BMC Urology

RESEARCH

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Outcomes of laparoscopic, robotic and open nephroureterectomy with bladder cuff excision in patients with T3T4 upper urinary tract urothelial carcinoma: a multi-center retrospective study

Jen-Kai Fang[1], Hsin-Chih Yeh[2,3,4,5], Hsiang-Ying Lee[3,4,6], Han-Yu Weng[7], Ta-Yao Tai[7], Chao-Yuan Huang[8], Jian-Hua Hong[8,9], Chih-Chin Yu[10,11], Shu-Yu Wu[10,11], Shiu-Dong Chung[12,13], Chung-You Tsai[13,14], Thomas Y. Hsueh[15,16], Allen W. Chiu[16], Yuan-Hong Jiang[11], Yu Khun[1], Lee[11], I-Hsuan Alan Chen[17], Jen-Tai Lin[17], Yung-Tai Chen[8,18,19], Chang-Min Lin[19], Ian-Seng Cheong[20], Hsu-Che Huang[21,22], Shih-Hsiu Lo[23], Wei-Yu Lin[24,25,26], Jen-Shu Tseng[27,28,29], Chia-Chang Wu[30,31,32], Shian-Shiang Wang[33,34,35], Yi-Huei Chang[1] and Chao-Hsiang Chang[1*]

Abstract

Background Nephroureterectomy with bladder cuff excision is the standard treatment for high-risk upper urinary tract urothelial carcinoma (UTUC). **The role of minimally invasive surgery in treating locally advanced UTUC remains controversial. This study aimed to compare the outcomes of open, laparoscopic, and robotic surgeries for managing locally advanced UTUC.**

Methods We retrospectively reviewed 705 patients with locally advanced UTUC from multiple institutions throughout Taiwan. Perioperative outcomes and oncological outcomes, **such as cancer-specific survival, overall survival, disease-free survival and bladder-free survival**, were compared between the open, laparoscopic and robotic groups.

Results The minimally invasive group had better overall and cancer-specific survival (CSS) rates. The 2-year CSS rates of the open, laparoscopic and robotic groups were 71%, 83%, and 77% respectively ($p < 0.001$). The robotic group had similar outcomes to the laparoscopic group. ($p = 0.061$, 0.825, 0.341 for OS, CSS, DFS respectively.) More lymph node dissections were performed and more lymph nodes were harvested in the robotic group ($p = 0.009$).

Conclusions Our results demonstrated that minimally invasive surgery, including laparoscopic and robotic surgery, for locally advanced UTUC resulted in oncological outcomes that are non-inferior to those of open surgery.

Keywords Upper tract urothelial carcinoma, Minimally invasive surgery, Robotic surgery

*Correspondence:
Chao-Hsiang Chang
urology8395@yahoo.com.tw

Full list of author information is available at the end of the article

Background

Upper urinary tract urothelial carcinoma (UTUC) is an uncommon cancer accounting for 5–10% of urothelial carcinomas in the United States [1]. However, in Taiwan, the incidence of UTUC is much higher, accounting for 25% of all urothelial carcinomas [2]. Nephroureterectomy with bladder cuff excision is the established standard treatment for high-risk UTUCs. With the evolution of minimally invasive procedures, laparoscopic and robotic nephroureterectomy have become widely accepted and are considered safe options. Minimally invasive surgery has the benefits of smaller incisions, fewer perioperative complications, less blood loss, pain, and a shorter length of stay [3].

However, for locally advanced tumors, such as T3/T4 N1, open nephroureterectomy is recommended in the European Association of Urology (EAU) guidelines. One systematic review reported better oncological outcomes for open nephroureterectomy (ONU) compared to laparoscopic nephroureterectomy (LNU) for locally advanced UTUC [4]. To date, due to the low incidence of UTUC, most previous studies comparing LNU and ONU have been retrospective with small sample sizes, and the role of minimally invasive surgery for locally advanced UTUC remains controversial. In addition, few studies have discussed robotic nephroureterectomy (RNU). Surgical techniques and experience have greatly progressed in recent years, particularly in areas with a high incidence of UTUC. **We hypothesize that minimally invasive surgery has similar oncological outcomes compared to open surgery in patients with locally advanced disease.** The aim of this multicenter study was to evaluate differences in oncologic outcomes between open, laparoscopic, and robotic surgery for UTUC.

Methods

Patient population

We retrospectively reviewed the medical records of 705 patients with UTUC who underwent surgery at 17 Taiwan hospitals participating in the Taiwan Upper Tract Urothelial Carcinoma Collaboration group between July 1988 and December 2020. All patient data were anonymized. The inclusion criteria were patients with pathologic stage T3 T4 and any N UTUC. Patients with clinical lymphadenopathy on preoperative imaging, concurrent muscle-invasive bladder cancer or distant metastasis were excluded from the study. The enrolled patients were divided into three groups based on their surgical approach: open, laparoscopic (including standard laparoscopic, hand-assisted laparoscopic, and laparoscopic single-site surgery), and robotic surgery. **There were no standardized selection criteria for open versus minimally invasive procedures, with variations across institutions, based on factors such as surgeon's preference, technique, and patient's clinical conditions. Most patients were followed according to the EAU guidelines, with regular monitoring of both the bladder and upper urinary tract. Cystoscopy and cytology were performed every three months for the first two years, every six months up to five years, and annually thereafter. Abdominal and chest CT scans were conducted every six months for the first two years, followed by annual imaging. Each institution ensured adherence to these guidelines through oversight by designated clinical monitors. To enhance accuracy, we recommended that at least two study members independently collect and meticulously review data at each hospital. Urology residents monitored the data. Regular meetings and discussions among centers were conducted to ensure consistency in data collection and recording practices.**

Outcomes

Perioperative outcomes were evaluated and compared among the three groups, including the number of lymph node dissections, surgical margins, and residual bladder cuff. In addition, 2-year oncological outcomes such as overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), and bladder-free survival were assessed.

