

Clinical Analysis of the Predictors for Intravesical Recurrence After Laparoscopic Radical Nephroureterectomy in Japanese Patients

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Abstract: Objectives: In this study, we evaluate the clinicopathological independent prognostic factors which to predict IVR in patients who underwent Laparoscopic-assisted radical nephroureterectomy (LRNU) for upper urinary tract carcinoma (UTUC). Methods: Between April 2008 to February 2019, we analyzed 100 Japanese patients who were underwent LRNU and 92 patients who were underwent open radical nephroureterectomy (ORNU) at our institutions by retrospectively. The Patients characteristics factors, the clinicopathologic factors were collected. The intravesical recurrence free survival (IVRFS) were analyzed using the Kaplan-Meier method and Univariate and multivariate method by using the Cox proportional hazards regression models were performed to identify independent risk factors for IVR after LRNU. Results: In LRNU group, IVR was observed in 39 cases (39%), and it was not significant difference compare with ORNU (P: 0.36). Tumor location (P=0.002), Tumor size (P=0.001), preoperative urine cytology (P<0.0001), the pneumoperitoneum time (P: 0.0005) and adjuvant chemotherapy (P=0.019) showed significant association with postoperative IVR. In the multivariate Cox hazard models, the tumor location (P=0.0003), positive preoperative urinary cytology (P=0.003), and absence of adjuvant chemotherapy (P=0.003) were independent risk factors for subsequent IVR. There were not associated with smoking, Brinkman index, hydronephrosis and ureterorenoscopy before RNU for IVR. Overall survival (OS) was not significant association for experience IVR (P=0.15). Conclusion: In this study, LRNU was not shown to have a significantly higher IVR compared to ORNU. Patients with ureteral cancer and positive preoperative urinary cytology had a higher risk of IVR after LRNU. The adjuvant chemotherapy was significantly decreased the risk for postoperative IVR.

Keywords: Intravesical Recurrence, Laparoscopic Nephroureterectomy, Upper tract Urothelial Carcinoma

1. Introduction

Radical nephroureterectomy (RNU) is widely performed as a standard procedure for treatment of the UTUC. In recently, the opportunities of laparoscopic surgery have increased in the RNU with the development of laparoscopic techniques. As a result, surgical invasiveness is reduced, and RNU can be performed relatively safely even in cases with many complications or elderly patients. However, there are disadvantages to LRNU. One of them is the risk of postoperative IVR. Some studies have discussed clinicopathologic specific risk factors for prediction of IVR [1, 2]. In Meta-analysis, laparoscopic procedure has been

reported to be a significant risk factor for IVR [3]. The IVR after RNU often occurs with an approximately 15%–50% incidence [4]. However, the certain mechanism of IVR after LRNU has been unclear. In this study we evaluate the association of the predictive factors for postoperative IVR in Japanese patients underwent LRNU.

2. Patients and Methods

2.1. Patients

From April 2008 to February 2019, we retrospectively identified a total of 192 UTUC patients who underwent either

ORNU or LRNU. 100 patients who were underwent LRNU and 92 patients were ORNU were entered in this study. The patient background factors (age, gender, smoking history, Blickmann index), Preoperative clinico-pathological data (presence of hydronephrosis, Preoperative urine cytology and Preoperative ureterorenoscopy (URS)) were retrospectively collected. The tumor location was defined as the renal pelvis and/or upper, middle, lower ureter. The pathological factors in the resected specimen, tumor size, pathological T stage (pT), vascular invasion, lymphatic vessel invasion, and presence of resection margin were examined. Perioperative clinical data including of total surgical time, pneumoperitoneum time and blood loss were examined. LRNU was performed according to the standard procedure. The kidney and upper-middle ureter are resected and liberated laparoscopically (retroperitoneal approach), and as soon as possible, the distal ureter is clipped, and then we performed that peeling and excavation of the lower ureter and bladder cuff resection and extracted the kidney and ureter en bloc by pararectal incision. The bladder cuff resection was performed through the extravesical technique of the ureteral orifice. There were no cases in which an immediately intravesical therapy for the IVR prevention. Lymphadenectomy was not performed regularly, except suspiciously enlarged lymph nodes. The infusing pressurized CO₂ gas was defined with a standard pressure of 8 mmHg to maximum pressure of 12 mmHg. Preoperative urine cytology was evaluated using voided samples. Preoperative diagnosis of hydronephrosis was made using computed tomography (CT). Preoperative URS was performed within 2 months before LRNU. No patients underwent neoadjuvant chemotherapy. Adjuvant chemotherapy was performed on the basis of pathological diagnosis (pT1 or above) or positive vascular invasion case.

