Impact of Non-synchronous Diagnostic Ureteroscopy on Intravesical Recurrence in Patients Underwent Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: A Propensity-Score Matched Analysis

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Abstract

Background: The effect of diagnostic ureteroscopy (DURS) on intravesical recurrence (IVR) after radical nephroureterectomy (RNU) were controversial. To investigate the impact of DURS, we carried out this single-center retrospective study by applying propensity-score matching (PSM) and Cox regression model.

Patients and Methods: The data of 160 patients with pTa-pT3 upper tract urothelial carcinoma (UTUC) were analyzed. Eighty-six patients underwent DURS (DURS group) and 74 patients without DURS (control group). The DURS group was further sub-grouped into synchronous DURS group (DURS followed by immediate RNU, n=45) and non-synchronous DURS group (DURS followed by delayed RNU, n=41). Baseline confounders were corrected by PSM. The impact of DURS on IVR was assessed by Kaplan-Meier analysis in PSM cohort and by Cox regression model in the full data set.

Results: The median follow-up time was 40.4 months. No difference of the 3-year IVRFS between DURS group and control group (72.6% vs. 65.3%, $p=0.263$). In subgroup analysis, the 3-year IVR-free survival of non-synchronous DURS group (51.4%) was significantly lower than that of synchronous DURS (78.3%) or control group (72.6%) ($p=0.027$). Further Cox regression analysis showed that non-synchronous DURS (HR 1.481, 95% CI 1.031-2.127, $p=0.034$) was independent risk factors for postoperative IVR.

Conclusions: Non-synchronous DURS was not recommended for the diagnosis and preoperative evaluation of UTUC, because it could raise the risk of IVR after RNU. For UTUC patients in need of DURS, synchronous DURS could be a safer choice than the non-synchronous DURS in terms of lowering the IVR risk.

Background

Ureteroscopy had become a powerful tool for the diagnosis and endoscopic treatment of upper tract urothelial carcinoma (UTUC). The diagnostic ureteroscopy (DURS) and biopsy were recommended by the European Association of Urology especially for cases where additional information would impact the final decision of treatment (1). For suspicious cases of renal pelvic or ureteral mass, the National Comprehensive Cancer Network also suggested a series of diagnostic tests including computed tomography urography (CTU), cytology, cystoscopy and ureteroscopy (2). With the help of DURS, surgeons could obtain not only the direct visualization of suspicious lesions, but also an opportunity of biopsy, which improved the accuracy of evaluating upper urinary tract filling defects, when abnormal findings in imaging studies were not necessarily the indicator of UTUC (3, 4).

The importance of DURS for the diagnosis of UTUC was undeniable, but as an invasive procedure, it may disturb the microenvironment of the tumor. To address the dilemma, many researches have been done to explore the oncological safety of DURS. These studies had tried to clarify the relationship between DURS and intravesical recurrence (IVR) after radical nephroureterectomy (RNU), but their results were remarkably inconsistent (5–14), and this might be partially caused by effects of confounding variable in these studies. In the observation studies of the real world, several methods could be applied for the control of confounding, such as the propensity-score matching (PSM), multivariate regression model, inverse-probability-of-treatment weighted logistic regression model and standardized mortality ratio-weighted logistic regression model (15). Thus, in order to investigate the impact of DURS on IVR after RNU by removing the influence of the confounders, we carried out this single-center retrospective study by applying PSM and Cox regression model.

Patients And Methods

From July 2013 to June 2016, 179 patients with pTa-pT3 UTUC were admitted to Shanghai Changhai Hospital, and underwent RNU (laparoscopic or robotic nephroureterectomy with extravesical bladder cuff excision and appropriate lymph node dissection following the lymphatic drainage). Nineteen patients were lost to follow-up, and finally the data of 160 patients were included in this study for analysis. The schema of treatment within this study was shown in Figure 1. Based on the preliminary results of CTU and urinary cytology, the arrangement of further DURS for the patients were decided. There were 86 patients underwent DURS because of negative CTU and/or cytology findings (the DURS group), and there were 74 patients with positive CTU and cytology findings underwent RNU without DURS (the control group). Patients with synchronous bladder cancer who required for radical cystectomy, and patients underwent DURS with negative findings were excluded from this study.

