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ORIGINAL ARTICLE – UROLOGIC ONCOLOGY

Long-Term Oncologic Outcomes of Laparoscopic Versus Open Radical Nephroureterectomy for Patients with T3N0M0 Upper Tract Urothelial Carcinoma: A Multicenter Cohort Study with Adjustment by Propensity Score Matching

Keisuke Shigeta, MD[1], Eiji Kikuchi, MD, PhD[1], Takayuki Abe, MD, PhD[2], Masayuki Hagiwara, MD, PhD[3], Koichiro Ogihara, MD[1], Tadanori Anno, MD[1,4,5], Kota Umeda, MD[6], Yuto Baba, MD[7], Tansei Sanjo, MD[8], Kazunori Shojo, MD[9], Ryuichi Mizuno, MD, PhD[1], and Mototsugu Oya, MD, PhD[1]

[1]Department of Urology, Keio University School of Medicine, Tokyo, Japan; [2]Department of Preventive Medicine and Public Health, Biostatistics Unit at the Clinical Translational Research Center, Keio University School of Medicine, Tokyo, Japan; [3]Department of Urology, Tokyo Dental College, Ichikawa General Hospital, Chiba, Japan; [4]Department of Urology, Saitama City Hospital, Saitama, Japan; [5]Department of Urology, Saitama Medical Hospital, Saitama, Japan; [6]Department of Urology, Kawasaki Municipal Hospital, Kanagawa, Japan; [7]Department of Urology, International University of Health and Welfare Mita Hospital, Tokyo, Japan; [8]Department of Urology, Isehara Kyodo Hospital, Kanagawa, Japan; [9]Department of Urology, National Hospital Organization Saitama National Hospital, Saitama, Japan

ABSTRACT

Background. This study aimed to investigate the long-term oncologic outcomes of laparoscopic radical nephroureterectomy (LRNU) and open radical nephroureterectomy (ORNU) for patients with clinical and pathologic T3N0M0 upper tract urothelial carcinoma (UTUC).

Methods. Among 375 UTUC patients who underwent radical nephroureterectomy, this study identified 144 pT3N0M0 patients as cohort 1 after propensity score (PS) matching. Among 399 UTUC patients, the study identified 110 cT3N0M0 patients as cohort 2 after PS matching. Oncologic outcomes such as intravesical recurrence-free survival (IVRFS) and cancer-specific survival (CSS) were assessed by multivariate Cox's regression analysis.

Results. Cohort 1 of pT3N0M0 UTUC had 3-year CSS and IVRFS rates of 67.9 and 52.7%, respectively, in the LRNU group, which were significantly lower than in the ORNU group (81.4%, $p = 0.039$ and 71.6%, $p = 0.046$). The multivariate Cox's regression analysis identified the type of surgical approach (LRNU vs. ORNU) as one of the independent prognostic factors for CSS (hazard rate [HR], 1.88, $p = 0.043$) and IVRFS (HR, 1.75, $p = 0.049$). Cohort 2 of cT3N0M0 UTUC had 3-year CSS and IVRFS rates of 48.5 and 41.4%, respectively, in the LRNU group, which were significantly lower than in the ORNU group (65.8%, $p = 0.049$ and 67.2%, $p = 0.047$), and the type of surgical approach (LRNU vs. ORNU) remained as one of the independent prognostic factors for CSS and IVRFS.

Conclusions. Based on clinical and pathologic T3N0M0 UTUC populations after PS adjustments, LRNU resulted in poorer CSS and IVRFS than ORNU.

Upper tract urothelial carcinoma (UTUC), which comprises cancer of the ureter and renal pelvis, is relatively uncommon and accounts for only about 5% of urothelial malignancies.[1] Radical nephroureterectomy with excision of the bladder cuff has long been recognized as the gold standard primary curative treatment for patients with localized UTUC since its description by Albarran in 1909.