2.2. Follow-up Regimen

Cystoscopy was performed on all patients and urine cytology every 3 months for the first 3 years, every 6 months after 3 years from LRNU. IVR was diagnosed as pathologic proof through transurethral biopsy and/or resection.

2.3. Factors to Consider, Statistical Methods

Association between clinic-pathological factors and IVR was examined using statistical analysis (Wilcoxon signed-rank test or Fisher's exact test for variables). Intravesical recurrence-free survival (IVRFS), and overall survival (OS) after LRNU were used the Kaplan-Meier method. The prognostic effect of clinic-pathological factors were estimated by Univariate and multivariate method by using the Cox proportional hazards regression models. The strength of individual variables were assessed using the hazard ratios (HRs) with 95% confidence intervals. We performed statistical analysis using JMP® 8.0 (SAS Institute Inc., Cary, NC, USA) and defined statistical significance as P value<0.05.

3. Results

3.1. Patients Background

A total of 66 (34.3%) patients experienced IVR. The median follow-up time was 19.4 months (range, 1–219 months), and the median interval between LRNU and the first IVR was 13.6 months (range 1–108 months).

3.2. The Comparison Between ORNU and LRNU of IVR

Table 1. Shows the background of 92 ORNU patients and 100 LRNU patients registered in this study. There was no significant difference of postoperative IVR rate compare with LRNU and ORNU (P: 0.36).

	ORNU	LRNU	P value
n	92	100	
Follow-up period, day	1450	1218	0.53
age, y	66 (42-88)	73 (50-92)	0.0002
Gender (Male/Female)	65/27	73/27	0.74
Laterality (left/right)	43/49	54/46	0.26
Tumor location			0.01
Renal pelvis	51	40	
Upper ureter	10	24	
Middle ureter	8	21	
Lower ureter	17	13	
multiple	6	2	
History of the Bladder cancer	11 (12%)	21 (21%)	0.09
Tumor grade			
low	7	2	
high	83	98	
unknown	2	0	
Pathologic T stage			<0.0001
pTa	0	21	
pT1	18	20	
pT2	20	19	
pT3	30	31	
pT4	10	2	
pTis	14	7	
Vascular invsion	28 (34%)	17 (17%)	0.01
Lymphovascular invasion	26 (30.5%)	22 (22%)	0.23
Pthologic N +	9 (10%)	3 (3%)	0.04
Ajuvant chemotherapy			0.31
No	43	56	
yes	49	44	
Intra vesical recurrence	28 (30%)	38 (38%)	0.36

ORNU=open radical nephroureterectomy.

LRNU=laparoscopic radical nephroureterectomy.

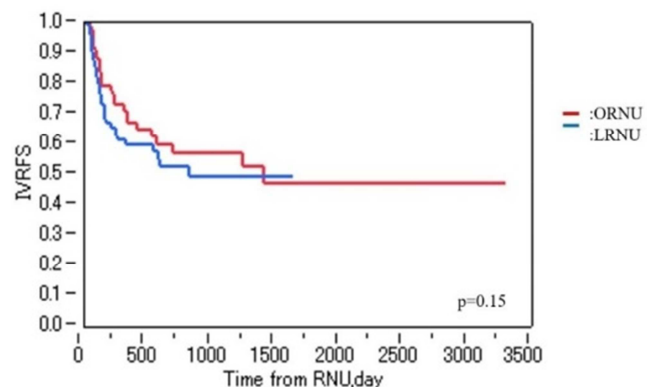


Figure 1. Showed that Kaplan-Meier curve of IVRFS in ORNU vs LRNU. There was no significant difference of IVR rate between the both groups (P=0.15).