Since patients in the DURS group and the control group had shown different baseline characteristics, this study adopted PSM to identify cohorts of patients with similar baseline characteristics. The propensity score was the conditional probability of having the particular exposure of DURS, given the set of baseline covariates. As shown in Table 1, the non-parsimonious multivariable logistic-regression model was used to calculate the propensity score with DURS as the dependent variable, and all the baseline confounders, including age, gender, smoking history, location and size (maximum diameter) of tumor, multifocality, synchronous bladder cancer and adjuvant bladder instillation, were corrected by PSM as covariates. As to the matching process, the 1:1 matching protocol without replacement (greedy-matching algorithm) was adopted with the caliper width equal to 0.2 of the standard deviation of the logit of the propensity score. In order to assess the level of pre-match and post-match balance, standardized differences were calculated for all the baseline covariates both before and after matching. For a given covariate, standardized differences less than 10.0% indicated the level of imbalance was relatively low.

In the PSM cohort, paired comparisons were performed with two-way ANOVA for continuous variables, and with Mann-Whitney U test for nonparametric variables. The risk of IVR to DURS was assessed with Fisher's exact test. To evaluate the prognosis effect of DURS on the postoperative intravesical recurrence-free survival (IVRFS), Kaplan-Meier univariate analysis was adopted for the PSM cohort and Cox regression multivariate analysis was adopted for the full data set.

Currently there was no unified standard on the timing of DURS. In this study according to the time interval between DURS and RNU, the DURS group were further sub-grouped into synchronous DURS (DURS followed by immediate RNU on the same operation day) and non-synchronous DURS (DURS followed by delayed RNU). In the full dataset before PSM, there were 45 patients in the synchronous DURS group and 41 patients in the non-synchronous DURS (Figure 1). Kaplan-Meier analysis and Log-rank (Mantel-Cox) test were used for the subgroup comparison within the PSM cohort. All the analyses were performed with

SPSS 25.0 (IBM) with integration plug-in for R package of PSM. All reported p-values were two-sided, and a p-value of 0.05 was set as cutoff for statistical significance.

Results

The median follow-up time of 160 patients was 40.4 months (1.1–76.7 months). The diagnosis of UTUC was confirmed by histopathology in all patients. For patients underwent non-synchronous DURS, the time interval between DURS and RNU was 7.4 ± 1.2 days, which was for the waiting of pathological results. Table 1 showed the characteristics of the initial study cohort of 160 patients before and after they were matched according to their propensity to undergo DURS. Of these patients, 86 (53.7%) underwent DURS and 74 (46.3%) did not. Before PSM, patients in the DURS group had a longer history duration (269.47 vs. 101.57 days, MD = 167.89, $p = 0.002$) and smaller tumor size (2.45 vs. 3.73 cm, MD = -1.27 , $p < 0.001$) than the control group. In addition, the DURS group had more ureter tumor than the control group (66.3% vs. 36.5%, $p = 0.001$). Using estimated propensity scores, 44 patients in the DURS group were matched 1:1 to patients in the control group. Figure 2 shows the distribution of the differences for the main covariates included in the propensity-score model, which was reduced significantly after matching.