Statistical methods

Differences between groups were compared using one-way ANOVA for continuous variables, and Pearson's chi-square test for categorical variables. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. The Kaplan-Meier method was used to estimate the rates of prognostic outcomes, and survival curves were compared using the stratified log-rank test. A Cox proportional hazard model was used to assess the effect of the surgical approach on the prognostic outcome, alone and after adjusting for potential confounders. All statistical assessments were two-tailed, and $p<0.05$ was considered statistically significant. Statistical analyses were carried out with SPSS version 26 (IBM Inc., Armonk, NY).

Results

A total of 705 patients who underwent nephroureterectomy for UTUC were enrolled, of whom 233 underwent open surgery, 415 underwent laparoscopic surgery, and 57 underwent robotic surgery. The three groups were comparable in most characteristics, except for age, rate of postoperative intravesical chemotherapy, follow-up duration, and surgical approach. Most of the open group and approximately half of the laparoscopic group underwent a retroperitoneal approach, while most of the robotic group underwent a transperitoneal approach (Table 1). **Bladder cuff excision was performed using the open**

Table 1 Patient characteristics

Variables	Open (*N* = 233)		Laparoscopy (*N* = 415)		Robot (*N* = 57)		*p*-value	Missing data	
	N	%	*N*	%	*N*	%	*N*	%	
Gender									
Men	104	(45.2)	198	(47.7)	25	(43.9)	0.758		
Women	126	(54.8)	217	(52.3)	32	(56.1)			
Age Mean ± SD	66.9 ± 10.9		70.1 ± 11.2		69.2 ± 10.5		0.003*	6	(2.15)
Laterality									
Left	104	(44.8)	207	(49.9)	28	(49.1)	0.490		
Right	124	(53.4)	204	(49.2)	28	(49.1)			
Bilateral	4	(1.7)	2	(0.5)	1	(1.8)			
Graft kidney	0	(0.0)	2	(0.5)	0	(0.0)			
Tumor location									
Renal pelvis	159	(68.2)	302	(72.8)	45	(78.9)	0.214		
Upper ureter	46	(19.7)	111	(26.7)	9	(15.8)	0.046*		
Middle ureter	39	(16.7)	54	(13.0)	4	(7.0)	0.127		
Lower ureter	54	(23.2)	79	(19.0)	16	(28.1)	0.190		
Bladder cuff	3	(1.3)	19	(4.6)	1	(1.8)	0.062		
Synchronous bladder tumor									
No	181	(78.7)	329	(79.9)	42	(75.0)	0.297	4	(1.43)
Previous Hx of bladder UC	16	(7.0)	24	(5.8)	1	(1.8)			
Concurrent Bladder UC	33	(14.3)	59	(14.3)	13	(23.2)			
Post operation intravesical C/T instillation								11	(3.94)
No	215	(96.0)	364	(92.6)	46	(85.2)	0.015*		
Yes	9	(4.0)	29	(7.4)	8	(14.8)			
Perioperative chemotherapy								2	(0.72)
Neo-adjuvant	2	(0.9)	10	(2.4)	2	(3.5)	0.356		
Adjuvant	71	(30.5)	118	(28.4)	15	(26.3)			
Adjuvant radiation therapy	12	(5.2)	25	(6.0)	1	(1.8)	0.154	2	(0.72)
Surgery									
Transperitoneal	56	(26.5)	208	(51.4)	47	(97.9)	< 0.001*		
Retroperitoneal	155	(73.5)	197	(48.6)	1	(2.1)			
Follow up (months) [c] median	14.68		28.55		18.86		< 0.001*	5	(1.79)

method in 269 patients (64.8%) in the LNU group, but in only 1 patient (1.8%) in the RNU group. The perioperative chemotherapy rates of open, laparoscopic, and robotic nephroureterectomy were 31.3%, 30.8%, and 29.8%, respectively ($p = 0.356$).

Comparing the pathological results and perioperative outcomes, it was found that the ONU patients had larger tumors and more pathological stage IV disease than the other two groups (ONU: 24% vs. LNU: 14.5% vs. RNU: 22.8%, $p = 0.007$). The lymph node dissection rates were 20.2%, 31.6%, and 57.9% for ONU, LNU, and RNU, respectively. If lymph node dissection was performed, more lymph nodes were harvested in the RNU group. The overall lymph node metastasis rate was 25.6%. More patients in the LNU group had lymphovascular invasion (ONU: 30.9%, LNU: 40.7%, RNU:35.1%, $p = 0.043$), and more patients in the minimally invasive group (LNU and RNU) had residual bladder cuffs (remaining tissue at the bladder cuff that was not fully excised during the nephroureterectomy) (ONU: 4.2%, LNU: 12%, RNU: 13.5%, $p = 0.045$) (Table 2).

Regarding survival outcomes, the ONU group had worse OS and CSS rates compared to the RNU and LNU groups, even after adjusting for confounders. The 2-year OS rates for ONU, LNU, RNU were 64%, 78%, 74% ($p < 0.001$). The 2-year CSS rates for ONU, LNU, and RNU were 71%, 83%, and 77%, respectively ($p < 0.001$). The LNU and RNU groups had similar survival outcomes ($p = 0.061$, 0.825, 0.341 for OS, CSS, DFS respectively.) (Fig. 1).

Regarding the recurrence patterns, 46 patients (19.7%), 94 patients (22.7%), and 8 patients (14.0%) experienced regional lymph node recurrence in the ONU, LNU, and RNU groups, respectively. Additionally, 79 patients (33.9%), 121 patients (29.1%), and 12 patients (21.1%) developed distant metastasis in the ONU, LNU, and RNU groups, respectively.