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E. Kikuchi, MD, PhD
e-mail: eiji-k@kb3.so-net.ne.jp

Clayman et al.[2] was the first to describe the technique of laparoscopic radical nephroureterectomy (LRNU) in 1991, and numerous studies have since compared oncologic and perioperative safety between open radical nephroureterectomy (ORNU) and LRNU. Together with systemic reviews, most of the case series conducted to date have reported better perioperative outcomes using the laparoscopic route, which is associated with less pain, lower blood loss volumes, and shorter hospital stays.[3] In contrast, the oncologic outcomes of LRNU remain controversial, particularly for locally advanced high-risk UTUC.[4] The sole randomized controlled trial to compare oncologic outcomes, with only 40 patients in each group of LRNU versus ORNU, cautioned that the laparoscopic procedure was inferior to the open procedure for cancer control, particularly for high-grade or pT3/4 UTUC cases.[5] Although research continued to prove the non-inferiority or even better oncologic safety of LRNU compared with ORNU, the oncologic efficacy of LRNU remains controversial for advanced UTUC due to the limitations of the heterogeneous patient background, small sample size, and short surveillance duration.

By adjusting patient backgrounds with the propensity score (PS)-matching method, the current study specifically aimed to compare oncologic efficacies for T3N0M0 UTUC patients who underwent LRNU and ORNU.

MATERIALS AND METHODS

Patient Samples

The current study was approved by the institutional review boards of eight institutions including Keio University Hospital and seven affiliated facilities. We identified 774 pTa-4N0M0 UTUC patients who underwent radical nephroureterectomy (RNU) between 1990 and 2015 and divided them into two cohorts, namely, one before and one after 2005 when CT urography became popular for a definitive diagnosis.

Among the 375 pTa-4N0M0 UTUC patients who underwent RNU between 1990 and 2004, we retrospectively collected data on 176 UTUC patients with a diagnosis of pT3N0M0 UTUC. By minimizing potential differences in patients with PS matching, we eventually identified 144 UTUC patients who underwent LRNU or ORNU (cohort 1). Furthermore, among the 399 pTa-4N0M0 UTUC patients who underwent RNU between 2005 and 2015, we retrospectively collected data on 143 UTUC patients with a preoperative diagnosis of cT3N0M0 UTUC based on radiographic examinations. By adjusting patient backgrounds with PS matching, we eventually identified 110 UTUC patients who underwent LRNU or ORNU (cohort 2). Patients treated with neoadjuvant chemotherapy and those who underwent surgical interventions by conservative therapies, such as ureteroscopic treatments, before RNU were excluded from the current study.

Surgical Procedure

In this study, ORNU was performed according to the standard procedure involving extrafascial dissection of the kidney, with removal of the entire ureter and the adjacent segment of the bladder cuff.[6] In contrast, LRNU was performed by extrafascial dissection of the kidney, with two-thirds of the ureter resected together in a pneumoperitoneum environment using either a transperitoneal or retroperitoneal approach.[7] A small iliac incision (Gibson incision) was made to retrieve the kidney and ureter en bloc and to perform resection of the bladder cuff. Regional lymph node dissection was not performed during ORNU or LRNU unless indicated by intraoperative findings or by suspicious lymph nodes seen on preoperative imaging. We did not administer intravesical chemotherapy early (within 48 h) after nephroureterectomy.[8]

Clinical and Pathologic Evaluations

The patients were preoperatively evaluated with computed tomography (CT), magnetic resonance imaging (MRI), or both. All the patients were evaluated using multidetector CT (MDCT), which includes CT urography with accurate radiographic image interpretation from 2005.[9] Patients unable to undergo CT due to renal impairment and those with contraindications for iodinated contrast media were evaluated by magnetic resonance (MR) urography with gadolinium-based contrast media.[1]