Within the PSM cohort, the DURS group and the control group had similar surgical and pathological outcomes in terms of operation type (robotic RNU or laparoscopic RNU), operating time, estimated blood loss (EBL), pathological T stage, regional positive lymph nodes, tumor grade, positive surgical margin, pathohistology, risk stratification, and intravesical recurrence (Table 2). In the entire PSM cohort of 88 patients, there were 42 patients had postoperative recurrence, including 29 of intravesical recurrence, 9 of retroperitoneal recurrence, and 4 of distant metastasis involving lung and/or bone. In subgroup analysis on the timing of DURS and postoperative recurrence, the Fisher's exact test showed that the non-synchronous DURS was a risk factor for the postoperative IVR, and could raise the risk of IVR after RNU by 3.55 fold compared to the control group (OR = 3.55, $p = 0.028$) and by 4.80 fold compared to the synchronous DURS group (OR = 4.80, $p = 0.029$), while this risk difference was not shown between the synchronous DURS group and the control group (Table 2). With respect to survival analysis, the 3-year IVRFS were similar in DURS group and control group (72.6% vs. 65.3%, $p = 0.264$), while in subgroup analysis, the 3-year IVRFS of non-synchronous DURS (51.4%) was significantly lower than that of synchronous DURS (78.3%) and control group (72.6%) ($p = 0.027$) (Figure 3).

In the multivariate analysis of the prematched full data set, Cox regression model showed that the non-synchronous DURS (HR 1.481, 95% CI 1.031–2.127, $p = 0.034$) and pathological T stage (HR 1.562, 95% CI 1.120–2.178, $p = 0.009$) were independent risk factors for postoperative IVR, while the pathological T stage (HR 2.144, 95% CI 1.313–3.499, $P = 0.002$) and adjuvant bladder instillation chemotherapy (HR 0.219, 95% CI 0.086–0.557, $P = 0.001$) were independent risk factors for postoperative cancer-specific survival (CS) (Table 4).

Discussion

As to the lesions in upper urinary tract, nephroureterectomy might not be a desirable option if the lesion was benign. Although an optimally protocolled CTU was very specific, some cases remained equivocal, leaving urologists and pathologists in dilemma. According to Tavora et al, among 76 consecutive cases where patients underwent DURS to evaluate a possible tumor, 32.9% were diagnosed as benign urothelium (16), which indicated the necessity of performing evidence-based measures to minimize the risk. In our full dataset before PSM, the patients in DURS group had smaller tumor size and more ureter tumors than the control group, suggesting that the diagnosis of small tumors located in ureter was more likely to depend on the assistance of DURS. Alongside the huge advancement of endoscopic techniques in recent years, DURS had played a critical role in assisting the diagnosis of UTUC, bringing down the misdiagnosis rate to about 2.1% (17). Furthermore, performing DURS would provide surgeons with more useful information to support the risk stratification of UTUC (1, 17). The preoperative findings from DURS, coupled with ureteroscopic biopsy, could improve the level of sensitivity and facilitate the determination of grade and stage (18, 19).

IVR would occur in 22–47% patients underwent RNU for UTUC (20, 21). Concerns had been raised about the possibility of tumor seeding secondary to the ureteroscopic manipulation of the UTUC (13), but up to date, the influence of DURS on IVR has still remained unclear, and the conclusions drawn by relative studies were inconsistent. According to Luo et al, for patients ($n = 115$) underwent DURS before RNU, the risk of IVR was higher than those who did not receive prior DURS ($n = 281$) (HR 1.44, 95% CI 1–2.08, $p = 0.05$) (9). Marchioni et al carried out a meta-analysis with the data of 2382 patients. The result indicated a 50% higher likelihood of IVR in patients who had DURS ($n = 765$), and the association between DURS prior to RNU and IVR was statistically significant (HR 1.56, 95% CI 1.33–1.88, $p < 0.001$) (10). However, the study carried out by Ishikawa et al ($n = 208$) showed no difference of IVR rates between DURS cohort and non-DURS cohort at 2 years (60% vs. 59%, $p = 0.972$) (7). In the study conducted by Yoo et al ($n = 387$), IVR occurred in 163 patients (42.1%). They also found out lower IVRFS in DURS group than non-DURS group (39.6% vs. 62.2%, $p = 0.012$) among patients with renal pelvic tumor, while for patients with ureteral tumor, the IVRFS showed no significant difference between DURS and non-DURS groups (36.7% vs. 45.8%, $p = 0.946$) (14). The inconsistency of these results could be caused by the heterogeneity in both the design of these studies and the histopathological findings (22).