Multivariable analysis showed that pathological stage, retroperitoneal approach, presence of diabetes mellitus,

Table 2 Perioperative variables

Variables	Open (*N* = 233)		Laparoscopy (*N* = 415)		Robot (*N* = 57)		*p*-value	Missing data	
	N	%	*N*	%	*N*	%		*N*	%
Tumor size								3	(1.08)
Non-visible	1	(0.7)	3	(0.7)	3	(5.4)	< 0.001*		
< 1 cm	2	(1.5)	7	(1.7)	1	(1.8)			
≥ 1 & < 2 cm	10	(7.4)	64	(15.5)	8	(14.3)			
≥ 2 & < 3 cm	17	(12.5)	87	(21.0)	14	(25.0)			
≥ 3 cm	106	(77.9)	253	(61.1)	30	(53.6)			
Cell Type									
urothelial	202	(86.7)	333	(80.2)	42	(73.7)	0.092		
adenocarcinoma	2	(0.9)	0	(0.0)	0	(0.0)			
squamous	0	(0.0)	1	(0.2)	0	(0.0)			
UC with variants	28	(12.0)	78	(18.8)	15	(26.3)			
others	1	(0.4)	3	(0.7)	0	(0.0)			
Harvested LN number Mean ± SD	7.32 ± 11.3		5.63 ± 6.47		10.79 ± 11.36		0.009*	9	(3.23)
Multiplicity								8	(2.87)
Not available	5	(2.2)	2	(0.5)	1	(1.9)	0.418		
No	135	(58.2)	243	(59.1)	31	(58.5)			
Yes	92	(39.7)	166	(40.4)	21	(39.6)			
Tumor histology									
Low grade	25	(2.6)	24	(5.7)	1	(1.8)	< 0.001*		
high grade	225	(97.4)	391	(94.3)	56	(98.2)			
Carcinoma in situ									
No	214	(91.8)	340	(81.9)	42	(73.7)	< 0.001*		
Yes	19	(8.2)	75	(18.1)	15	(26.3)			
Lymphovascular invasion									
No	161	(69.1)	246	(59.3)	37	(64.9)	0.043*		
Yes	72	(30.9)	169	(40.7)	20	(35.1)			
Surgical margin									
Free	219	(94.0)	382	(92.0)	54	(94.7)	0.557		
Positive	14	(6.0)	33	(8.0)	3	(5.3)			
Tumor Necrosis								11	(3.94)
No	192	(85.7)	311	(74.9)	42	(73.7)	0.005*		
Yes	32	(14.3)	104	(25.1)	15	(26.3)			
Pathological stage									
stage III	177	(76.0)	355	(85.5)	44	(77.2)	0.007*		
stage IV	56	(24.0)	60	(14.5)	13	(22.8)			
Pathological stage T									
pT3	185	(79.4)	380	(91.6)	49	(86.0)	< 0.001*		
pT4	48	(20.6)	35	(8.4)	8	(14.0)			
Pathological stage N									
pN0	34	(15.1)	98	(23.6)	25	(43.9)	< 0.001*		
pN1	4	(1.8)	17	(4.1)	3	(5.3)			
pN2	9	(4.0)	16	(3.9)	5	(8.8)			
pNx	178	(79.1)	284	(68.4)	24	(42.1)			
Clavien-Dindo classification								4	(1.43)
No	166	(71.9)	272	(65.7)	33	(61.1)	0.039*		
Grade I	18	(7.8)	40	(9.7)	13	(24.1)			
Grade II	30	(13.0)	69	(16.7)	7	(13.0)			
Grade III	9	(3.9)	15	(3.6)	0	(0.0)			
Grade IV	3	(1.3)	11	(2.7)	0	(0.0)			
Grade V	5	(2.2)	7	(1.7)	1	(1.9)			
Residual bladder-cuff									

Table 2 (continued)

Variables	Open (*N* = 233)		Laparoscopy (*N* = 415)		Robot (*N* = 57)		*p*-value	Missing data	
	N	%	*N*	%	*N*	%		*N*	%
No	68	(95.8)	132	(88.0)	32	(86.5)	0.045*		
Yes	3	(4.2)	18	(12.0)	5	(13.5)			

