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Original Article

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Comparative study of lymph node dissection, and oncological outcomes of laparoscopic and open radical nephroureterectomy for patients with urothelial carcinoma of the upper urinary tract undergoing regional lymph node dissection

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Abstract

Objective: To assess the number of lymph nodes removed as a surrogate marker of the extent of lymph node dissection, and compare survival outcomes between laparoscopic radical nephroureterectomy (LRNU) and open radical nephroureterectomy (ORNU) in patients undergoing standardized lymph node dissection.

Methods: We retrospectively analyzed the data of 214 cTanyN0M0 patients undergoing radical NU with regional lymph node dissection according to the tumor location. The Kaplan–Meier method and Cox hazards model were utilized for survival analyses, including recurrence-free survival (RFS), cancer-specific survival (CSS) and overall survival (OS).

Results: A total of 114 patients underwent LRNU and 100 underwent ORNU. There was no significant difference in the pT stage, pN stage, or tumor grade, but distal ureteral tumors were more frequent in the LRNU group. The number of lymph nodes removed did not differ between the two groups [LRNU: 12 (median), ORNU: 11.5, $P = 0.3852$]. Lymph node metastasis was pathologically identified in 19 patients (8.9%). The 5-year RFS (ORNU: 71.7%, LRNU: 74%, $P = 0.7829$), CSS (77.8 and, 80%, $P = 0.8441$) and OS (72.8, and 75.9%, $P = 0.3456$) did not differ between the two groups. In the sub-analysis of pT3/4 patients ($n = 83$), there were no significant differences in RFS, CSS, or OS between the two groups, although Kaplan–Meier survival curves were slightly better for those receiving ORNU. In the multivariate model, LRNU was not significantly correlated with a poorer RFS, CSS or OS.

Conclusion: Our data support the feasibility of lymph node dissection with a laparoscopic approach and the equivalent oncological outcome of LRNU compared with ORNU when regional

lymph node dissection is performed. However, LRNU should be performed after careful patient selection for advanced disease.

Key words: urothelial carcinoma, upper urinary tract, laparoscopic nephroureterectomy, open nephroureterectomy, lymph node dissection

Introduction

Based on early postoperative convalescence and a better cosmetic outcome, laparoscopic radical nephroureterectomy (LRNU) has now emerged as an alternative treatment method to open radical nephroureterectomy (ORNU) for patients with urothelial carcinoma (UC) of the upper urinary tract (UUT). A robot-assisted procedure has also been introduced, with acceptable short-term outcomes (1,2). So far, a number of studies have compared oncological outcomes, including disease recurrence and survival, between LRNU and ORNU. A recent meta-analysis (21 eligible studies) revealed that there were no significant differences in terms of the 2-year cancer-specific survival (CSS) rate, 5-year recurrence-free survival (RFS) rate or 5-year overall survival (OS) rate between the two approaches (3). On the other hand, Simone et al. reported in their prospective randomized study that patients undergoing ORNU showed a significantly more favorable cancer-specific or recurrence-free survival than those undergoing LRNU when matched for pT3 and high-grade disease (4). Based on their observation, in the EAU guidelines 2017, invasive or large (T3/T4 and/or N+/M+) tumors are considered to be contraindications for LRNU until proved otherwise (5). When interpreting the conflicting observations of previous studies, one potential drawback is regional lymph node dissection (LND) was frequently skipped (6,7), which may have caused node staging migration.

Aiming at accurate disease staging and considering potential therapeutic benefits, our group and the Tokyo Women's Medical University group (TWMU) have been actively performing regional LND, and published several studies. Our group has favored LRNU (8,9) regardless of tumor location, whereas ORNU has been favored for patients with renal pelvic or upper ureteral tumors by TWMU (10,11). The aim of the present study was to compare the number of lymph nodes (LNS) removed as a surrogate for the dissection extent, and survival outcomes between LRNU and ORNU in patients who underwent standardized regional LND.

Patients and methods

This multi-institutional retrospective study was performed after approval from each institutional review board. Between 2000 and 2015, a total of 350 patients underwent radical nephroureterectomy with excision of the bladder cuff at Hokkaido University Hospital ($n = 106$) and Tokyo Women's Medical University Hospital ($n = 244$). In order to homogenize the cohort, patients without regional LND ($n = 90$), with only LN sampling ($n = 3$), with neo-adjuvant chemotherapy ($n = 17$), with regular hemodialysis before surgery ($n = 17$), with clinical node disease preoperatively ($n = 15$), with a history of prior radical cystectomy for bladder cancer ($n = 8$), with bilateral disease ($n = 7$), with distant metastasis or an unknown distant status ($n = 6$), without cancer at the final pathology ($n = 3$), with metastatic disease from the esophagus or colon cancer ($n = 2$), with disease in a horse-shoe kidney ($n = 2$) or with a history of renal transplant surgery ($n = 1$), were excluded, and the remaining 179 patients were analyzed. Furthermore, we incorporated the 35 patients treated by LRNU plus regional LND for cTanyN0M0 without neo-adjuvant chemotherapy at Hokkaido Cancer Center between 2009 and 2015 who participated in our previously reported LN study (9). In total, 214 cTanyN0M0 patients undergoing either ORNU ($n = 100$) or LRNU ($n = 114$) with regional LND were included in the present analysis.