Two meta-analyses had identified the major risk factors of IVR as patient-, tumor- and treatment-specific factors (21, 23). The risk factors for IVR that had been recognized include the presence of carcinoma in situ, synchronous bladder tumor, multifocality, tumor location, stage and grade (24–29). In this study, within the PSM cohort the baseline potential confounders that could influence the IVR after RNU such as male gender, smoking history, hydronephrosis, tumor size, tumor location, multifocality, synchronous bladder cancer, adjuvant bladder instillation were well balanced between the DURS group and the control group. Also, the prognosis factors from surgical and pathological outcomes that correlated with the IVR, such as the pathological tumor stage, grade, positive surgical margins, variant histology and risk stratification were similar in both groups. Thus, the potential confounding on IVR after RNU were strictly controlled by PSM in this study, and the impact of particular exposure of DURS was investigated independently.

In this study, two kinds of DURS exposure were analyzed: synchronous DURS (DURS followed by immediate RNU on the same operation day) and non-synchronous DURS (DURS followed by delayed RNU). In our center, both kinds of DURS were offered to patients for choice before RNU. For patients who chose synchronous DURS, both DURS and RNU were booked on the same operation day, but the RNU would be cancelled and necessary biopsy would be done if there was no positive findings of tumor lesions during the DURS in some patients. Delayed RNU would be arranged if the biopsy results showed UTUC. For patients underwent non-synchronous DURS, biopsy were performed in all. According to the results of Kaplan-Meier univariate analysis and Fisher's exact test within the PSM cohort, we found that non-synchronous DURS was a predictor for the IVR and could raise the risk of IVR after RNU, comparing with the synchronous DURS (OR = 4.80, $p = 0.029$) or no DURS (OR = 3.55, $p = 0.028$). This result was further confirmed by Cox regression multivariate analysis in full data set, that the non-synchronous DURS (HR 1.481, 95% CI 1.031–2.127, $p = 0.034$) and pathological T stage (HR 1.562, 95% CI 1.120–2.178, $p = 0.009$) were independent predictors for IVR after RNU, although we failed to show other previously confirmed risk factors, such as positive margins or tumor multifocality (21, 23). When we analyzed the non-synchronous DURS group and synchronous DURS group as a whole in the PSM cohort, the predictor effect of DURS on IVR was not revealed by the Kaplan-Meier analysis (3-year IVRFS, DURS group vs. control group) (72.6% vs. 65.3%, $p = 0.264$). One potential explanation could be that the different effect of the two have cancelled each other out. In this study, we found out that the DURS on different timing would lead to different prognosis. The lack of the analysis on the timing of DURS might be another reason for the inconsistency in results of those previous studies (5–14).

The studies attempting to answer the question of whether delaying the RNU to DURS would incur more dreadful oncological outcomes came up with similar research results. According to Sankin et al, the delay in time of performing RNU (the median of delay time was 20 days) and prior DURS were associated with higher IVR risk after RNU (HR 2.58, 95% CI 1.47–4.54, $p = 0.001$) (12). Through the analysis of 104 cases, Lee et al found out that the delay of RNU after DURS resulted in the significant increase of IVR risk in UTUC patients (HR 3.61, 95% CI 1.039–12.557, $p = 0.043$). Furthermore, Lee et al also maintained that the IVR rate of the one-session group (in which patients received RNU immediately after DURS) (24.2%) was quite similar to that of the no DURS group (16.7%), while the IVR rates of both groups were statistically lower than the two-session group (51.2%, $p = 0.004$) (30). The exact mechanism underlying this phenomenon has not been completely understood. One possible explanation could be the theory of tumor seeding. In patients underwent non-synchronous DURS and biopsy, the double-J stents were necessarily inserted, ensuring continuous urine drainage from pelvis and ureter into bladder. Hence the viable upper tract tumor cells would not only slough off during DURS, but also keep drifting downstream via double-J stent after DURS, and consequently implanted in the bladder mucosa. Meanwhile, the inflammation or injury of mucosa after DURS, especially in the area of ureteral orifice, could make the mucosa more susceptible to the implantation when at the exposure of tumor cells. Thus the patients underwent non-synchronous DURS would be under a relative longer and stronger exposure of tumor than the patients underwent synchronous DURS or without DURS, resulting in a higher risk of IVR.