Surgical specimens were processed according to standard pathologic procedures at each institution. Tumors were staged according to the 2002 American Joint Committee on Cancer/Union Internationale Contre le Cancer tumor-node-metastasis (TNM) classification and graded according to the 2004 World Health Organization (WHO) classification.[10] Lymphovascular invasion (LVI) was defined as the unequivocal presence of tumor cells within endothelial-lined lymphatic and vascular channels based on the criteria in the WHO Classification of Tumours of the Urinary System and Male Genital Organs.[11]

Statistical Analysis

Medians and interquartile ranges were generated for continuously coded variables. The Mann–Whitney *U* test and Chi square test were used to assess the significance of differences between medians and proportions, respectively.

Due to inherent differences between patients undergoing ORNU and LRNU in terms of baseline patient characteristics, we relied on PS-matching analyses to adjust for these differences. In observational studies, PS matching is a common technique used to select control subjects matched with treated subjects on controlled background covariates.[12] When matching is performed, the covariates of the two groups are balanced, and biases are reduced to a minimum.

In the current study, PS matching was calculated for each patient using a multivariable logistic regression model including age, sex, Eastern Cooperative Oncology Group Performance Status, tumor location, tumor grade, LVI, administration of adjuvant chemotherapy, and a history of bladder tumors. We adopted a 1:1 matching ratio to maintain a large sample size, which maximized the power while maintaining a balance in each cohort (cohorts 1 and 2).

After PS adjustments, clinical and pathologic parameters were assessed in multivariate models using Cox's proportional hazard regression models with a stepwise forward selection method. A Kaplan–Meier analysis with the log-rank test also was performed to evaluate the relationship between surgical techniques and oncologic outcomes. Cancer-specific death was defined as mortality due to UTUC based on a death certificate and medical history. Intravesical recurrence (IVR) was defined as detection of a bladder tumor at cystoscopy after RNU.

In all statistical analyses, the tests were two-sided, and a p value lower than 0.05 was considered to indicate significance. All statistical analyses were performed using the Statistical Package of Social Sciences software, version 24.0 (SPSS, Chicago, IL, USA) and Statistical Analysis System (SAS) version 9.4 (SAS, Institute, Cary, NC, USA).

RESULTS

Baseline Characteristics of Patients with a Diagnosis of pT3N0M0 UTUC Before and After PS Adjustments (Cohort 1)

The clinical and pathologic features of cohort 1 are shown in Table 1. Of the 176 patients, 104 (59.1%) underwent ORNU, and 72 (40.9%) received LRNU. After PS adjustments, 72 (50%) of the patients who underwent ORNU were matched with LRNU patients. Significant differences were observed among tumor grades, LVI, and administration of adjuvant chemotherapy between the two surgical approaches before adjustments, but no significant differences were noted after PS matching. After PS matching, the median age of the 144 patients was 72 years (range, 36–91 years), and the median follow-up period was 65.4 months (range, 3.8–316.9 months).

Among the 144 patients, 52 (36.1%) subsequently had IVR, 44 (30.6%) died of UTUC, and 55 (38.2%) died of other causes.

Oncologic Analysis of Cancer-Specific Survival (CSS) and IVR for 144 Patients With a Diagnosis of pT3N0M0 UTUC After PS Adjustments

According to the univariate analysis after PS adjustments (Table 2), the surgical procedure (LRNU vs. ORNU) and the presence or absence of LVI correlated with CSS. The multivariate Cox's regression analysis identified LRNU (hazard ratio [HR], 1.88; $p = 0.043$) and positive LVI (HR, 3.24; $p < 0.001$) as independent prognostic factors for cancer death. The Kaplan–Meier curve showed 3- and 5-year CSS rates of 67.9 and 60.7%, respectively, in the LRNU group, which were significantly lower than those in the ORNU group (81.4 and 75.7%, respectively; $p = 0.039$; Fig. 1a).