ORNU was performed via a retroperitoneal approach, according to a previously described procedure (12), and LRNU was performed via a four-port retroperitoneal approach or a four-port transperitoneal approach in conjunction with an open lower abdominal incision for specimen removal and bladder cuff resection. The surgical procedures were similar among the three hospitals. The template for LND was also previously reported (9) (13). Briefly, for right renal pelvic/upper ureter tumors (higher than the crossing of the common iliac artery), the right renal hilar, paracaval, retrocaval, and interaortocaval LNs were resected. For a left renal pelvic/upper ureteral tumor, the left renal hilar and paraaortic LNs were resected. In patients with renal pelvic/upper ureter tumors treated by LRNU, LND was performed laparoscopically. For tumors of the distal ureter, the common iliac, external iliac, internal iliac, and obturator LNs were resected via an open abdominal incision either by ORNU or LRNU. Since 2011 (Tokyo) and 2014 (Hokkaido group), presacral LNs have also been included among regional LNs.

Pathological staging was performed according to the TNM classification system. Tumor grading was assessed according to the 1973 WHO/International Society of Urologic Pathology (WHO/ISUP) consensus classification. Patients were followed according to the follow-up protocol for each site. In general, patients underwent lung and abdominal CT every 6 months for the first two years, with cystoscopy every 3 months. If disease relapse did not occur for two years after surgery, the follow-up interval was extended. The survival outcomes included recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS). RFS was defined as the interval between the date of surgery and first documented disease recurrence or death. In the present study, intravesical recurrence was not defined as disease recurrence. CSS was defined as the interval between the dates of surgery and death from UC. Overall survival was evaluated from the dates of surgery to death from any cause.

For the present analysis, the upper ureter was defined as the part above the iliac crossing, and the distal ureter as that below the iliac crossing. Regarding the thoroughness of LND, it was reviewed using operative records and/or pathological reports. When all of the regional LNs were dissected, it was considered complete LND, whereas it was considered incomplete LND when the LN area did not include all of the regional area. As described previously, the presacral area had not been initially included among the regional LNs; therefore that area did not need to be included in the complete LND cohort for the present analyses.

Statistical analyses

The χ^2 and Mann–Whitney U tests were used to compare the characteristics between the two groups. The Kaplan–Meier method and

Table 1. Patient characteristics

	Total, $n = 214$	Open, $n = 100$	Lap, $n = 114$	P-value
Age, year	median 70.5 (range, 35–93)	median 69 (range, 38–84)	median 72 (range, 35–93)	0.1041
Sex male/female				
Male	151 (71%)	71 (71%)	80 (70%)	0.8949
Female	63 (29%)	29 (29%)	34 (30%)	
History of bladder cancer				
Yes or concurrent	34 (16%)	11 (11%)	23 (20%)	0.0212
No	177 (83%)	86 (86%)	91 (80%)	
Unknown	3 (1%)	3 (3%)	0	
Tumor location				
Renal pelvis	127 (59%)	67 (67%)	60 (53%)	0.0009
Upper ureteral tumor	26 (12%)	17 (17%)	9 (8%)	
Distal ureteral tumor	56 (26%)	15 (15%)	41 (36%)	
Renal pelvis+ureter	5 (2%)	1 (1%)	4 (2%)	
Number				
Solitary	141 (66%)	69 (69%)	72 (63%)	0.2161
Multiple	71 (33%)	31 (31%)	40 (35%)	
Unknown	2 (1%)	0	2 (2%)	
Operative time, minutes, $n = 211$	median 303 (range, 135–564)	median 274 (range, 145–564)	median 330 (range, 135–522)	0.0016
Adjuvant chemotherapy				
No	200 (93%)	91 (91%)	109 (96%)	0.1721
Yes	14 (7%)	9 (9%)	5 (4%)	
Pathology				
Pure urothelial carcinoma	210 (98%)	98 (98%)	112 (98%)	0.8948
Others	4 (2%)	2 (2%)	2 (2%)	
Size				
>3 cm	89 (42%)	47 (47%)	42 (37%)	0.3774
1–3 cm	99 (46%)	44 (44%)	55 (48%)	
<1 cm	23 (11%)	8 (8%)	15 (13%)	
Unknown	3 (1%)	1 (1%)	2 (2%)	
pT stage				
pTa-is	42 (20%)	12 (12%)	30 (26%)	0.0712
pT1	48 (22%)	26 (26%)	22 (19%)	
pT2	41 (19%)	18 (18%)	23 (20%)	
pT3	75 (35%)	39 (39%)	36 (32%)	
pT4	8 (4%)	5 (5%)	3 (3%)	
Grade				
Grade 1, 2	100 (47%)	41 (41%)	59 (52%)	0.1388
Grade 3	113 (53%)	59 (59%)	54 (47%)	
Unkown	1 (0.5%)	0	1 (1%)	
Lymphovascular invasion				
Yes	96 (45%)	62 (62%)	34 (30%)	<0.0001
No	112 (52%)	35 (35%)	77 (68%)	
Unknown	6 (3%)	3 (3%)	3 (3%)	
pN stage				
pN0	195 (91%)	89 (89%)	106 (93%)	0.3071
pN+	19 (9%)	11 (11%)	8 (7%)	
Surgical margin				
pR0	194 (91%)	88 (88%)	106 (93%)	0.3933
pR1	11 (5%)	6 (6%)	5 (4%)	
pRx	9 (4%)	6 (6%)	3 (3%)	

Cox hazards model were used to analyze survival data. Data entry into the multivariable analysis was set at a P-value <0.05 in the univariate analysis. Statistical analysis was performed with JMP® Pro 12.01 (SAS Institute, Japan).

Results

Table 1 summarizes the patient characteristics by surgical approach. A total of 114 patients underwent LRNU and 100 underwent ORNU. Baseline characteristics were similar between the two groups, except for that those receiving LRNU had a more frequent history of bladder cancer (20 vs. 11%, respectively, $P = 0.0212$), more frequently had distal ureteral tumors (36 vs. 15%, respectively, $P = 0.0009$), and less frequently exhibited lymphovascular invasion (30 vs. 62%, respectively, $P < 0.0001$). LN metastasis was pathologically identified in 9% (19/214) of the patients. The operative time was longer in the LRNU group than in the ORNU group (ORNU, median 274 min; LRNU, 330 min, respectively, $P = 0.0016$).