LN: lymph node

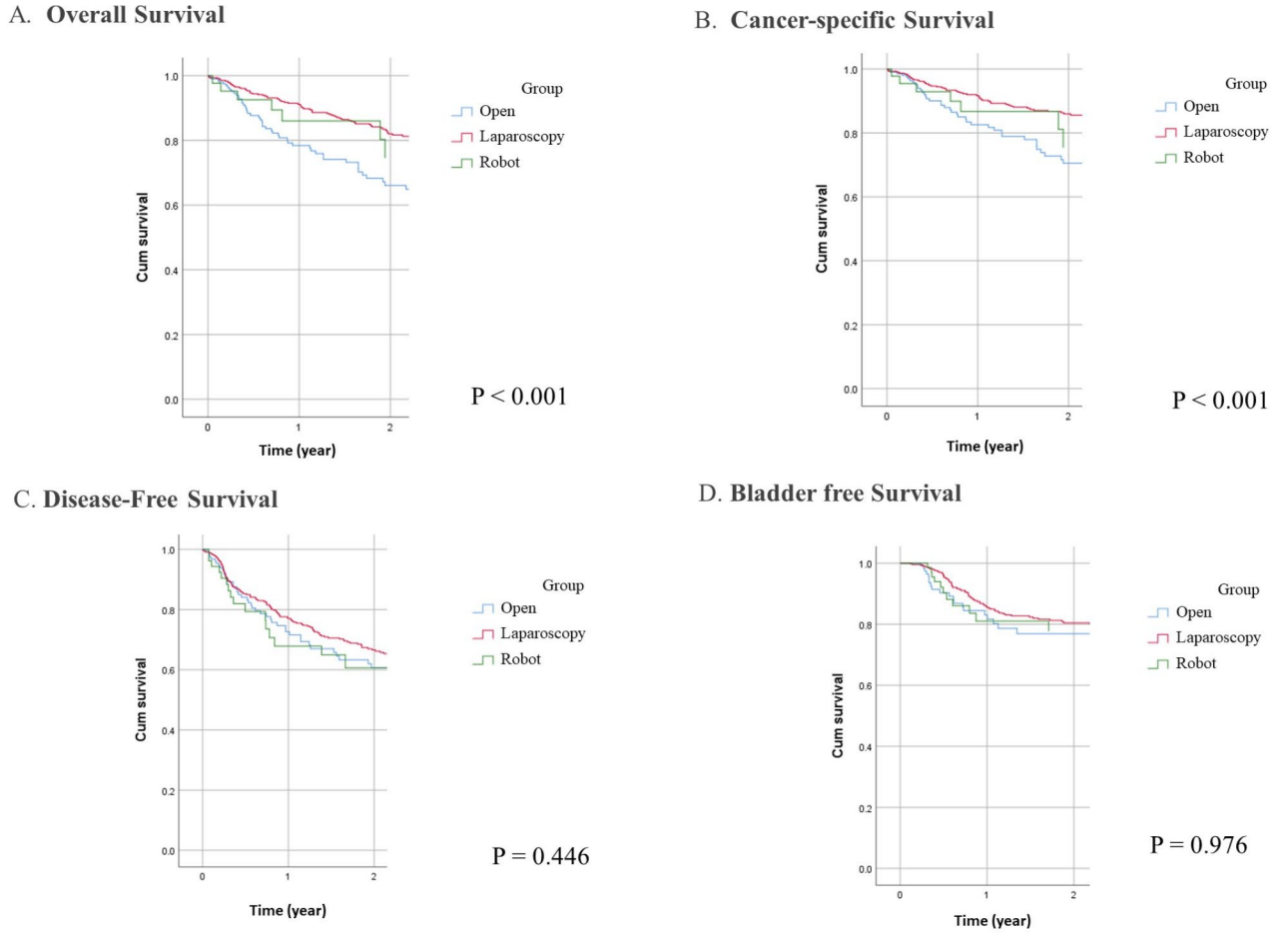

Fig. 1 Kaplan–Meier estimates of (**A**) overall, (**B**) cancer-specific, (**C**) disease-free, and (**D**) bladder-free survival among the three groups after adjusting for confounders

and lack of perioperative chemotherapy were significant predictors of poor OS (Tables 3 and 4).

In terms of period distribution, ONU patients were distributed as follows: 56 patients (24.0%) in the first decade, 62 patients (26.6%) in the second decade, and 115 patients (49.4%) in the third decade. For LNU patients, there were no cases in the first decade, 66 patients (15.9%) in the second decade, and 349 patients (84.1%) in the third decade. Notably, all RNU patients are found in the third decade.

Discussion

Laparoscopic nephroureterectomy was first described in 1991 by Clayman et al. [5]. Despite the better perioperative outcomes with minimally invasive surgery, adverse effects such as urine spillage, high risk of local recurrence, difficulty in lymph node dissection and bladder cuff excision, and troca site metastasis have been reported [6]. In our real-world data, 58.9% of the locally advanced patients received LNU, followed by ONU (33.0%) and then RNU (8.1%). Minimally invasive surgery accounted for 81% of all nephroureterectomies in the recent 5 years, unlike previous studies, in which ONU was the predominant method for UTUC. In an updated

Table 3 Comparative univariate survival analysis the UTUC patients

Univariate analysis	OS		CSS		DFS		BRFS	
	HR (95% CI)	*p*-value	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value
Group								
Open	1		1		1		1	
LPS/ HALPS/ LESS	0.552 (0.421, 0.725)	< 0.001**	0.509 (0.372, 0.696)	< 0.001**	0.639 (0.499, 0.818)	< 0.001*	1.008 (0.705, 1.442)	0.963
Robot	0.496 (0.265, 0.929)	0.029*	0.553 (0.285, 1.075)	0.081	0.808 (0.510, 1.280)	0.364	1.370 (0.748, 2.507)	0.308
Sex								
Male	1		1		1		1	
Female	1.030 (0.793, 1.337)	0.824	0.974 (0.720, 1.317)	0.865	1.177 (0.932, 1.486)	0.171	0.732 (0.534, 1.003)	0.052
Age								
< 70	1		1		1		1	
>=70	1.600 (1.228, 2.084)	< 0.001**	1.435 (1.058, 1.945)	0.020*	1.242 (0.984, 1.567)	0.068	1.229 (0.897, 1.685)	0.2
Tumor size								
< 2 cm	1		1		1		1	
≥ 2 & < 3 cm	0.729 (0.425, 1.249)	0.249	0.853 (0.438, 1.658)	0.638	1.370 (0.833, 2.254)	0.215	0.673 (0.407, 1.112)	0.122
≥ 3cm	1.300 (0.852, 1.982)	0.223	1.669 (0.985, 2.830)	0.057	1.977 (1.289, 3.032)	0.002*	0.635 (0.419, 0.962)	0.032*
Renal pelvis								
No	1		1		1		1	
Yes	0.768 (0.579, 1.019)	0.067	0.728 (0.527, 1.005)	0.053	0.746 (0.583, 0.955)	0.020*	0.966 (0.684, 1.366)	0.847
Upper ureter								
No	1		1		1		1	
Yes	0.918 (0.677, 1.244)	0.58	0.962 (0.679, 1.365)	0.83	1.000 (0.765, 1.308)	0.999	1.165 (0.818, 1.658)	0.398
Middle ureter								
No	1		1		1		1	
Yes	1.208 (0.849, 1.720)	0.293	1.055 (0.690, 1.613)	0.806	1.252 (0.916, 1.712)	0.159	1.238 (0.812, 1.886)	0.321
Lower ureter								
No	1		1		1		1	
Yes	1.614 (1.194, 2.183)	0.002**	1.692 (1.202, 2.383)	0.003**	1.699 (1.307, 2.207)	< 0.001**	1.724 (1.206, 2.463)	0.003**
Bladder cuff								
No	1		1		1		1	
Yes	1.794 (1.022, 3.148)	0.042*	1.921 (1.012, 3.644)	0.046*	2.736 (1.648, 4.541)	< 0.001**	2.114 (1.077, 4.149)	0.030*
Laterality								
Left	1		1		1		1	
Right	1.064 (0.818, 1.383)	0.644	1.042 (0.770, 1.411)	0.788	0.905 (0.717, 1.142)	0.401	0.774 (0.563, 1.064)	0.114
CIS								
No	1		1		1		1	
Yes	0.929 (0.644, 1.340)	0.693	0.941 (0.619, 1.431)	0.777	0.810 (0.578, 1.135)	0.221	1.292 (0.862, 1.937)	0.215
Multiplicity								
No	1		1		1		1	
Yes	1.395 (1.071, 1.816)	0.013*	1.392 (1.025, 1.890)	0.034*	1.391 (1.100, 1.760)	0.006**	1.980 (1.443, 2.719)	< 0.001**