3.3. The Association Between Clinical Factors and IVR Rate in LRNU Patients

Table 2. Was shows the clinic-pathological factors and operative outcome of 100 LRNU patients. A total 39 (39%) patients experienced IVR. There was no significant association for IVR in gender, age and previous history of bladder cancer. However, there was significant association in tumor location ($P=0.0002$), smoking history ($P=0.03$), Blickmann index ($P=0.01$), hydronephrosis ($P=0.007$) and Preoperative URS ($P=0.002$).

Cgacterteristics	total no	Negative IVR (%)	Positive IVR (%)	P value
n	100	61	39	
Age, y		73 (55-92)	72 (50-86)	0.65
Gender				0.64
male	73	43 (70.5)	29 (74.3)	
female	27	18 (29.5)	9 (25.7)	
Tumor location				0.002
renal pelvis	50	36 (59)	14 (35.9)	
upper ureter	15	9 (14.8)	6 (15.4)	
middle -	14	11 (18)	3 (7.7)	
lower -	19	5 (8.2)	14 (35.9)	
multiple	2	0	2 (5.1)	
History of Bladder cancer				0.62
no	79	50 (81.9)	30 (76.9)	
yes	21	12 (18.1)	9 (25.7)	
Preoperative urine cytology				<0.0001
negative	53	42 (68.8)	11 (28.2)	
positive	47	19 (31.2)	28 (71.8)	
Multifocality				0.12
negative	87	57 (93.4)	30 (76.9)	
positive	13	4 (6.6)	9 (23.1)	
Tumor size, mm		27	39	0.001
Pathologic T stage				0.01
pTa	14	13 (21.3)	1 (2.5)	
pT1	26	17 (27.8)	9 (23.1)	
pT2	26	16 (19.1)	10 (25.6)	
pT3	25	9 (14.7)	16 (41)	
pT4	2	2 (3.3)	0	
pTis	7	4 (6.6)	3 (7.7)	
Concomitant CIS				0.8
negative	79	48 (78.7)	31 (79.5)	
positive	21	13 (21.3)	8 (20.5)	
Vascular invasion				0.67
negative	82	51 (83.6)	33 (84.6)	
positive	17	10 (16.4)	6 (15.4)	
Lymphovascular invasion				0.62
negative	78	48 (78.7)	30 (76.9)	
positive	22	13 (21.3)	9 (23.1)	
Pathologic N stage				0.28
pN0	97	58 (95.1)	39 (100)	
pN1-2	3	3 (4.9)	0	
Resection margin				0.7
negative	86	53 (86.9)	33 (84.6)	
positive	8	6 (9.8)	2 (5.1)	
unknown	6	2 (3.3)	4 (10.3)	
Total operation time (min, med)		370	396	0.25
pneumoperitoneum time (min, med)		197	237	0.0005
Blood loss (ml, med)		197	275	0.26
Adjuvant chemotherapy				0.019
no	60	31	29	

Cgacterteristics	total no	Negative IVR (%)	Positive IVR (%)	P value
yes	40	30	10	
Smoking history				0.034
no	41	30	11	
yes	59	31	28	
Blickmann index		373	716	0.01
Previous hydronephrosis				0.007
negative	48	36 (50.2)	12 (30.8)	
positive	52	25 (49.8)	27 (69.2)	
Preoperative URS				0.002
not performed	53	40 (65.6)	13 (33.3)	
performed	47	21 (34.4)	26 (66.7)	

IVR=intravesical recurrence; CIS=carcinoma in situ.

3.4. The Association Between Surgical Outcome Factors and IVR

Though, the total operation time was 370 min (206 to 570) in the non-IVR group and 396 min (238 to 690) in the IVR group, with no significant association ($P=0.25$), the pneumoperitoneum time was 197 min (95-390) in the non-IVR group and 237 min (120-390) in the IVR group, with significant difference ($P=0.0005$).

3.5. The Association Between Pathological Factors and IVR Rate

Preoperative urine cytology was highly significant association for IVR (<0.0001). The tumor size was 27 mm in the non-IVR group and 39 mm in the IVR group, with significant difference ($P=0.001$). Furthermore, the pT stage was 34 (55.7%) for equal or lower than pT1, 16 (26.2%) for pT2, and 11 (18%) for equal or higher than pT3 in non-IVR group, and respectively 13 (33.3%), 10 (25.6%), 16 (41%) in IVR group, with significant difference ($P=0.01$). No significant difference was observed with regard to concomitant CIS, vascular invasion, lymphovascular invasion, pathological N stage, and resected margin.