A summary of LND is presented in Table 2. Overall, 85% (181/214) of the total cohort underwent complete LND. There was no

Table 2. Summary of lymph node dissection

	Total, $n = 214$	Open, $n = 100$	Lap, $n = 114$	*P*-value
Lymphadenectomy				
Complete	181 (85%)	87 (87%)	94 (82%)	0.3564
Incomplete	33 (15%)	13 (13%)	20 (18%)	
Node count, overall ($n = 214$)	median 11 (range, 1–59)	median 11.5 (range, 2–36), $n = 100$	median 12 (range, 1–59), $n = 114$	0.3852
Node count, renal pelvis or upper tumor ($n = 153$)	median 11 (range, 1–59)	median 11 (range, 2–36), $n = 84$	median 12 (range, 1–59), $n = 69$	0.9692

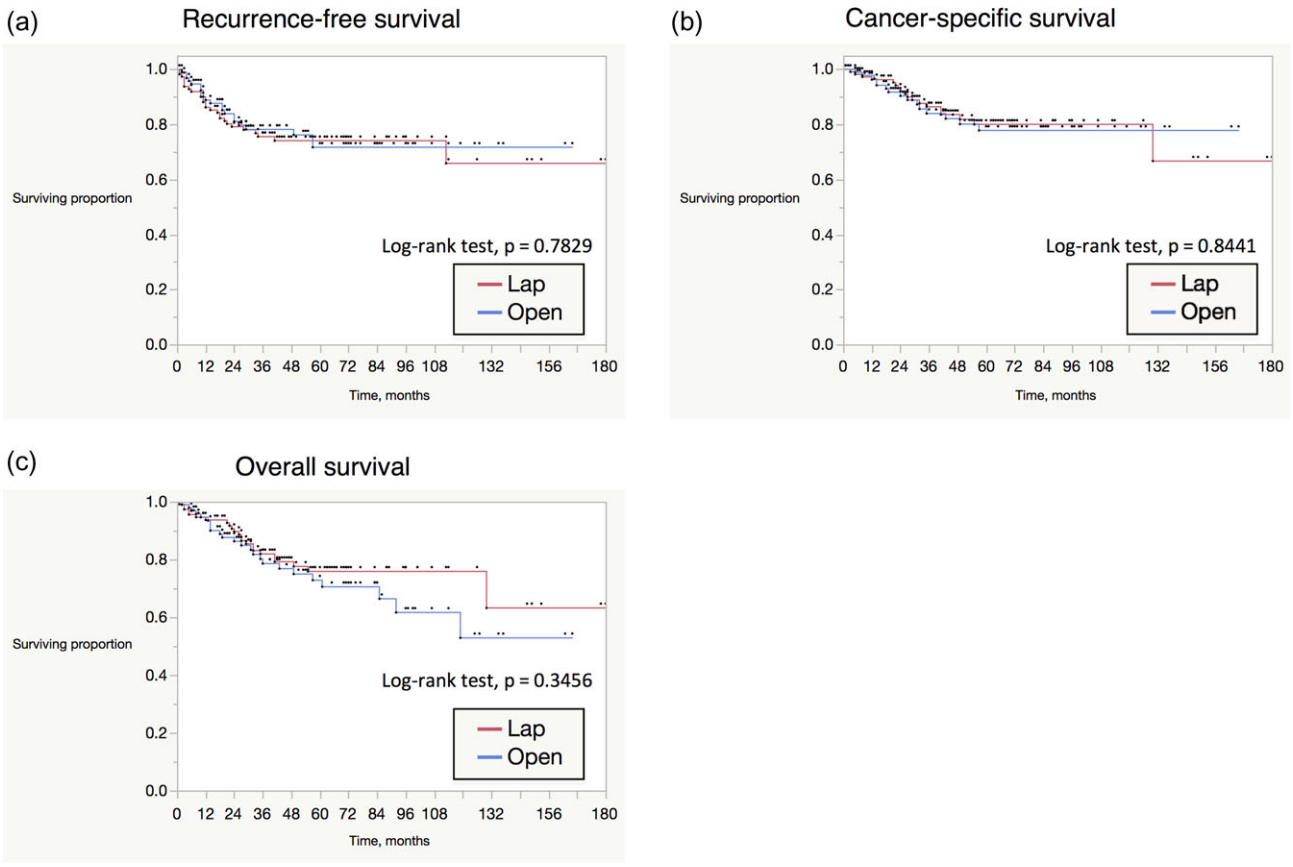

Figure 1. Kaplan–Meier estimates for RFS, CSS and OS stratified by surgical approach in the entire cohort. The estimated 5-year RFS (ORNU 71.7%, LRNU 74%, $P = 0.7829$), CSS (77.8 and 80%, respectively $P = 0.8441$) and OS (72.8 and 75.9%, respectively, $P = 0.3456$) did not differ significantly between the ORNU and LRNU groups.

significant difference in the rate of performing complete LND between the two groups. In addition, no significant difference was noted in the number of nodes removed between the two groups. When examining only at patients with renal pelvic or upper ureteral tumors ($n = 153$), because laparoscopic LND was performed in the LRNU group, whereas LND was performed via an open incision in patients with distal ureteral tumors either in LRNU or ORNU, the number of nodes removed did not differ significantly between the two groups (LRNU, $n = 69$: median 12, ORNU, $n = 84$: median 11, $P = 0.9692$).