Table 3 (continued)

Univariate analysis	OS		CSS		DFS		BRFS	
	HR (95% CI)	*p*-value	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value	HR(95% CI)	*p*-value
Lymphovascular invasion								
No	1		1		1		1	
Yes	1.275 (0.976, 1.664)	0.075	1.450 (1.069, 1.967)	0.017*	1.555 (1.231, 1.963)	< 0.001**	1.077 (0.777, 1.491)	0.657
Surgical margin								
free	1		1		1		1	
positive	2.719 (1.837, 4.025)	< 0.001	3.123 (2.038, 4.786)	< 0.001	2.773 (1.942, 3.958)	< 0.001**	0.883 (0.433, 1.800)	0.733
Tumor Necrosis								
No	1		1		1		1	
Yes	1.306 (0.971, 1.756)	0.077	1.084 (0.758, 1.552)	0.658	1.024 (0.774, 1.355)	0.868	1.064 (0.727, 1.557)	0.75
NUx histology								
low grade	1		1		1		1	
high grade	2.917 (1.201, 7.086)	0.018	5.450 (1.351, 21.990)	0.017	6.365 (2.039, 19.867)	0.001	0.743 (0.412, 1.340)	0.323
Synchronous bladder tumor								
No	1		1		1		1	
Previous Hx of bladder UC	1.417 (0.834, 2.409)	0.197	1.326 (0.715, 2.460)	0.37	0.903 (0.526, 1.551)	0.713	2.691 (1.562, 4.637)	< 0.001**
Concurrent Bladder UC	1.624 (1.160, 2.272)	0.005**	1.606 (1.088, 2.370)	0.017*	1.521 (1.126, 2.055)	0.006**	2.899 (2.011, 4.180)	< 0.001**
NxUx access								
Transperitoneal	1		1		1		1	
Retroperitoneal	1.483 (1.122, 1.960)	0.006**	1.526 (1.105, 2.108)	0.010*	1.229 (0.966, 1.564)	0.093	0.837 (0.605, 1.157)	0.281
Harvested LN number								
< 4	1		1		1		1	
>= 4	0.667 (0.402, 1.108)	0.118	0.630 (0.358, 1.109)	0.109	0.935 (0.614, 1.422)	0.752	0.726 (0.386, 1.366)	0.321
Post operation intravesical C/T instillation								
No	1		1		1		1	
Yes	1.647 (1.014, 2.677)	0.044*	1.743 (1.023, 2.972)	0.041*	1.756 (1.171, 2.635)	0.007**	1.931 (1.110, 3.360)	0.020*
Pathological stage T								
pT3	1		1		1		1	
pT4	2.798 (2.031, 3.854)	< 0.001**	3.179 (2.226, 4.540)	< 0.001**	2.497 (1.855, 3.363)	< 0.001**	0.345 (0.153, 0.780)	0.011*
Pathological stage N								
pN0	1		1		1		1	
pN1	2.291 (1.209, 4.342)	0.011*	2.689 (1.358, 5.326)	0.005**	2.477 (1.372, 4.472)	0.003**	1.425 (0.596, 3.409)	0.426
pN2	1.615 (0.834, 3.127)	0.156	2.106 (1.064, 4.168)	0.033*	3.068 (1.847, 5.096)	< 0.001**	0.539 (0.165, 1.761)	0.306
pNx	1.148 (0.821, 1.604)	0.42	1.118 (0.758, 1.649)	0.574	1.261 (0.928, 1.713)	0.138	1.237 (0.836, 1.830)	0.288
DM								
No	1		1		1		1	
Yes	1.427 (1.068, 1.908)	0.016*	1.275 (0.903, 1.799)	0.167	1.127 (0.859, 1.478)	0.389	1.396 (0.977, 1.997)	0.067

meta-analysis, among a total of 10,730 patients in 18 studies, 5959 (55.5%) and 4771 (44.5%) underwent ONU and LNU, respectively. In the subgroup of pT3/T4 and pTany N+patients, 802 (63.9%) ONU and 453 (36.1%) LNU were performed [7]. LNU for UTUC is a mature and broadly accepted procedure in Taiwan.

Peyronnet et al. reviewed 42 studies involving 7554 patients, and all of the studies except three found no significant difference in oncological outcomes between ONU and LNU. These three studies concluded that ONU had significantly better oncological outcomes in the subgroup of patients with locally advanced UTUC. Bladder cuff excision with laparoscopy was a poor prognostic factor [4, 8]. However, the enrolled studies were published before August 2016, and a more recent meta-analysis showed comparable oncological outcomes between the two groups [7]. Moreover, Kim et al. analyzed the conditional CSS to minimize bias caused by inherent time data properties, and found no significant difference in conditional CSS between the two modalities [9]. In our series, patients in the minimally invasive group had better OS and CSS than those in the open surgery group, even after adjusting for confounding factors. Although more patients in the minimally invasive group had residual bladder cuffs, it was not an independent predictor of CSS, OS or DFS in the multivariate analysis.

The trend towards RNU began after the first robotic nephrectomy was reported in 2001 [8]. In the last decade, the utilization of RNU has increased by 16% and ONU has decreased by 14%, with no impact on OS [10]. In a single-center study in Korea, the utilization rate of RNU reached 67% with 3-year OS, PFS, and CSS rates comparable to those of ONU and LNU [11]. In our series, the utilization of RNU also increased, with 13% of patients undergoing RNU in the last three years. RNU achieved equivalent oncological outcomes to LNU, which is consistent with the conclusions of several other retrospective studies [12, 13].