3.6. The Association Between Postoperative Therapy and IVR Rate

Adjuvant chemotherapy was performed 30 (49%) patients in the non-IVR group and 10 (25.6%) patients in the IVR group, with significant association ($P=0.019$).

3.7. IVR Free Survival (IVRFS) According to Respectively Factors

We further examined the impact of clinico-pathological factors on IVRFS (Figure 2). The Kaplan-Meier Curves showed that the IVRFS estimates after LRNU were 72% for the renal pelvic cancer compared with 52% for the ureteric cancer ($P=.003$), 52% for positive smoking history compared with 68% for negative smoking history ($P=.004$), 48% for positive hydronephrosis compared with 75% for negative hydronephrosis ($P=.003$), 40% for positive urine cytology compared with 79% for negative urine cytology ($P<.0001$), 45% for tumor > 3 cm compared with 83% for

tumor ≤ 3 cm ($P=.001$), 44% for underwent URS compared with 75% for not underwent URS ($P=.006$), 48% for pneumoperitoneum time >200 minutes compared with 83% for pneumoperitoneum time ≤ 200 minutes ($P=.002$), and

75% for performed Adjuvant chemotherapy compared with 52% for not performed Adjuvant chemotherapy ($P=.001$). However, Blickmann Index did not show statistically significant differences with respect to IVRFS.

