URS, with or without tumor biopsy, should be reserved for cases where this information might influence further treatment decisions. Prospective randomized trials using intravesical therapy after diagnostic procedures are needed to investigate if this will further reduce this risk.

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Statement of Ethics

Ethics Committee approval for the study was obtained from the Ethics Committee of the University of Çukurova (approval number – September 4, 2019; 91/60).

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to disclose.

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Author Contributions

V.I., M.D., and Y.B.: conception or design of the work; acquisition, analysis, or interpretation of data; and drafting or revising the work. I.T., E.O., and D.B.: conception or design of the work; drafting or revising the work; and acquisition of data. B.A., S.B., O.C., and H.M.A.: conception or design of the work; drafting or revising the work; and interpretation of data.

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