Limitations

This was a single-center, retrospective study, and the sample size of the data set ($n = 160$) was relatively small, and this might cause the selection bias within this study, although PSM and multivariate regression model were applied. Considering the low incidence of UTUC and limited research focus on the DURS timing, we think this study could provide some useful information for the clinical practice, while further large-scale multicenter prospective study are still needed.

Conclusions

DURS had its role in assisting the diagnosis and preoperative evaluation of UTUC, but non-synchronous DURS (DURS followed by delayed RNU) was not recommended, because it could raise the risk of IVR after RNU. For UTUC patients in need of DURS, synchronous DURS (DURS followed by immediate RNU on the same operation day) could be a safer choice than the non-synchronous DURS in terms of lowering the IVR risk.

Abbreviations

CS = cancer-specific survival

CTU = computed tomography urography

DURS = diagnostic ureteroscopy

EBL = estimated blood loss

IVR = intravesical recurrence

IVRFS = intravesical recurrence-free survival

PSM = propensity-score matching

RNU = radical nephroureterectomy

UTUC = upper tract urothelial carcinoma

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All subjects gave their informed consent for inclusion before they participated in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards from the Ethics Committee of Shanghai Changhai Hospital, the Second Military Medical University.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

H Ye and X Feng: Project development, Manuscript writing

Y Wang: Data collection, Data analysis, Manuscript writing

R Chen: Data collection, Data analysis

M Hua, X Lu, X Jiang and Y Fang: Data collection

Z Wu: Data analysis, Manuscript editing

Q Yang and B Yang: Manuscript editing

Chen Lu: Project development, Data collection, Data analysis, Manuscript writing, Manuscript editing

L Wang: Project development, Manuscript editing

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Tables

Table 1. Perioperative patient data and tumor characteristics in all patients, in propensity-score matched patients and in unmatched patients