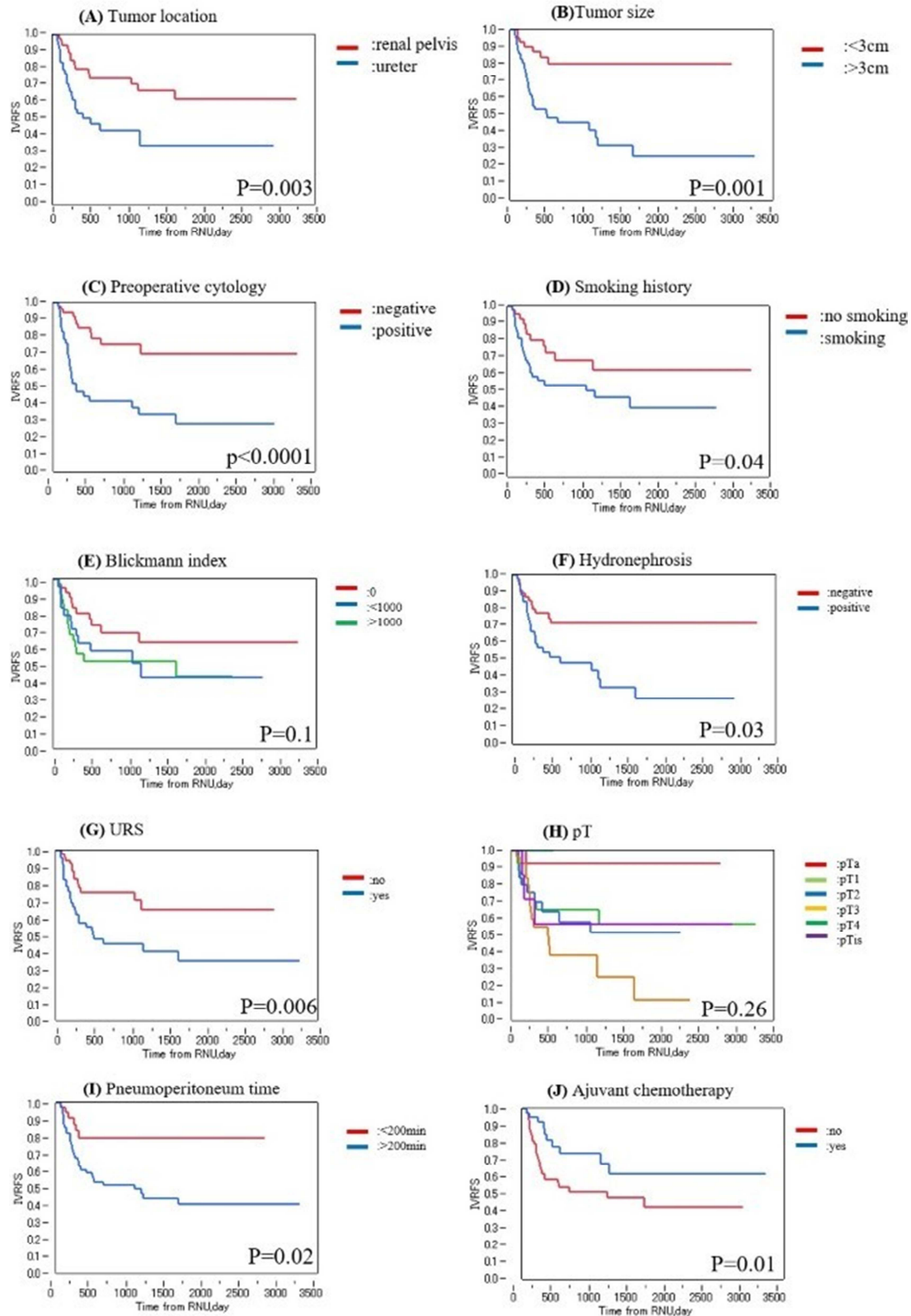


Figure 2. Kaplan-Meier Curves of the IVRFS stratified by tumor location (A), tumor size (B), preoperative urinary cytology (C), smoking history (D), and Blickmann index (E), hydronephrosis (F), receipt of URS before LRNU (G), pathologic T stage (H), pneumoperitoneum time (I), and receipt of ajuvant chemotherapy (J).

Univariate analysis showed that tumor location (HR, 2.6; 95% CI, 1.358-5.193; $P=0.004$), tumor size (HR, 2.075; 95% CI, 1.979-8.152; $P=0.02$), positive preoperative urinary cytology (HR, 3.87; 95% CI, 1.979-8.152; $P<0.0001$), hydronephrosis (HR, 2.579; 95% CI, 1.332-5.299; $P=0.005$), URS before LRNU (HR, 2.425; 95% CI, 1.268-4.872; $P=0.007$), pneumoperitoneum time (HR, 2.87; 95% CI,

1.289-7.618; $P=0.008$), smoking history (HR, 1.967; 95% CI, 1.007-4.130; $P=0.04$), and Blickmann index (HR, 1.938; 95% CI, 1.028-3.745; $P=0.04$), were poor prognostic factors for IVR. However, Adjuvant chemotherapy (HR, 0.458; 95% CI, 0.212-0.909; $P=0.003$) was decreased the probability of IVR (Table 3).

Table 3. Univariate and Multivariate Cox Regression Analyses Predicting IVR in 100 Patients Who Underwent LRNU for UTUC.

	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Age, y	0.99	0.952-1.032	0.68			
Gender (male vs female)	0.81	0.362-1.641	0.57			
Tumor location (renal pelvis vs ureter)	2.6	1.358-5.193	0.004	3.119	1.448-7.035	0.003
Preoperative urine cytology (negative vs. positive)	3.87	1.979-8.152	<0.0001	3.1289	1.444-7.261	0.003
Tumor size (3cm> vs 3cm<)	2.075	1.099-3.958	0.02	1.67	0.834-3.381	0.14
Pathologic T stage	1.19	0.963-1.476	0.1			
Concomitant CIS (negative vs. positive)	0.76	0.308-1.639	0.51			
vascular invasion (negative vs. positive)	0.94	0.358-2.13	0.91			
Lymphovascular invasion (negative vs. positive)	0.74	0.299-1.583	0.45			
Resection margin (negative vs. positive)	0.68	0.11-2.249	0.577			
Pneumoperitoneum time (200min>vs200min<)	2.87	1.289-7.618	0.0081	1.9897	0.836-5.533	0.12
Adjuvant chemotherapy (no vs. yes)	0.458	0.212-0.909	0.025	0.3829	0.17-0.799	0.01
Smoking (no vs. yes)	1.967	1.007-4.13	0.04	2.993	0.882-9.062	0.08
Blickmann index (700>vs700<)	1.938	1.028-3.745	0.04	0.6945	0.264-2.17	0.5
Hydronephrosis (negative vs positive)	2.579	1.332-5.23	0.0045	1.1881	0.534-2.737	0.6755
Preoperative URS (not performed vs. performed)	2.425	1.268-4.872	0.007	1.0506	0.492-2.325	0.8998