Regarding IVR, the multivariate Cox's regression analysis indicated that LRNU (HR, 1.75; $p = 0.049$) and a history of bladder cancer (HR, 2.35; $p = 0.007$) are independent risk factors for subsequent IVR. The Kaplan–Meier curve showed 3- and 5-year IVR-free survival rates of 52.7 and 38.7%, respectively, in the LRNU group, which were significantly lower than those in the ORNU group (71.6 and 64.3%, respectively; $p = 0.046$; Fig. 1b).

Baseline Characteristics of Patients with a Diagnosis of cT3N0M0 UTUC Before and After PS Adjustments (Cohort 2)

The clinical and pathologic features of cohort 2 are shown in Table S1. Among 143 patients, 88 (61.5%) underwent LRNU, and 55 (38.5%) received ORNU. After PS adjustments, 55 (50%) patients who underwent LRNU were matched with ORNU patients. The median age of the 110 patients was 76 years (range, 48–89 years), and the median follow-up period was 37 months (range, 3.7–120.1 months). Among the 110 patients, 42 (38.2%) subsequently had IVR, 41 (37.3%) died of UTUC, and 25 (22.7%) died of other causes.

Oncologic Analysis of CSS and IVR for 110 Patients with a Diagnosis of cT3N0M0 UTUC After PS Adjustments

According to the univariate analysis, after PS adjustments (Table 3), the pathologic T stage (< 3 vs. ≥ 3), surgical procedure (LRNU vs. ORNU), tumor grade (high vs. low grade), and presence or absence of LVI correlated

TABLE 1 Patient characteristics of pT3 upper tract urothelial carcinoma patients; before and after propensity scoring matched analysis

Characteristics		Before propensity score matching				After propensity score matching			
		Total n = 176, (%)	Open RNU n = 104, (%)	Laparoscopic RNU n = 72 (%)	*p* value	Total n = 144 (%)	Open RNU n = 72 (%)	Laparoscopic RNU n = 72 (%)	*p* value
Age	< 75	114 (64.8)	68 (59.6)	46 (63.9)	0.481	90 (62.5)	44 (61.1)	46 (63.9)	0.863
	≥ 75	62 (35.2)	36 (40.4)	26 (36.1)		54 (37.5)	28 (38.9)	26 (36.1)	
Gender	Male	133 (75.6)	78 (75.0)	55 (76.4)	0.489	107 (74.3)	52 (72.2)	55 (76.4)	0.352
	Female	43 (24.4)	26 (25.0)	17 (23.6)		37 (25.7)	20 (27.8)	17 (23.6)	
ECOG-PS	0–1	123 (69.9)	78 (75.0)	45 (62.5)	0.072	94 (65.3)	49 (68.1)	45 (62.5)	0.757
	2	53 (30.1)	26 (25.0)	27(37.5)		50 (34.7)	23 (31.9)	27 (37.5)	
Tumor location	Pelvis	103 (58.5)	59 (56.7)	44 (61.1)	0.336	84 (58.3)	40 (55.6)	44 (61.1)	0.306
	Ureter	73 (41.5)	45 (43.3)	28 (38.9)		60 (41.7)	32 (44.4)	28 (38.9)	
Tumor multiplicity	Yes	55 (31.2)	34 (32.7)	21 (29.2)	0.372	44 (30.6)	23 (31.9)	21 (29.2)	0.428
	No	121 (68.8)	70 (77.3)	51 (70.8)		100 (69.4)	49 (68.1)	51 (70.8)	
Clinical T stage	< 3	89 (50.6)	51 (49.0)	38 (52.8)	0.648	69 (47.9)	31 (43.1)	38 (52.8)	0.158
	≥ 3	87 (49.4)	53 (51.0)	34 (47.2)		75 (52.1)	41 (56.9)	34 (47.2)	
Tumor grade	Low	60 (34.1)	30 (28.8)	30 (41.7)	0.015	53 (36.8)	23 (31.9)	30 (41.7)	0.150
	High	116 (65.9)	74 (71.2)	42 (58.3)		91 (63.2)	49 (68.1)	42 (58.3)	
LVI	Present	105 (59.7)	70 (67.3)	35 (48.6)	0.01	76 (52.8)	41 (56.9)	35 (48.6)	0.202
	Absent	71 (40.3)	34 (32.7)	37 (51.4)		68 (47.2)	31 (43.1)	37 (51.4)	
Adjuvant chemotherapy	Yes	69 (39.2)	48 (46.2)	21 (29.2)	0.017	49 (34.0)	28 (38.9)	21 (29.2)	0.146
	No	107 (60.8)	56 (53.8)	51 (70.8)		95 (66.0)	44 (61.1)	51 (70.8)	
Previous history of bladder cancer	Yes	31 (17.6)	20 (19.2)	11 (15.3)	0.32	24 (16.7)	13 (18.1)	11 (15.3)	0.412
	No	145 (82.4)	84 (80.8)	61 (84.7)		120 (83.3)	59 (81.9)	61 (84.7)	