SD or n	All Patients					Propensity-score matched patients					Unmatched patients		
	DURS, n=86	No DURS, n=74	MD/OR	95% CI	p	DURS, n=44	No DURS, n=44	MD/OR	95% CI	p	DURS, n=42	No DURS, n=30	MD/OR
SD age,	65.53±8.17	66.49±9.32	-0.95	-	0.340	67.86±7.83	65.95±9.77	1.90	-	0.512	63.10±7.88	66.20±8.84	-3.10
n (%)			0.69	0.35-1.32	0.266			0.82	0.34-1.96	0.658			0.22
	52(60.5)	51(68.9)				27(61.4)	29(65.9)				25(59.5)	26(86.7)	
e	34(39.5)	23(31.1)				17(38.6)	15(34.1)				17(40.5)	4(13.3)	
g History,			0.51	0.21-1.23	0.133			0.83	0.25-2.71	0.764			0.28
	10(11.6)	15(20.3)				6(13.6)	7(15.9)				4(9.5)	8(26.7)	
	76(88.4)	59(79.7)				38(86.4)	37(84.1)				38(90.5)	22(73.3)	
ms, n (%)			1.70	0.82-3.53	0.150			0.75	0.26-2.14	0.597			2.46
nephrosis	60(69.8)	59(79.7)				36(81.8)	34(77.3)				24(57.1)	23(76.7)	
nephrosis	26(30.2)	15(20.3)				8(18.2)	10(22.7)				18(42.9)	7(23.3)	
SD duration,	269.47±571.21	101.57±140.00	167.89	-	0.002	158.07±236.25	134±168.51	23.09	-	0.261	386.17±768.529	72.77±111.50	313.4
ocation			-	-	0.001					0.915			-
pelvis	29(33.7)	47(63.5)				22(50.0)	24(54.5)				7(16.7)	25(83.3)	
ureter	9(10.5)	4(5.4)				4(9.1)	3(6.8)				5(11.9)	2(6.7)	
ureter	19(22.1)	4(5.4)				3(6.8)	4(9.1)				16(38.1)	-	
ureter SD	29(33.7)	19(25.7)				15(34.1)	13(29.6)				14(33.3)	3(10.0)	
l tumor	2.45±1.28	3.73±2.19	-1.27	-	<0.001	2.73±1.52	2.99±1.68	-0.26	-	0.486	2.16±0.90	5.04±2.16	-2.87
al			0.96	0.35-2.64	0.944			0.67	0.19-2.32	0.534			0.68
, n (%)	9(10.5)	8(10.8)				5(11.4)	7(15.9)				4(9.5)	4(13.3)	
	77(89.5)	66(89.2)				39(88.6)	37(84.1)				38(90.5)	26(86.7)	
nous (%)			0.98	0.33-2.84	0.973			0.63	0.16-2.42	0.502			0.94
	8(9.3)	7(9.5)				4(9.1)	6(13.6)				4(9.5)	3(10.0)	
	78(90.7)	67(90.5)				40(90.9)	38(86.4)				38(90.5)	27(90.0)	
t bladder ion, n (%)			1.44	0.76-2.70	0.255			0.75	0.32-1.76	0.517			2.23
	53(61.6)	39(52.7)				24(54.5)	27(61.4)				29(69.0)	15(50.0)	
	33(38.4)	35(47.3)				20(45.5)	17(38.6)				13(31.0)	15(50.0)	

DURS, diagnostic Ureteroscopy; SD, standard deviation; MD, mean difference; OR, odds ratio.

Table 2. Surgical and pathological outcomes for DURS group and control group before and after propensity-score matching

Mean ± SD or n (%)	Before propensity-score matching					After propensity-score matching				
	DURS, n=86	No DURS, n=74	MD/OR	95% CI	p	DURS, n=44	No DURS, n=44	MD/OR	95% CI	p
Operation, n (%)			0.30	0.12-0.76	0.008			0.389	0.11-1.37	0.133
Robotic RNU	22(25.6)	7(9.5)				9(20.5)	4(9.1)			
Laparoscopic RNU	64(74.4)	67(90.5)				35(79.5)	40(90.9)			
Mean ± SD operating time, min	280.05±89.93	251.84±92.17	28.20	-	0.027	268.05±84.75	254.43±95.81	13.61	-	0.218
Mean ± SD EBL, mL	241.63±269.21	188.31±156.31	53.31	-	0.337	238.64±314.35	186.48±167.80	52.15	-	0.496
Pathologic T stage, n (%)			-	-	0.439			-	-	0.101
pTa	11(12.8)	14(18.9)				6(13.6)	9(20.5)			
pT1	23(26.7)	13(17.6)				12(27.3)	5(11.4)			
pT2	30(34.9)	25(33.8)				11(25.0)	19(43.2)			
pT3	22(25.6)	22(29.7)				15(34.1)	11(25.0)			
Regional lymph nodes, n (%)			0.49	0.11-2.16	0.344			0.48	0.39-0.60	0.153
pN(+)	3(3.5)	5(6.8)				0(0.0)	2(4.5)			
pN(-)	83(96.5)	69(93.2)				44(100.0)	42(95.5)			
Tumor grade			0.76	0.39-1.47	0.416			1.00	0.41-2.41	1.000
Low grade	32(37.2)	23(31.1)				15(34.1)	15(34.1)			
High grade	54(62.8)	51(68.9)				29(65.9)	29(65.9)			
Surgical margin, n (%)			0.84	0.30-2.37	0.751			1.36	0.28-6.49	0.69
Positive	8(9.3)	8(10.8)				4(9.1)	3(6.8)			
Negative	78(90.7)	66(89.2)				40(90.0)	41(93.2)			
Pathohistology, n (%)			0.70	0.20-2.39	0.567			1.00	0.19-5.24	1.000
Pure urothelial carcinoma	68(91.9)	81(94.2)				41(93.2)	41(93.2)			
Accompanied by other histological variants *	6(8.1)	5(5.8)				3(6.8)	3(6.8)			
Risk stratification, n (%)			0.64	0.18-2.29	0.496			1.00	0.23-4.27	1.000
High risk	79(91.9)	70(94.6)				40(90.0)	40(90.0)			
Low risk	7(8.1)	4(5.4)				4(9.1)	4(9.1)			
Intravesical Recurrence, n (%)			1.79	0.89-3.61	0.099			1.67	0.68-4.12	0.257
Yes	30(34.9)	17(23.0)				17(38.6)	12(27.3)			
No	56(65.1)	57(77.0)				27(61.4)	32(72.7)			