During the follow-up with a median of 41 months (interquartile range, 21–71), 48 patients developed disease relapse, 33 died due to cancer progression, and 47 died from any cause. In terms of initial relapse sites, distant recurrence was the most common after both procedures (ORNU, $n = 9$; LRNU, $n = 17$, respectively), following locoregional recurrence ($n = 6$, and $n = 5$, respectively) and synchronous recurrence at both distant and locoregional sites ($n = 3$, and $n = 5$, respectively). The recurrence site was unknown in the three patients who underwent ORNU. Fig. 1 shows the Kaplan–Meier estimates for RFS, CSS and OS stratified by surgical approach in the overall cohort. The estimated 5-year RFS (ORNU, 71.7%; LRNU, 74%, respectively, $P = 0.7829$), CSS (77.8 and 80%, respectively, $P = 0.8441$) and OS (72.8 and 75.9%, respectively, $P = 0.3456$) did not differ significantly between the ORNU and LRNU groups. We subsequently performed the same survival analysis for patients with renal pelvic or upper ureteral tumors ($n = 153$), in which patients underwent open nephroureterectomy with open lymphadenectomy or laparoscopic nephroureterectomy with laparoscopic lymphadenectomy. This sub-analysis also demonstrated an equivalent 5-year RFS (ORNU, 74.4%; LRNU, 75.4%, respectively, $P = 0.5304$), CSS (78.5 and 80.4%, respectively, $P =$

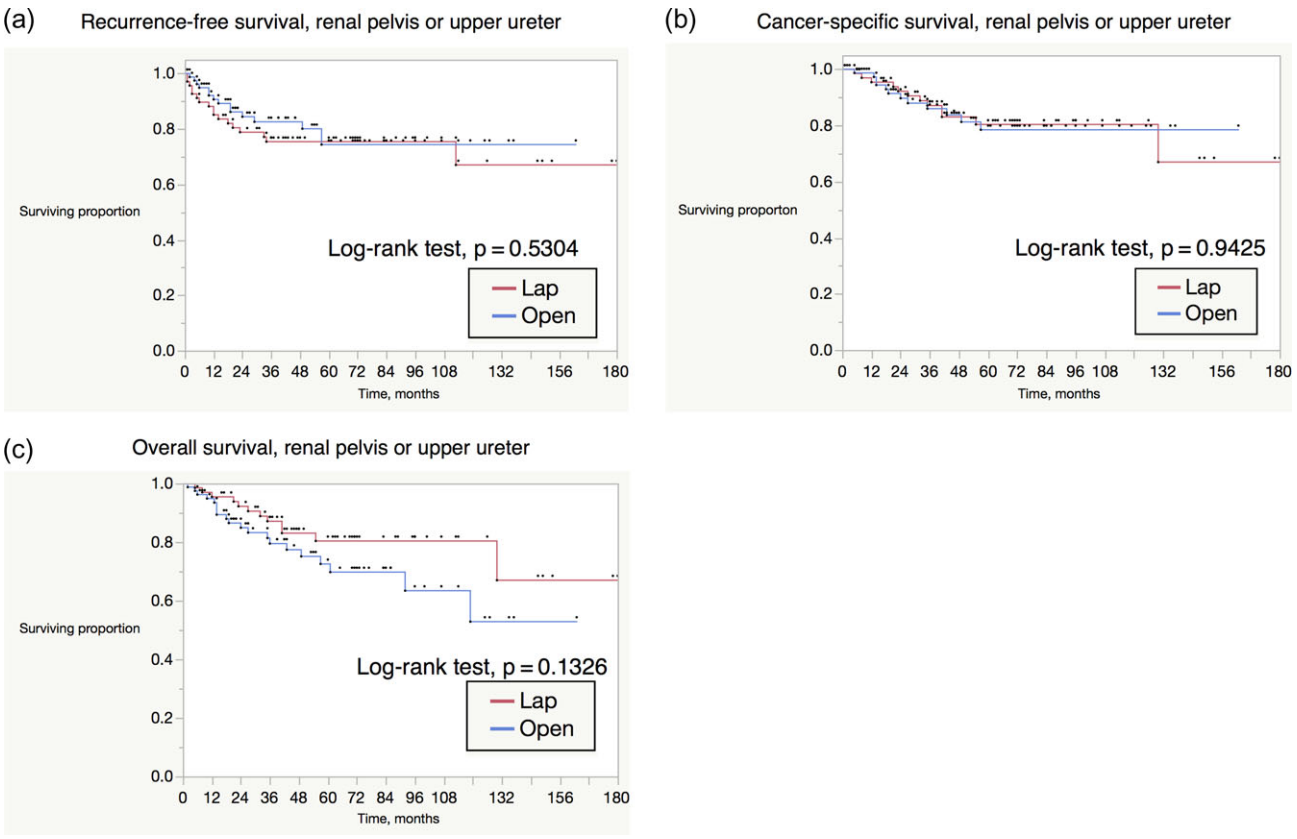

Figure 2. Kaplan–Meier estimates for RFS, CSS and OS stratified by surgical approach in the sub-analysis of patients with renal pelvic or upper ureteral tumors ($n = 153$). The estimated 5-year RFS (ORNU 74.4%, LRNU 75.4%, $P = 0.5304$), CSS (78.5 and 80.4%, respectively $P = 0.9425$) and OS (72.5 and 80.4%, respectively, $P = 0.1326$) did not differ significantly between the ORNU and LRNU groups.

0.9425) and OS (72.5 and 80.4%, respectively, $P = 0.1326$) between the two groups (Fig. 2). Table 3 shows the results of uni- and multivariate analyses for RFS, CSS, and OS in the entire cohort. In the univariate Cox proportional hazards model, LRNU was not associated with a poorer RFS, CSS or OS. Multivariate analyses revealed that both the pT3-4 stage and pN+ were independent adverse factors for both RFS and CSS, whereas the *P*-value of pN+ was marginal in terms of OS ($P = 0.0642$).