RNU radical nephroureterectomy, *ECOG-PS* Eastern Cooperative Oncology Group-Performance Status, *LVI* lymphovascular invasion

with CSS. The multivariate Cox's regression analysis identified positive LVI (HR, 2.41; $p = 0.012$) and LRNU (HR, 1.92; $p = 0.047$) as independent prognostic factors for cancer death. The Kaplan–Meier curve showed 3- and 5-year CSS rates of 48.5 and 44.8%, respectively, in the LRNU group, which were significantly lower than those in the ORNU group (65.8 and 60.0%, respectively; $p = 0.049$; Fig. 2a).

Regarding IVR, multivariate Cox's regression analysis identified ureteral cancer (HR, 1.90; $p = 0.048$), pT lower than 3 (HR, 2.78; $p = 0.003$), a history of bladder cancer (HR, 1.98; $p = 0.036$), and LRNU (HR, 2.64; $p = 0.005$) as independent risk factors for subsequent IVR. The Kaplan–Meier curve showed 3- and 5-year IVR-free survival rates of 41.4 and 31.1%, respectively, in the LRNU group, which were significantly lower than in the ORNU group (67.2 and 56.0%, respectively; $p = 0.047$; Fig. 2b).

DISCUSSION

Previous studies have cautioned that LRNU showed CSS as inferior to ORNU in pT3/4 and/or high-grade UTUC patients[5,13]. A recent systemic review of 42 studies also emphasized that LRNU is inferior to ORNU, particularly when the bladder cuff is excised laparoscopically and when performed on locally advanced high-risk (pT3/T4 and/or high-grade) UTUC.[14] Therefore, in the current guidelines, LRNU still is recommended as a contraindication for locally advanced UTUC patients.[1] However, the selection of patients for LRNU is always challenging because current evidence is based on the tumor grade and stage from definitive pathologic specimens. Furthermore, it has been established that a poor correlation exists between clinical and pathologic T stage diagnoses.[15,16] We also questioned whether to include T4 patients when selecting surgical indications because T4 is relatively rare, is likely to involve lymph node metastasis, and has a markedly poorer prognosis than T3.[17] Furthermore, to maintain homogeneity, we limited the patient cohort to T3N0M0 patients only in order to clarify the appropriateness of laparoscopic surgical indications, thereby minimizing the heterogeneous background with PS matching.