DURS, diagnostic Ureteroscopy; EBL, estimated blood loss; SD, standard deviation; MD, mean difference; OR, odds ratio.

* Other histological variants included squamous cell carcinoma, squamous metaplasia, sarcomatous change and collecting duct carcinoma.

Table 3. Subgroup analysis of postoperative recurrence related to DURS in propensity-score matched patients (Fisher's exact test)

operative recurrence Sites	Non-synchronous DURS vs Control					Non-synchronous DURS vs Synchronous DURS					Synchronous DURS vs Control				
	Non-synchronous DURS, n=21	Without DURS, n=44	OR	95% CI	p	Non-synchronous DURS, n=23	Synchronous DURS, n=23	OR	95% CI	p	Synchronous DURS, n=23	Without DURS, n=44	OR	95% CI	p
vesical recurrence, n	12(57.1)	12(27.3)	3.55	1.19-10.57	0.028	12(57.1)	5(21.7)	4.80	1.28-17.87	0.029	5(21.7)	12(27.3)	0.74	0.22-2.44	0.770
operitoneal recurrence, n	3(14.3)	3(6.8)	2.27	0.41-12.38	0.379	3(14.3)	3(13.0)	1.11	1.19-6.22	1.000	3(13.0)	3(6.8)	2.05	0.37-11.07	0.406
distal metastasis*, n	1(4.8)	2(4.5)	1.05	0.09-12.27	1.000	1(4.8)	1(4.3)	1.10	0.06-18.77	1.000	1(4.3)	2(4.5)	0.95	0.08-11.12	1.000

DURS, diagnostic Ureteroscopy; OR, odds ratio.

* Distant metastasis refers to the bone and/or pulmonary metastasis.

Table 4. Cox regression model for the IVRFS and OS after RNU in full data set.

	Independent risk factor	Partial regression coefficient (B)	HR	95% CI	p
IVRFS	Non-synchronous DURS	0.393	1.481	1.031-2.127	0.034
	Pathologic T stage	0.446	1.562	1.120-2.178	0.009
CS	Pathologic T stage	0.763	2.144	1.313-3.499	0.002
	Adjuvant bladder instillation	1.517	0.219	0.086-0.557	0.001

IVRFS, intravesical recurrence-free survival; CS, cancer-specific survival.

Figures

Figure 1

Schema of treatment for upper tract urothelial carcinoma within this study.

Figure 2

Balance diagnostics for comparing the distribution of baseline covariates between DURS group and control group. (A) Jitter plot of individual cases. (B) Line plot of individual differences. (C, D) Histogram of standardised differences.

Figure 3

Kaplan-Meier estimated IVRFS of patients underwent DURS vs. without DURS (A), Kaplan-Meier estimated IVRFS of patients underwent synchronous DURS, non- synchronous DURS and without DURS (B).