Template-based lymph node dissection is considered to have therapeutic benefits for locally advanced UTUC with a tumor stage of ≥pT2 [14, 15], and a better OS has been reported for pN0 patients with more lymph node dissections [16]. However, in the current study, the lymph node dissection rate was only 31.1% in the patients with locally advanced UTUC, with the lowest rate for ONU and highest rate for RNU. A possible explanation for this finding is that more open surgery was performed in the earlier period, and the role of lymph node dissection was unclear during this period. Another possible explanation is that it is difficult to stage the disease precisely before surgery. The advantages of robotic surgery, including 3-D magnified view and flexible EndoWrist instruments, make lymph node dissection easier and safer compared with laparoscopic surgery, and this may explain why more robotic surgeons performed lymph node dissection. In addition, the number of harvested lymph nodes was highest in the RNU group. Although some experts have recommended that open surgery should be preferred for lymph node dissection in locally advanced disease [17], we believe that robotic surgery can achieve optimal lymph node dissection.

The lymph node-positive rate was 25.6% among the patients with lymph node dissection in our study. A systematic review reported that the incidence of pN+in patients with high-stage (pT≥2) UTUC ranged from 14.3 to 40% [14]. This reflects the potential benefit of lymph node dissection in patients with high-stage UTUC. Lymph node dissection not only helps with disease staging but also removes all cancer cells and can cure the disease.

Adjuvant gemcitabine-platinum combination chemotherapy is recommended in patients with pT2-T4 pN0-N3 M0 or pTany N1-3 M0 UTUC after nephroureterectomy, according to the results of the POUT trial [18]. On the other hand, neoadjuvant chemotherapy has been reported to be effective in downstaging UTUC and to provide better OS and PFS [19]. In the current study, we also found that perioperative chemotherapy was an independent predictor of better OS.

The multiplicity of urothelial carcinoma is commonly considered as high risk disease, no matter bladder or upper tract. The multifocality of UTUC is poor prognosis of cancer-specific survival and disease progression [20]. It results from more aggressive biologic potential of tumors or delay in diagnosis. However, in our multivariable survival analysis, the multifocality doesn't impact the OS or CSS.

We categorized tumor sizes into the following groups: <1 cm, 1–2 cm, 2–3 cm, and >3 cm, recognizing that tumor size is a potentially significant prognostic factor. However, the multivariable survival analysis did not indicate that tumor size is a prognostic factor. Instead, the TNM stage more accurately reflects the patients' prognosis.

In this study, the patients with diabetes mellitus had worse OS. Patients with diabetes have more comorbidities including cardiovascular, renal and neurological diseases, and a previous study reported that diabetes was a poor predictor for RFS in UTUC [21]. Tai et al. also reported that patients with poorly controlled diabetes had shorter bladder recurrence survival after nephroureterectomy [22]. Chronic exposure to hyperglycemia may induce cancer cell proliferation and metastasis [23].

The strengths of this study include the large sample size, multi-institutional nature and the high prevalence of UTUC in Taiwan. RNU was included in the analysis, and its advantages were discussed. However, some limitations should also be mentioned, including the retrospective

Table 4 Comparative multivariable survival analysis

Multivariable analysis	OS		Multivariable analysis	OS	
	HR (95% CI)	*p*-value		HR (95% CI)	*p*-value
Age			NxUx access		
< 70	1		Transperitoneal	1	
>=70	1.721 (1.247, 2.375)	0.001*	Retroperitoneal	1.698 (1.212, 2.379)	0.002*
Lower ureter			Post operation intravesical C/T instillation		
No	1		No	1	
Yes	1.213 (0.827, 1.780)	0.323	Yes	1.716 (0.997, 2.952)	0.051
Bladder cuff			Pathological stage T		
No	1		pT3	1	
Yes	1.154 (0.569, 2.340)	0.691	pT4	2.785 (1.811, 4.284)	< 0.001*
Multiplicity			Pathological stage N		
No	1		pN0	1	
Yes	1.328 (0.965, 1.827)	0.082	pN1	2.560 (1.288, 5.089)	0.007*
Surgical margin			pN2	0.707 (0.299, 1.672)	0.429
Free	1		pNx	0.785 (0.529, 1.166)	0.231
Positive	1.597 (0.921, 2.769)	0.096	HTN		
NUx histology			No	1	
low grade	1		Yes	1.119 (0.815, 1.537)	0.487
high grade	2.158 (0.872, 5.345)	0.096	DM		
Synchronous bladder tumor			No	1	
No	1		Yes	1.900 (1.346, 2.681)	< 0.001*
Previous Hx of bladder UC	1.491 (0.820, 2.711)	0.191	Perioperative chemotherapy		
Concurrent Bladder UC	1.230 (0.820, 1.844)	0.317	No	1	
Residual bladder cuff			Yes	0.599(0.414, 0.866)	0.006*
No	1				
Yes	1.219(0.733, 2.027)	0.445			
Group			NUx histology		
Open	1		low grade	1	
LPS/ HALPS/ LESS	0.465 (0.323, 0.670)	< 0.001*	high grade	3.809 (0.932, 15.566)	0.063
Robot	0.585 (0.249, 1.373)	0.218	Synchronous bladder tumor		
Age			No	1	
< 70	1		Previous Hx of bladder UC	1.322 (0.677, 2.582)	0.414
>=70	1.563 (1.094, 2.232)	0.014*	Concurrent Bladder UC	1.287 (0.823, 2.013)	0.269
Lower ureter			NxUx access		
No	1		Transperitoneal	1	
Yes	1.225 (0.801, 1.873)	0.349	Retroperitoneal	1.571 (1.076, 2.293)	0.019*
Bladder cuff			Post operation intravesical C/T instillation		
No	1		No	1	
Yes	1.028 (0.462, 2.290)	0.946	Yes	1.754 (0.970, 3.175)	0.063