In our study of cohort 1, we found that the laparoscopic procedure led to poor CSS for the pT3N0M0 UTUC patients. The oncologic outcomes for the pT3N0M0 UTUC patients only after PS adjustments currently remain

TABLE 2 Propensity score-adjusted uni- and multivariate logistic regression analyses for oncological outcomes of pT3N0M0 upper tract urothelial carcinoma

Clinical indicators	CSS						IVR					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age ≥ 75 vs. age < 75	1.60	0.93–2.75	0.089				0.54	0.600–5.49	0.267			
Gender (male vs. female)	1.27	0.67–2.43	0.464				1.49	0.33–1.37	0.271			
ECOG-PS (2 vs. 0–1)	1.22	0.49–2.75	0.495				0.94	0.68–1.30	0.703			
Tumor location (ureter vs. renal pelvis)	1.20	0.68–2.12	0.534				1.98	1.07–3.65	0.030			
Clinical T stage (≥ 3 vs. < 3)	1.22	0.68–2.21	0.507				1.35	0.78–2.34	0.278			
Tumor grade (high vs. low)	1.48	0.78–2.80	0.233				1.16	0.64–2.10	0.620			
Surgical procedure (laparoscopic vs. open)	2.33	1.20–4.53	0.012	1.88	1.02–3.45	0.043	1.69	0.94–3.04	0.082	1.75	1.02–3.05	0.049
Previous history of bladder tumor	1.33	0.74–2.39	0.736				2.51	1.29–4.91	0.007	2.35	1.27–4.37	0.007
LVI (positive vs. negative)	2.94	1.95–4.44	< 0.001	3.24	2.51–5.18	<0.001	1.37	0.58–2.11	0.284			
Adjuvant chemotherapy (yes vs. no)	0.82	0.46–1.46	0.341				0.901	0.47–1.72	0.751			

IVR intravesical recurrence, *CSS* cancer-specific survival, *HR* hazard ratio, *CI* confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group-Performance Status, *LVI* lymphovascular invasion

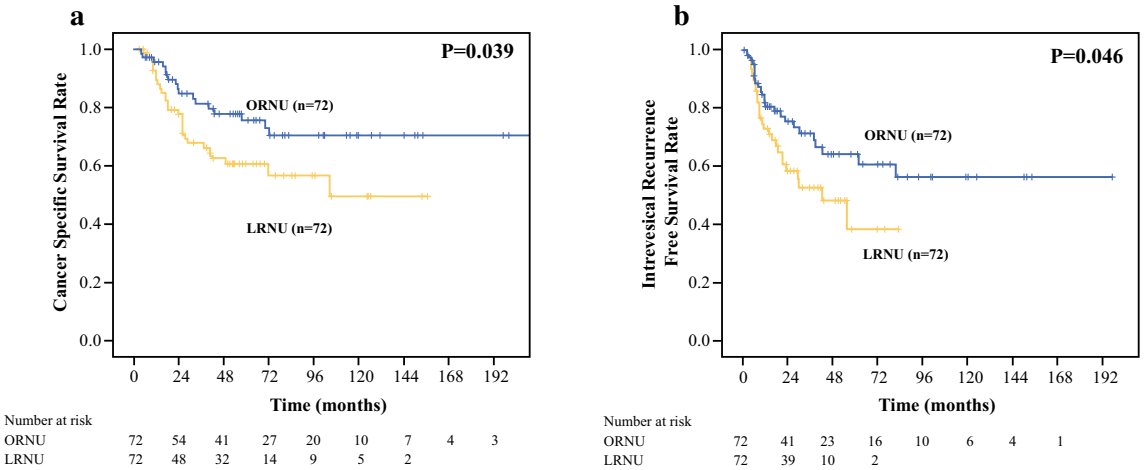

FIG. 1 Cumulative survival of 144 pT3N0M0 upper tract urothelial carcinoma (UTUC) patients treated with radical nephroureterectomy (RNU) stratified by the surgical approach (ORNU vs. LRNU). **a** Cancer-specific survival. **b** Intravesical recurrence-free survival. *ORNU* open radical nephroureterectomy, *LRNU* laparoscopic radical nephroureterectomy

unknown. We assumed that several plausible reasons for poor oncologic outcomes were derived from tumor spillage caused by manipulations in a pneumoperitoneum environment. One of the potential assumptions to explain this result is that the limited working space may increase the risk of tumor spillage.[18] Because locally advanced UTUC is likely to involve tissue adhesion or hydronephrosis, technical difficulty may increase, and operation handling often becomes more cumbersome than for lower-stage UTUC. Therefore, surgeons are required to perform a careful maneuver for completion in the closed system, which requires extensive laparoscopic experience and a