Fig. 3 shows the Kaplan–Meier estimates for RFS, CSS and OS stratified by surgical approach in the sub-analysis of pT3/4 patients ($n = 83$). The survival curves were higher for ORNU, although the differences were not significant between the two approaches in all three survival analyses. Table 4 shows the results of uni- and multivariate models for the pT3/4 patients. The multivariate model for OS revealed that the age, distal ureteral tumors, and pN+ were independent adverse factors, whereas pN+ was significant and distal ureteral tumors were marginal in the univariate model for RFS and CSS. After adjusting for the age, tumor location, and pN stage for CSS and OS, and tumor location and pN stage for RFS, LRNU continued to demonstrate no association with a poorer RFS, OS or CSS in pT3/4 patients (Table 5).

Discussion

In the present study, we compared the number of LNs removed and survival outcomes between patients treated with LRNU and those with ORNU. There was no significant difference in the rate of performing complete LND or number of nodes removed between the two groups. As LND was performed via an open incision for both LRNU and ORNU in patients with distal ureteral tumors, we performed a sub-analysis in which we compared the number of LNs resected only in patients with renal pelvic or upper ureteral tumors. Again, there was no significant difference in the number of LNs removed between the two methods, confirming the feasibility of laparoscopic LND. As described above, as TWMU favored ORNU for patients with renal pelvic or upper ureteral tumors based on their preference for open LND, we considered that patients undergoing LRNU more frequently had distal ureteral tumors. We have no clear explanation for why the patients who underwent LRNU had a more frequent history of bladder cancer and less frequently exhibited lymphovascular invasion.

In terms of operative time, it was almost one hour longer in the LRNU group than that in the ORNU group (ORNU, median 274 min; LRNU, 330 min, respectively, $P = 0.0016$). Data for postoperative complications were not fully collected in the present database. However, we previously observed that out of the 45 patients who underwent LRNU with LND, six patients developed minor complications, including pneumonia ($n = 2$), chylous leakage after dietary intake ($n = 2$) and miscellaneous events ($n = 4$). Although a 93-year-old male developed grade five gastrointestinal bleeding after aspiration pneumonia on the 45th postoperative day, we consider it to have been incidental, and not directly associated with LND. Overall, we believe that LRNU with LND can be safely performed.

Table 3. Results of uni- and multivariate analyses for recurrence-free survival, cancer-specific survival, and overall survival in the entire cohort.

	Recurrence-free survival				Cancer-specific survival				Overall survival			
	Univariate analysis Hazard ratio (95% CI)	*P*-value	Multivariate analysis Hazard ratio (95% CI)	*P*-value	Univariate analysis Hazard ratio (95% CI)	*P*-value	Multivariate analysis Hazard ratio (95% CI)	*P*-value	Univariate analysis Hazard ratio (95% CI)	*P*-value	Multivariate analysis Hazard ratio (95% CI)	*P*-value
Age, year												
Continuous	1.017 (0.987–1.051)	0.2801			1.045 (1.005–1.089)	0.0282	1.051 (1.008–1.098)	0.0187	1.058 (1.22–1.096)	0.001	1.054 (1.016–1.094)	0.0046
Sex male / female												
Male	1				1				1			
Female	0.740 (0.369–1.381)	0.3547			0.836 (0.368–1.738)	0.6429			0.683 (0.331–1.298)	0.2534		
History of bladder cancer												
No	1				1				1			
Yes or concurrent	0.630 (0.218–1.446)	0.2985			0.551 (0.132–1.547)	0.2858			1.166 (0.505–2.371)	0.6975		
Tumor location												
Renal pelvis	1				1				1			
Upper ureteral tumor	1.020 (0.380–2.319)	0.9657			0.923 (0.268–2.448)	0.8824			0.821 (0.277–1.964)	0.6791		
Distal ureteral tumor	1.407 (0.726–2.631)	0.3023			1.152 (0.498–2.461)	0.7282			1.366 (0.695–2.570)	0.3546		
Renal pelvis +ureter	1.008 (0.0564–4.749)	0.9939			5.55E-09	0.2592			1.219 (0.0683–5.754)	0.8504		
Number												
Solitary	1				1				1		1	
Multiple	1.620 (0.901–2.880)	0.1055			1.861 (0.915–3.751)	0.0854			1.986 (1.102–3.565)	0.0228	1.464 (0.784–2.734)	0.2325
Approach												
Open	1				1				1			
Laparoscopic	1.083 (0.614–1.937)	0.7835			0.934 (0.471–1.879)	0.8446			0.760 (0.427–1.352)	0.3487		
Adjuvant chemotherapy												
No	1				1				1			
Yes	2.378 (0.974–4.983)	0.0565			2.628 (0.890–6.275)	0.0763			1.850 (0.637–4.283)	0.2316		
Pathology												
Pure urothelial carcinoma	1				1				1			
Others	1.831 (0.299–5.929)	0.4442			2.530 (0.409–8.391)	0.2645			1.820 (0.297–5.909)	0.4488		
Size												
<1 cm	1				1				1			
1–3 cm	1.515 (0.632–4.483)	0.3785			1.826 (0.620–7.782)	0.299			2.321 (0.813–9.759)	0.1251		