Table 4 (continued)

Multivariable analysis	OS		Multivariable analysis	OS	
	HR (95% CI)	*p*-value		HR (95% CI)	*p*-value
Multiplicity			Pathological stage T		
No	1		pT3	1	
Yes	1.322 (0.921, 1.897)	0.13	pT4	2.515 (1.563, 4.045)	< 0.001*
Lymphovascular invasion			Pathological stage N		
No	1		pN0	1	
Yes	1.315 (0.930, 1.861)	0.122	pN1	2.557 (1.227, 5.330)	0.012*
Surgical margin			pN2	0.912 (0.383, 2.175)	0.836
Free	1		pNx	0.836 (0.538, 1.299)	0.426
Positive	1.563 (0.845, 2.892)	0.155			
Group			Surgical margin		
Open	1		Free	1	
LPS/ HALPS/ LESS	0.787 (0.564, 1.099)	0.16	Positive	2.007 (1.260, 3.197)	0.003*
Robot	0.969 (0.540, 1.739)	0.917	NUx histology		
Tumor size			low grade	1	
< 2 cm	1		high grade	5.924 (1.459, 24.054)	0.013*
≥ 2 & < 3 cm	1.627 (0.953, 2.775)	0.074	Synchronous bladder tumor		
≥ 3cm	1.984 (1.244, 3.167)	0.004*	No	1	
Renal pelvis			Previous Hx of bladder UC	1.027 (0.563, 1.872)	0.931
No	1		Concurrent Bladder UC	1.169 (0.802, 1.706)	0.416
Yes	0.728 (0.506, 1.048)	0.088	Post operation intravesical C/T instillation		
Lower ureter			No	1	
No	1		Yes	1.813 (1.109, 2.963)	0.018*
Yes	1.200 (0.837, 1.721)	0.32	Pathological stage T		
Bladder cuff			pT3	1	
No	1		pT4	1.555 (1.003, 2.411)	0.048*
Yes	1.465 (0.790, 2.717)	0.226	Pathological stage N		
Multiplicity			pN0	1	
No	1		pN1	2.407 (1.282, 4.518)	0.006*
Yes	1.366 (0.997, 1.872)	0.052	pN2	1.814 (0.985, 3.343)	0.056
Lymphovascular invasion			pNx	1.117 (0.797, 1.567)	0.519
No	1		Perioperative chemotherapy		
Yes	1.317 (0.988, 1.756)	0.06	No	1	
			Yes	0.456(0.324, 0.642)	< 0.001
Group			Pathological stage T		
Open	1		pT3	1	
LPS/ HALPS/ LESS	0.888 (0.546, 1.443)	0.632	pT4	0.127 (0.030, 0.529)	0.005*
Robot	1.017 (0.478, 2.164)	0.965	Perioperative chemotherapy		
Tumor size			No	1	

Table 4 (continued)

Multivariable analysis	OS		Multivariable analysis	OS	
	HR (95% CI)	*p*-value		HR (95% CI)	*p*-value
< 2 cm	1		Yes	0.552 (0.366, 0.832)	0.005*
≥ 2 & < 3 cm	0.842 (0.484, 1.466)	0.544			
≥ 3cm	0.827 (0.519, 1.317)	0.424			
Lower ureter					
No	1				
Yes	1.267 (0.804, 1.997)	0.307			
Bladder cuff					
No	1				
Yes	1.376 (0.597, 3.174)	0.454			
Multiplicity					
No	1				
Yes	1.438 (0.961, 2.153)	0.077			
Synchronous bladder tumor					
No	1				
Previous Hx of bladder UC	2.338 (1.243, 4.395)	0.008			
Concurrent Bladder UC	2.408 (1.507, 3.849)	< 0.001*			
Post operation intravesical C/T instillation					
No	1				
Yes	1.455 (0.786, 2.693)	0.233			

design and that the surgical approaches were based on **surgeon's and patient's** preferences. Potential selection bias may have affected the oncologic outcomes in the different groups. In addition, large tumors and tumors extending to surrounding tissue on preoperative imaging may have led the surgeons to choose the open method. **Surgical volume and experience at each institution may influence the outcomes.** Another limitation is that the type of surgery performed may have differed according to the period of the study. For example, more ONU was performed in the earlier periods. In addition, the lymph node dissection template was not mentioned. Lastly, the laparoscopic group contained various surgical techniques, including hand-assisted, pure laparoscopic and laparoscopic nephroureterectomy with open bladder cuff excision.

Conclusion

In conclusion, our results demonstrated that minimally invasive surgery, including laparoscopic and robotic surgery, for locally advanced UTUC resulted in oncological outcomes that are non-inferior to those of open surgery. While robotic surgery was found to be comparable to laparoscopic surgery, it was able to achieve more complete lymph node dissection. Our findings suggest that minimally invasive surgery should be the preferred treatment approach for patients with locally advanced UTUC in Taiwan, as it offers excellent perioperative and oncological outcomes. We need further prospective research to confirm these findings.

Abbreviations

UTUC	Urinary tract urothelial carcinoma
ONU	Open nephroureterectomy
LNU	Laparoscopic nephroureterectomy
RNU	Robotic nephroureterectomy
OS	Overall survival
CSS	Cancer-specific survival
DFS	Disease-free survival