TABLE 3 Propensity score-adjusted uni- and multivariate logistic regression analyses for oncological outcomes of cT3N0M0 upper tract urothelial carcinoma

Clinical indicators	CSS						IVR					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age ≥ 75 vs. age < 75	1.12	0.66–1.92	0.68				0.855	0.44–1.67	0.645			
Gender (male vs. female)	1.62	0.90–2.92	0.109				1.05	0.52–2.09	0.900			
ECOG-PS (2 vs. 0–1)	0.86	0.64–1.15	0.302				2.54	0.99–6.54	0.054			
Tumor location (ureter vs. renal pelvis)	1.16	0.68–2.00	0.589				1.9	0.96–3.75	0.065	1.90	1.01–3.48	0.048
Pathological T stage (< 3 vs. ≥ 3)	0.52	0.29–0.91	0.021				2.44	1.16–4.76	0.010	2.78	1.42–5.38	0.003
Tumor grade (high vs. low)	1.75	1.02–3.00	0.044				0.96	0.52–1.79	0.906			
Surgical procedure (laparoscopic vs. open)	1.75	1.02–3.00	0.043	1.92	1.01–3.65	0.047	2.65	1.33–5.27	0.005	2.64	1.33–5.22	0.005
LVI (positive vs. negative)	2.08	1.21–3.55	0.008	2.41	1.21–4.80	0.012	1.28	0.64–2.89	0.479			
Previous history of bladder tumor	1.72	0.81–3.67	0.161				1.68	1.19–2.38	0.003	1.98	1.38–2.86	0.036
Adjuvant chemotherapy (yes vs. no)	1.02	0.58–1.80	0.983				2.16	1.00–4.48	0.046			

IVR intravesical recurrence, *CSS* cancer-specific survival, *CI* confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group-Performance Status, *LVI* lymphovascular invasion

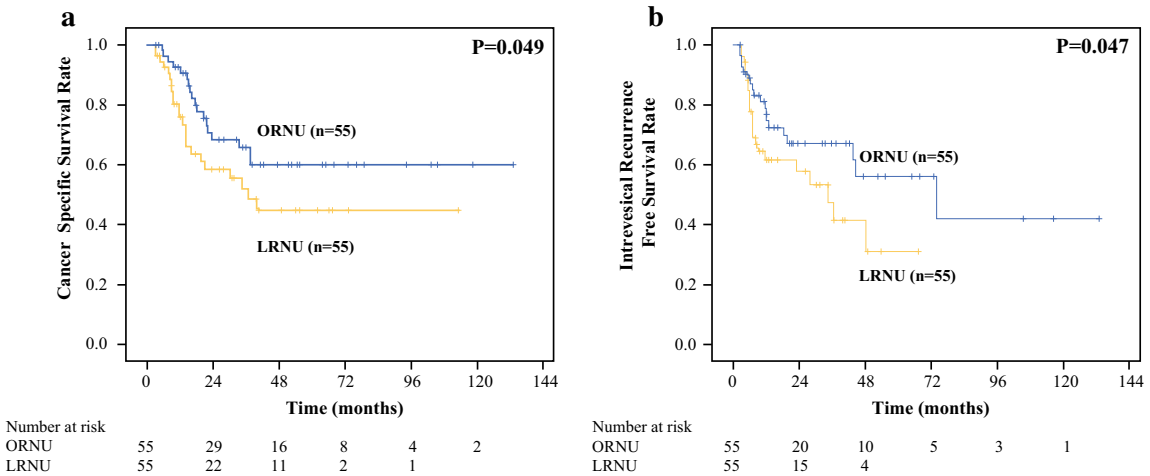

FIG. 2 Cumulative survival of 110 cT3N0M0 upper tract urothelial carcinoma (UTUC) patients after radical nephroureterectomy (RNU) stratified by the surgical approach (ORNU vs. LRNU). **a** Cancer-specific survival. **b** Intravesical recurrence-free survival. *ORNU* open radical nephroureterectomy, *LRNU* laparoscopic radical nephroureterectomy