Multivariate analysis also showed that tumor location (HR, 3.12; 95% CI, 1.448-7.035; $P=0.003$) and positive preoperative urinary cytology (HR, 3.128; 95% CI, 1.444-7.261; $P=0.003$), were independent risk factors of IVR. However, enforcement of Adjuvant chemotherapy (HR, 0.382; 95% CI, 0.170-0.799; $P=0.001$) was associated with a significant reduction in the risk of IVR.

We further examined the impact of IVR on overall survival (OS). 28 (28%) patients died. The median duration of OS was 33 months (range, 1–118.5). No significant association of a IVR with OS ($p=0.48$) was observed in the Kaplan-Meier Curves of OS (Figure 3).

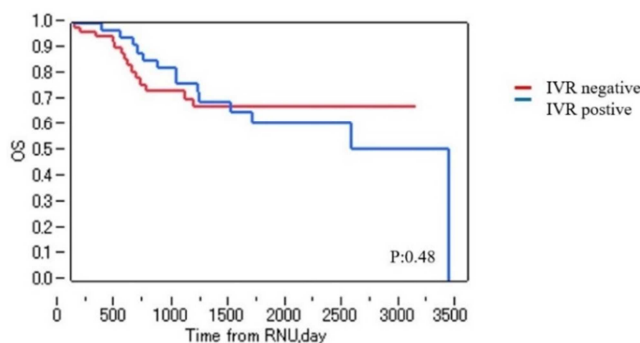


Figure 3. Kaplan-Meier Survival Curves of the overall survival stratified according to IVR status. there is no significant difference between positive IVR and negative IVR.

4. Discussion

In recent years, laparoscopic surgery can be safely performed even in RNU with the development of

laparoscopic techniques. Postoperative IVR is relatively frequent at approximately 15 to 50% after RNU [5]. The previous study showed the several risk factors for IVR, including the laparoscopic procedure [3]. In our study, we found that 34.3% of patients with UTUC experienced IVR within a median interval of 13.6 months between RNU and the first IVR. However, LRNU was not significantly more frequent more than in ORNU ($P=0.36$). In LRNU patients, the ureteral cancer was an independent risk factor for IVR compare with renal pelvic cancer ($P=0.0003$). In particular, the tendency was more strong influence in the lower ureter. Under laparoscopic procedure, the clamping of ureter below the tumor is difficult, thus there is a possibility that a large amount of cancer cells may flow into the bladder. In addition, Tumor size > 3 cm was a risk factor for IVR in our study (univariate analysis, $P=0.02$). The recent study has shown that tumor size was significantly associated with IVR [6]. The previous studies describing the prognostic factor of positive preoperative urinary cytology [7, 8]. In our study, the similar results were obtained. Furthermore, we obtained the result that preoperative hydronephrosis was significantly associated for IVR ($P=0.007$). Previous multicenter analysis described that presence of the hydronephrosis had multifocal tumors and positive urinary cytology (all $P<0.001$), and these factors may be responsible for the increased rate of IVR [6]. We think that the presence of hydronephrosis is likely to pass through the urinary tract, many cancer cells may fall in the bladder and may cause increasing IVR. We found that preoperative URS increased the risk of IVR ($P=0.002$). The Cancer cell transplantation during URS can be explained as a cause of increased IVR. Previous studies also reported