>3 cm	0.906 (0.355–2.772)	0.8492			1.025 (0.319–4.539)	0.9691			1.581 (0.530–6.777)	0.4411		
pT stage												
pTa-is	1		1						1		1	
pT1	0.441 (0.0205–4.607)	0.4902	0.447 (0.0206–2.236)	0.5011	0.925 (0.0366–23.37)	0.9558	1.068 (0.0411–28.00)	0.9637	1.830 (0.482–8.680)	0.3803	2.493 (0.574–10.82)	0.206
pT2	3.724 (0.899–25.00)	0.0711	3.796 (0.866–26.52)	0.0788	2.081 (0.199–44.81)	0.5377	2.042 (0.183–46.35)	0.5617	0.998 (0.184–5.405)	0.998	1.212 (0.222–6.614)	0.8243
pT3-4	12.50 (3.826–76.90)	<0.0001	9.355 (2.549–61.00)	0.0002	18.03 (3.850–321.5)	<0.0001	11.51 (2.109–219.3)	0.002	7.128 (2.561–29.63)	<0.0001	6.279 (1.659–23.76)	0.0013
Grade												
Grade 1, 2	1		1		1		1		1		1	
Grade 3	2.461 (1.360–4.668)	0.0026	0.889 (0.467–1.764)	0.7272	3.836 (1.804–9.015)	0.0003	1.464 (0.658–3.616)	0.3621	2.815 (1.536–5.441)	0.0007	1.351 (0.647–2.821)	0.4174
Lymphovascular invasion												
No	1		1		1		1		1		1	
Yes	1.929 (1.084–3.506)	0.0253	1.162 (0.647–2.133)	0.6174	2.986 (1.449–6.602)	0.0027	2.110 (0.988–4.839)	0.0539	1.833 (1.018–3.360)	0.0433	1.326 (0.697–2.520)	0.3877
Incomplete LND	1				1				1			
Complete LND	0.719 (0.371–1.532)	0.3723			0.630 (0.293–1.518)	0.2845			0.812 (0.413–1.758)	0.5777		
pN stage												
pN0	1		1		1		1		1		1	
pN+	7.843 (4.113–14.29)	<0.0001	3.447 (1.723–6.721)	0.0007	8.546 (3.955–17.43)	<0.0001	2.982 (1.335–6.351)	0.0089	4.826 (2.327–9.241)	<0.0001	2.080 (0.994–4.354)	0.0642
Surgical margin												
pR0	1				1				1			
pR1	1.280 (0.208–4.161)	0.7428			1.904 (0.308–6.324)	0.4214			2.107 (0.509–5.822)	0.2626		

LND, lymph node dissection; CI, confidence interval.

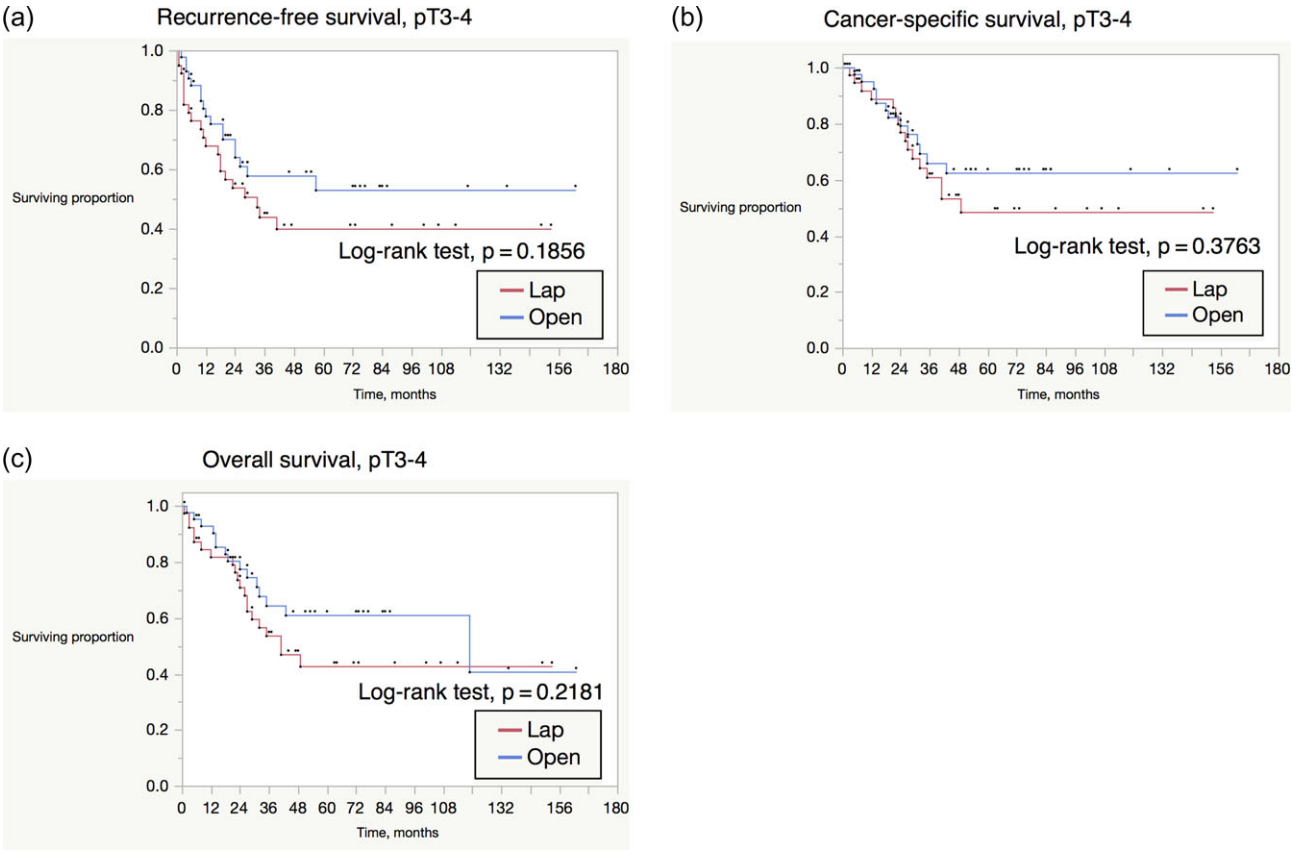

Figure 3. Kaplan–Meier estimates for RFS, CSS and OS stratified by surgical approach in the sub-analysis of pT3/4 patients ($n = 83$). The survival curves were higher in the ORNU group, although there was no significant difference in RFS, CSS or OS between the two surgical methods.