more skilled technique than the open procedure.[19] Moreover, previous studies have proposed that a pneumoperitoneum environment may have a negative impact on tumor seeding during manipulations.[6] They ultimately concluded that manipulations under a pneumoperitoneum environment may cause a rapid increase in intrarenal-pelvic pressure, resulting in the spread and dispersal of cancer cells flowing back into the blood and perinephric space.

Another assumption is that the quality of lymph node dissection differs between LRNU and ORNU.[20] Although we did not perform routine lymphadenectomy, previous studies have cautioned against insufficient lymph node dissection during LRNU. Based on these assumptions, the current results suggest that UTUC with a high pT stage has a negative impact on the laparoscopic procedure in terms of technical difficulty and tumor dissemination under a pneumoperitoneum environment.

We also showed that LRNU was inferior to ORNU in terms of CSS for the cT3N0M0 patients in cohort 2. The findings showed that LRNU had a more negative impact on oncologic efficacy for the cT3N0M0 patients than for the pT3N0M0 patients. This may be explained by cT3 inclusion of some pT4 patients or lymph node involvement, the tumor aggressiveness of which still is challenging to predict by imaging interpretations beforehand. In actual clinical settings, the surgical approach generally was selected preoperatively based on interpretations of radiographic images and considerations of the patients' general health conditions. Because imaging studies for the diagnosis of UTUC have improved with the introduction of MDCT, we limited our study cohort from 2005 when CT urography became popular for definitive diagnoses. However, a dissociation between clinical and pathologic stages often exists because of the limited diagnostic tools available for the diagnosis of UTUC. Although many indicators such as hydronephrosis,[21] tumor length,[22] and preoperative tumor grade[23] have been identified as predictive factors for clinical staging, selecting the best surgical approach still is challenging. Therefore, our results suggest that ORNU is recommended when the preoperative diagnosis is suspected to be cT3 or more advanced disease to ensure optimal oncologic outcomes.

Based on the results of cohorts 1 and 2, the multivariate Cox's regression analysis identified LRNU as an independent risk factor for IVR in cT3 and pT3N0M0 UTUC patients. Seisen et al.[24] concluded in a systemic review that LRNU has the potential to increase the risk of subsequent IVR. Furthermore, our study group showed identification of LRNU as a sustained predictive factor for IVR over time in a conditional survival analysis of localized UTUC patients.[25] Based on this evidence and the current results, a strict follow-up evaluation to detect IVR after LRNU is needed, even for T3N0M0 UTUC patients.

This study had some limitations. It was performed with a retrospective and non-randomized design. Although we conducted PS matching to minimize the heterogeneous background, only a small number of patients were included. Furthermore, because multiple surgeons in eight institutions performed ORNU and LRNU, the learning curve of each surgeon may have become a source of bias. Moreover, the inclusion of only T3N0M0 patients may have created a selection bias. We also included limited numbers of covariants for the PS-matching method, which was unable to control for selection bias and other unmeasurable cofounders.

In conclusion, we demonstrated that LRNU showed poorer oncologic efficacy than ORNU for T3N0M0 UTUC patients. Based on clinical and pathologic points of view, LRNU still needs to be considered carefully as a surgical indication for locally advanced UTUC. Although decision making regarding a surgical approach in the preoperative setting is challenging, a more accurate diagnostic device is warranted for selecting the most appropriate surgical technique.

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DISCLOSURE There are no conflicts of interest.

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