similar results for the effect of preoperative URS on IVR [9, 10]. In the large tumor, we could easily diagnose UTUC by contrast-enhanced CT scan. Furthermore, we recently performed PET-CT scan with diuretic drug for small size tumor and we have to be able to relatively easily diagnosed. As a result, the patients who underwent preoperative URS tend to decrease and LRNU was performed without preoperative URS to prevent the delay of definitive surgical treatment. Prospective studies are needed to clarify increased positive urine cytology in bladder urine sample after URS. We demonstrated that positive smoking history and higher Blickmann index were significant risk factor for IVR ($P=0.03$ and 0.01). Smoking are generally at risk for developing bladder cancer, we think that it can also be a risk factor for IVR after the LRNU. In the group who received postoperative chemotherapy, we showed that the frequency of IVR decreased (multivariate analysis, HR: 0.3829, 95%CI: 0.17-0.799, $P=0.01$) and this result suggested that adjuvant systemic chemotherapy had an effect of preventing IVR. Chan Ho Lee et al also found that the adjuvant systemic chemotherapy decreased the risk of IVR [6]. Soga et al and Ku et al indicated that the reduction of IVR risk with adjuvant chemotherapy. On the other hand, a study from Canadian Upper Tract Collaboration indicated that the increase of IVR risk with adjuvant chemotherapy [11-13]. We generally apply and administer an adjuvant systemic chemotherapy to more pathological T1 case or positive vascular invasion case. In general, postoperative chemotherapy is performed for the purpose of preventing local recurrence or distant metastasis, as a result, the effect to reduce IVR risk was also suggested. In this study, there is no significance IVR rate between ORNU and LRNU. However, we found that extension of pneumoperitoneum time in LRNU was significant risk factor for IVR ($P=.0005$). Previous studies also reported similar results for the risk of extension of pneumoperitoneum time on IVR [14]. Several studies have pointed out that the procedure-related elevated-pressure pneumoperitoneum may causes the gravitational migration of tumor cells, which leads to tumor cell seeding to the bladder [1, 15, 16]. Prolonged pneumoperitoneum time under the LRNU may be associated with higher rate IVR [17]. In this reason, we hypothesized that one is CO₂ gas high pressure was associated with excitation of the sympathetic nervous system and it coursed the promotion of peristaltic movement of the ureter. In our institution, we normally perform laparoscopic surgery by CO₂ gas pressure setting 8cmHg (12cmHg at the time of bleeding). The early ligation of the ureter distal to the tumor site during RNU has been suggested to avoid tumor spillage into the bladder [18, 19]. However, lower ureteral tumor case is difficult to clamping of the ureter distal to the tumor site duaring laparoscopic procedure. In our study, the lower ureteric tumor patients were significant higher IVR rate than renal pelvic and upper ureteral tumor. This result suggested that early clamping of distal ureter was important procedure for preventing IVR. On the other hand, the previous study showed that clamping the ureter before the ligation of renal vessels had a worse impact on CSS. They

ultimately concluded that early ureteral ligation may cause a rapid increase of intrarenal-pelvic pressure, which results in the spread and dispersal of cancer cells flowing back into the blood and perinephric space [20]. Therefore, early ureteral clamping may be decrease postoperative IVR rate, but this procedure may be increased postoperative hematogenous metastasis. We think that it is important to keep more lower CO₂ gas pressure, shorten the pneumoperitoneum time, earlier clamping of the ureter distal to the tumor site and supportive laparoscopic procedure. As a matter of course, we think that it is important to check the presence of IVR regularly after LRNU, but we also consider the follow-up of metastasis. We demonstrated that the independent predictive risk factor for IVR were ureteral tumor (lower) and positive preoperative urine cytology. High risk patients who has these risk factors are needed the perioperative intravesical therapy such as intravesical instillation of pirarubicin or adjuvant systemic chemotherapy. Several studies had been reported that immediately intravesical instillation therapy after RNU is effective for prevention of IVR. In a multicenter randomized study, the intravesical instillation of mitomycinC after RNU was significantly suppressed the IVR [21]. In Japanese randomized trial study, the IVR prevention effect of single intravesical instillation of pirarubicin was significantly suppressed compare with control group [22].

We report a study of IVR after LRNU in our department. Though, the previous clinical studies showed that postoperative IVR were significantly higher in laparoscopic surgery, there was not significant difference between LRNU and ORNU in our study. We were showed that the independent predictive risk factor for IVR were lower ureteral tumor and positive preoperative urine cytology, and adjuvant systemic chemotherapy reduced the risk of IVR. In this study, we suggest that high risk patients who has these risk factors are needed the perioperative intravesical therapy and/or adjuvant systemic chemotherapy for the prevention of IVR.

Conflict of Interest

None declared.

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