Acknowledgements

All members of the Taiwan Upper Tract Urothelial Carcinoma Collaboration group: Allen W. Chiu, Bing-Juin Chiang, Chao-Hsiang Chang, Chao-Yuan Huang, Cheng-Huang Shen, Cheng-Kuang Yang, Cheng-Ling Lee, Chen-Hsun Ho, Che-Wei Chang, Chia-Chang Wu, Chieh-Chun Liao, Chien-Hui Ou, Chih-Chen Hsu, Chih-Chin Yu, Chih-Hung Lin, Chih-Ming Lu, Chih-Yin Yeh, Ching-Chia Li, Chi-Ping Huang, Chi-Rei Yang, Chi-Wen Lo, Chuan-Shu Chen, Chung-Hsin Chen, Chung-You Tsai, Chung-Yu Lin, Chun-Hou Liao, Chun-Kai Hsu, Fang-Yu Ku, Hann-Chorng Kuo, Han-Yu Weng, Hao-Han Chang, Hong-Chiang Chang, Hsiao-Jen Chung, Hsin-Chih Yeh, Hsu-Che Huang, Ian-Seng Cheong, I-Hsuan Alan Chen, Jen-Kai Fang, Jen-Shu Tseng, Jen-Tai Lin, Jian-Hua Hong, Jih-Sheng Chen, Jungle Chi-Hsiang Wu, Kai-Jie Yu, Keng-Kok Tan, Kuan-Hsun Huang, Kun-Lin Hsieh, Lian-Ching Yu, Lun-Hsiang Yuan, Hao-Lun Luo, Marcelo Chen, Min-Hsin Yang, Pai-Yu Cheng, Po-Hung Lin, Richard Chen-Yu Wu, See-Tong Pang, Shin-Hong Chen, Shin-Mei Wong, Shiu-Dong Chung, Shi-Wei Huang, Shuo-Meng Wang, Shu-Yu, Wu, Steven Kuan-Hua Huang, Ta-Yao Tai, Thomas Y. Hsueh, Ting-En Tai, Victor Chia-Hsiang Lin, Wei-Chieh Chen, Wei-Ming Li, Wei-Yu Lin, Wen-Hsin Tseng, Wen-Jeng Wu, Wun-Rong Lin, Yao-Chou Tsai, Yen-Chuan Ou, Yeong-Chin Jou, Yeong-Shiau Pu, Yi-Chia Lin, Yi-Hsuan Wu, Yi-Huei Chang , Yi-sheng Lin, Yi-Sheng Tai, Yu-Khun Lee, Yuan-Hong Jiang, Yu-Che Hsieh, Yu-Chi Chen, Yu-Ching Wen, Yung-Tai Chen, Zhe-Rui Yang.

Author contributions

Chao-Hsiang Chang contributed to the study design. Hsin-Chih Yeh, Hsiang-Ying Lee, Han-Yu Weng, Ta-Yao Tai, Chao-Yuan Huang, Jian-Hua Hong, Chih-Chin Yu, Shu-Yu Wu, Shiu-Dong Chung, Chung-You Tsai, Thomas Y. Hsueh, Allen W. Chiu, Yuan-Hong Jiang, Yu Khun, Lee, I-Hsuan Alan Chen, Jen-Tai Lin, Yung-Tai Chen, Chang-Min Lin, Ian-Seng Cheong, Hsu-Che Huang, Shih-Hsiu Lo, Wei-Yu Lin, Jen-Shu Tseng, Chia-Chang Wu, Shian-Shiang Wang, conducted data collection and performed preliminary data preparations. Yi-Huei Chang conducted data analyses and contributed to the interpretation of data. Jen Kai Fang carried out the literature search, wrote the main manuscript text, prepared the figure and tables . All authors read and approved the final manuscript.

Funding

None applicable.

Data availability

All data is available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Approved by the Institutional Review Board of Taipei Tzu Chi Hospital (Protocol No. 06-X34-105). The need for informed consent to participate was waived by the Institutional Review Board of Taipei Tzu Chi Hospital because it is a retrospective chart review study. Personal identifiers were completely removed and data were analyzed anonymously.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Urology, China Medical University Hospital, China Medical university, Taichung, Taiwan
[2]Department of Urology, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan
[3]Department of Urology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[4]Department of Urology, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[5]Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[6]Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[7]Department of Urology, College of Medicine, National Cheng Kung University Hospital, National Cheng Kung University, Tainan, Taiwan
[8]Department of Urology, College of Medicine, National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan
[9]Institute of Biomedical Engineering, National Taiwan University, Taipei, Taiwan
[10]Division of Urology, Department of Surgery, Taipei Tzuchi Hospital, The Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan
[11]Department of Urology, School of Medicine, Buddhist Tzu Chi University, Hualien, Taiwan
[12]Sleep Research Center, Taipei Medical University Hospital, Taipei, Taiwan
[13]Division of Urology, Department of Surgery, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[14]Department of Electrical Engineering, Yuan Ze University, Taoyuan, Taiwan
[15]Division of Urology, Department of Surgery, Taipei City Hospital Renai Branch, Taipei, Taiwan
[16]Department of Urology, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[17]Division of Urology, Department of Surgery, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
[18]Department of Urology, Postal Hospital, Taipei, Taiwan
[19]Department of Urology, Taiwan Adventist Hospital, Taipei, Taiwan

[20]Department of Urology, Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi 600, Taiwan
[21]Division of Urology, Department of Surgery, Cardinal Tien Hospital, New Taipei City 23148, Taiwan
[22]Department of Life Science, College of Science, National Taiwan Normal University, Taipei 11677, Taiwan
[23]Department of Urology, Taipei Medical University Hospital, Taipei Medical University, Taipei City, Taiwan
[24]Division of Urology, Department of Surgery, Chang Gung Memorial Hospital, Chia-Yi, Taiwan
[25]Chang Gung University of Science and Technology, Chia-Yi, Taiwan
[26]Department of Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[27]Department of Urology, MacKay Memorial Hospital, Taipei, Taiwan
[28]Mackay Medical College, Taipei, Taiwan
[29]Institute of Biomedical Informatics, National Yang Ming Chiao Tung University, Taipei, Taiwan
[30]Department of Urology, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan
[31]Department of Urology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[32]TMU Research Center of Urology and Kidney (TMU-RCUK), Taipei Medical University, Taipei, Taiwan
[33]Division of Urology, Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan
[34]Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan
[35]Department of Applied Chemistry, National Chi Nan University, Nantou, Taiwan

Received: 11 March 2024 / Accepted: 8 October 2024
Published online: 21 October 2024

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