Survival analyses revealed that LRNU was not associated with a poorer RFS, CSS or OS. In addition, LRNU continued to demonstrate no association with a poorer RFS, OS or CSS for the pT3/T4 patients after controlling for the other prognostic characteristics in the multivariate model, although the Kaplan–Meier survival curves were higher for the ORNU group in all three survival analyses. The Cox model analyses strengthened the importance of the pN stage as a prognostic factor, as it was a significant factor, not only in the total cohort, but also for pT3/T4 patients.

As described in section Introduction, the potential risk associated with minimally invasive extirpative surgery for UC, such as tumor seeding at the port site or unexpected tumor spread due to the pneumoperitoneum, has been of concern. For example, in their retrospective review of 383 patients undergoing open radical cystectomy (ORC) ($n = 120$) or robot-assisted radical cystectomy (RARC) ($n = 263$), Nguyen et al. observed that extrapelvic lymph node recurrence (ORC: 15% vs. RARC: 23%) and peritoneal carcinomatosis (ORC: 8% vs. RARC: 21%) were more frequent after RARC than after ORC, although RARC was not a risk factor for recurrence in the multivariate model (14). In terms of UC of the UUT, Kim et al. recently reported in their retrospective study ($n = 371$) that the 5-year OS and CSS rates were lower in the LRNU group than those in the ORNU group, and after stratifying their cohort by pathological stages, significant differences remained only among pT3/T4 disease patients (15), although LND was not performed for most of their cohort. They concluded that LRNU should be performed for locally advanced UC of the UUT patients after careful consideration of its impact on survival. As mentioned above, although we did not observe any significant correlation with a poorer RFS, OS, or CSS in the pT3/T4 patients treated by LRNU, the Kaplan–Meier survival curves were higher in the ORNU group. Based on these observations, we also consider that LRNU should be performed after careful patient selection in the case of advanced disease. For example, considering the potential risk of tumor spillage during surgery due to renal pelvic rupture, we do not select LRNU for patients with severe hydronephrosis. If CT leads to suspicion of node metastasis, or perirenal or peri-ureteral fat invasion, we consider neo-adjuvant chemotherapy first before extirpative surgery. Surgeons should always consider resectability with an adequate surgical margin before surgery, and both skills and sufficient experience in manipulating around great vessels are required to complete laparoscopic retroperitoneal lymphadenectomy.

Regarding the adverse survival impact of the distal ureteral tumor location in pT3/T4 patients, our observation was consistent with previous studies. Tai et al. reported that patients with pT3 ureteral tumors had a poorer RFS than those with pT3 renal pelvis tumors (5-year RFS: 50 vs. 71%, respectively, $P = 0.047$) (16). Park et al. also found that the ureteral tumor location had an adverse prognostic impact only in patients with pT3 disease (17). As one hypothesis to explain the poorer outcome in patients with ureteral tumors, Yafi et al. stated that: ① the presence of a thinner layer of adventitia around the ureter, with an extensive plexus of blood vessels and lymphatics, may facilitate disease metastases, ② the smooth muscle layer of the ureter is thinner, leading to a more advanced

Table 4. Results of uni- and multivariate models in the sub-analysis of pT3/4 patients ($n = 83$)

Variables	RFS Univariate analysis Hazard ratio (95% CI)	*P*-value	CSS Univariate analysis Hazard ratio (95% CI)	*P*-value	OS Univariate analysis Hazard ratio (95% CI)	*P*-value	OS Multivariate analisis Hazard ratio (95% CI)	*P*-value
Age, year								
Continuous	1.014 (0.978–1.053)	0.4617	1.038 (0.997–1.083)	0.0683	1.050 (1.011–1.092)	0.0106	1.058 (1.020–1.099)	0.0025
Sex male/female								
Male	1		1		1			
Female	0.653 (0.310–1.282)	0.2215	0.629 (0.261–1.369)	0.2502	0.581 (0.257–1.196)	0.1447		
History of bladder cancer								
No	1		1		1			
Yes or concurrent	1.656 (0.565–3.896)	0.3247	0.986 (0.235–2.811)	0.9817	1.480 (0.502–3.514)	0.441		
Tumor location								
Renal pelvis	1		1		1		1	
Upper ureteral tumor	0.951 (0.278–2.487)	0.9256	1.186 (0.277–3.536)	0.7897	1.017 (0.239–2.993)	0.978	0.959 (0.224–2.849)	0.9469
Distal ureteral tumor	1.955 (0.902–4.013)	0.087	2.211 (0.936–4.889)	0.0692	2.670 (1.248–5.507)	0.0125	3.264 (1.498–6.904)	0.0036
Renal pelvis+ureter	0.821 (0.0458–3.920)	0.8422	6.00E-09	0.2238	1.191 (0.0662–5.777)	0.8687	1.292 (0.0711–6.469)	0.812
Number								
Solitary	1		1		1			
Multiple	1.421 (0.735–2.714)	0.291	1.542 (0.722–3.250)	0.2577	1.743 (0.884–3.440)	0.1078		
Approach								
Open	1		1		1			
Laparoscopic	1.530 (0.808–2.939)	0.1908	1.387 (0.668–2.938)	0.3795	1.515 (0.778–3.012)	0.2216		
Adjuvant chemotherapy								
No	1		1		1			
Yes	1.114 (0.450–2.389)	0.799	1.118 (0.376–2.703)	0.8222	0.935 (0.318–2.216)	0.8896		
Pathology								
Pure urothelial carcinoma	1		1		1			
Others	0.710 (0.115–2.334)	0.6212	0.913 (9.147–3.057)	0.9001	0.803 (0.130–2.655)	0.7557		
Size								
< 1 cm	1		1		1			
1-3 cm	0.970 (0.363–3.355)	0.9568	2.202 (0.621–13.99)	0.2476	2.440 (0.701–15.38)	0.1796		
> 3 cm	0.464 (0.166–1.638)	0.2095	0.899 (0.241–5.812)	0.8914	0.998 (0.274–6.396)	0.9979		
Grade								
Grade 1, 2	1		1		1			
Grade 3	1.051 (0.535–2.214)	0.8883	1.688 (0.755–4.278)	0.2103	1.727 (0.818–4.082)	0.1576		
Lymphovascular invasion								
No	1		1		1			
Yes	1.591 (0.806–3.361)	0.1854	2.096 (0.931–5.336)	0.0749	1.890 (0.912–4.294)	0.0885		
LND								
Incomplete	1		1		1			
Complete	0.786 (0.378–1.840)	0.5542	0.664 (0.297–1.683)	0.3646	0.643 (0.311–1.459)	0.2741		
pN stage								
pN0	1		1		1		1	
pN+	3.093 (1.553–5.931)	0.0018	3.270 (1.487–6.873)	0.0041	2.317 (1.085–4.645)	0.031	2.566 (1.190-5.218)	0.0177
Surgical margin								
pR0	1		1		1			
pR1	1.026 (0.166–3.388)	0.9716	1.222 (0.197–4.085)	0.7898	1.017 (0.165–3.356)	0.982		

RFS, recurrence-free survival; CSS, cancer-specific survival; OS, overall survival; CI, confidence interval.

Table 5. Multivariate analysis adjusted for surgical approach and other prognostic factors identified in the present study for pT3/4 patients ($n = 83$).

	Hazard ratio (95% CI)	*P*-value
(a) Recurrence-free survival		
Tumor location		
Renal pelvis	1	
Upper ureteral tumor	0.996 (0.280–2.811)	0.995
Distal ureteral tumor	1.761 (0.801–3.681)	0.1532
Renal pelvis+ureter	0.903 (0.0.493–4.645)	0.9209
Approach		
Open	1	
Laparoscopic	1.411 (0.695–2.935)	0.342
pN stage		
pN0	1	
pN+	3.105 (1.553–5.993)	0.0019
(b) Cancer-specific survival		
Age, year		
Continuous	1.045 (1.004–1.089)	0.0314
Tumor location		
Renal pelvis	1	
Upper ureteral tumor	1.131 (0.248–3.830)	0.8565
Distal ureteral tumor	2.540 (1.040–5.853)	0.0412
Renal pelvis+ureter	5.01E-09	0.2554
Approach		
Open	1	
Laparoscopic	1.188 (0.533–2.758)	0.6768
pN stage		
pN0	1	
pN+	3.188 (1.438–6.771)	0.0053
(c) Overall survival		
Age, year		
Continuous	1.057 (1.018–1.099)	0.0033
Tumor location		
Renal pelvis	1	
Upper ureteral tumor	1.040 (0.233–3.367)	0.952
Distal ureteral tumor	3.188 (1.449–6.801)	0.0047
Renal pelvis+ureter	1.200 (0.0651–6.293)	0.866
Approach		
Open	1	
Laparoscopic	1.168 (0.563–2.503)	0.6792
pN stage		
pN0	1	
pN+	2.519 (1.165–5.147)	0.0202

stage when minimal tumor invasion occurred, and ③ in contrast, the renal pelvis has a thicker adventitia with associated abundant renal parenchyma that allowed for adequate surgical margins, which may provide a better oncological outcome (18).

In the present study, 92 patients developed intravesical recurrence during follow-up. As described in section Patients and methods, we did not include intravesical recurrence as an endpoint for recurrence-free survival analyses because our main interest was the impact of the laparoscopic procedure on survival after surgery. Consistent with previous studies demonstrating that intravesical recurrence did not influence disease-specific survival after radical nephroureterectomy (19,20), we also observed that intravesical recurrence did not negatively impact cancer-specific survival (patients with intravesical recurrence; $n = 92$, 5-year cancer-specific survival 79.25% vs. patients without intravesical recurrence; $n = 122$, 5-year cancer-specific survival 78.94%, log-rank test, $P = 0.9293$, data not shown). The probability of intravesical recurrence in the present cohort was 50.6% at two years after open nephroureterectomy and 38.0% at two years after laparoscopic nephroureterectomy in the total cohort (log-rank test, $P = 0.0575$, data not shown), and 50.4% and 38.1%, respectively, for the 177 patients without previous or concomitant bladder cancer (log-rank-test, $P = 0.0784$, data not shown).

Our study had several limitations. First, the data were retrospectively collected. Second, a centralized pathological review was not performed. Third, the cohort size was small, as patients were derived from only three institutions in Japan. Although we actively performed LND during the study period, 90 patients were excluded because of a lack of regional LND, due to the physicians' decision based on the patients' comorbidity and performance status. Our findings should be further validated in a larger cohort with standardized LND. We hope that the recent introduction of robot-assisted radical nephroureterectomy and the relatively high performance rate with LND in robotic series will make this possible in the near future (21). Fourth, the 16-year study period was subject to variations in practices and surgical expertise, which may have affected the survival outcomes. Fifth, as mentioned above, LND was performed via an open incision for patients with distal ureteral tumors in the LRNU group. Although the current study has several potential weaknesses, we believe our findings to be important.

Conclusions

Our data support the feasibility of lymph node dissection with a laparoscopic approach, and demonstrated that the oncological outcomes of LRNU and ORNU are equivalent when regional LND is performed. However, LRNU should be performed after careful patient selection for advanced disease.

Conflict of interest statement

The authors state that they have no conflicts of interest.

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