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원위부 요관의 요로상피암에 대한 개복 및 최소침습 신우요관절제술의 종양학적 결과 비교

Oncological Outcomes of

Open Versus Minimally Invasive Nephroureterectomy

for Urothelial Carcinoma of the Distal Ureter

울 산 대 학 교 대 학 원

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류 제 만

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이 논문을 의학석사 학위 논문으로 제출함

2017 년 12 월

울 산 대 학 교 대 학 원

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류제만의 의학석사학위 논문을 인준함

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Abstract

Purpose: We compared the oncological outcomes of patients with upper tract urothelial carcinoma who underwent open nephroureterectomy and minimally invasive nephroureterectomy after stratification by tumor location.

Materials and Methods: Among 514 patients who underwent radical nephroureterectomy for upper tract urothelial carcinoma at our institution from 1998 to 2012, patients with tumor confined in distal ureter and those with tumor confined in renal pelvis were included. We excluded patients with metastatic disease, pathologic T4 or node-positive tumor, previous or concomitant bladder tumor, and positive resection margin on pathologic examination. Ultimately, a total of 270 patients (distal ureteral tumor, n=100; renal pelvic tumor, n=170) were included in present study. Kaplan–Meier and Cox proportional regression analyses were used to evaluate survival data.

Results: There were more renal pelvic tumors in the minimally invasive nephroureterectomy group than the open nephroureterectomy group (70.3% vs. 53.0%, p=0.004), but clinicopathological characteristics did not differ significantly overall. More patients underwent lymph node dissection (48.7% vs. 20.0%, p<0.001) in the open nephroureterectomy group. In patients with distal ureteral tumors, 5-year intravesical recurrence-free survival (37.3% vs. 41.4%, p=0.242), extravesical recurrence-free survival (63.9% vs. 71.1%, p=0.606), and overall survival (66.1% vs. 73.8%, p=0.166) rates did not differ between the 2 groups. In patients with renal pelvic tumors, the 5-year intravesical recurrence-free survival rate was lower in the open nephroureterectomy group (45.1% vs. 69.4%, p=0.001). Five-year extravesical recurrence-free survival (89.1% vs. 87.0%, p=0.738) and overall survival (83.5% vs. 83.8%, p=0.256) rates were comparable. Multivariable Cox proportional regression analysis showed that surgical approach was a risk factor for intravesical recurrence in patients with renal pelvic tumors (hazard ratio 0.50, p=0.006) and overall mortality in those with distal ureteral tumors (hazard ratio 0.46, p=0.032).

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Conclusions: Minimally-invasive nephroureterectomy was not associated with poorer intravesical and extravesical recurrence-free survival or overall survival, even in patients with distal ureteral tumor.

Introduction

Radical nephroureterectomy (RNU) with bladder cuff excision has been the standard treatment of localized upper tract urothelial carcinoma (UTUC) due to the high recurrence rate of remnant ureter[1]. However, recurrence of various types of tumors can occur despite radical surgery. The rate of intravesical recurrence (IVR) after RNU has been found to be 15%–50%[2-6], and extravesical recurrence (EVR) has also been reported in up to 50% of UTUC patients within 5 years of RNU[7,8]. In addition, approximately 80% of UTUC patients with EVR die within 2 years[9].

In the past decade, we have seen a significant trend toward the utilization of minimally invasive approaches to RNU for the treatment of UTUC. Laparoscopic nephroureterectomy (LNU), first performed by Clayman et al. in 1991, has provided shorter hospitalizations, reduced blood loss, and less pain than open nephroureterectomy (ONU)[10]. Moreover, hand-assisted laparoscopic nephroureterectomy (HALNU) allows the surgeon to place a hand into the operative field, incorporating tactile sensation and three-dimensional orientation[11]. To date, several retrospective reports[10,12-23] and one prospective series[24] comparing oncological outcomes between ONU and minimally-invasive nephroureterectomy (MINU) have been reported, and none of these studies have shown that surgical approach has a significant impact on overall survival (OS) and cancer-specific survival (CSS). Only a few studies have reported a higher risk of IVR in patients who underwent MINU[18,25]. However, one issue with these studies is that entire cohorts of UTUC patients were included. One of the most controversial and challenging features of MINU is the technical management of the distal ureter[26], and ureteral tumors have been associated with a higher local or distant recurrence rate than that of renal pelvic tumors[27,28]. However, to the best our knowledge, no previous study has focused on the oncological outcomes of MINU in the subgroup of patients with distal ureteral tumors. We hypothesized that MINU in patients with tumors located within the distal ureter would be associated with an increased risk of IVR and EVR and poor overall survival compared with ONU. Hence, we investigated the impact of surgical approach on oncological outcomes in patients with distal ureteral tumors and assessed patients with renal pelvic tumors as a control group.

Materials and Methods

Patients

This study was approved by the institutional review board approval of our institution. A retrospective review of 514 patients who underwent RNU for UTUC at our institute from 1998 to 2012 was performed. Among them, only patients with tumors confined to the distal ureter (n=122) and those with tumors confined to the renal pelvis (n=210) on preoperative computerized tomography (CT) scan were included in this study. The distal ureter was defined as the ureter between the lower border of the sacrum and the bladder. Exclusion criteria were the distant metastasis at the time of surgery, pathological T4 or node-positive tumors, previous or concomitant bladder tumors, and positive resection margins on pathological examination. Ultimately, 270 patients (distal ureter, n=100; renal pelvis, n=170) were included in the present study.

Preoperative evaluations, including blood tests, urinalysis, urine cytology, cystoscopy, chest X-ray, CT scan, and/or bone scan were performed for each patient before RNU. In select patients, diagnostic ureteroscopy with biopsies was used to confirm tumor histology before RNU based on the clinician's assessment of the preoperative CT scan. No patients underwent neoadjuvant chemotherapy.

Surgical procedures

The choice of surgical approach between ONU, HALNU, and LNU was made based on the surgeon's or patient's preference, clinical stage, nodal status, and history of abdominal surgery. ONU and LNU were performed using the standard techniques, and bladder cuff excision was performed extravesically in all patients. Lymph node dissection was generally performed in patients with abnormal lymph node findings on preoperative CT scan or palpable lymph nodes at the time of surgery. The resection range of HALNU was the same as that of ONU and LNU. However, all HALNU surgical procedures, including bladder cuff excision, were performed under hand-assisted laparoscopy in contrast with LNU in which en bloc excision of the juxtavesical ureter and bladder cuff was performed with an open

technique using a camera port or Gibson incision. Surgical approaches were categorized into 2 groups: (1) ONU and (2) MINU (LNU and HALNU).

Clinicopathological evaluation

All surgical specimens were processed according to standard pathological procedures, and all slides were reviewed by genitourinary pathologists. Tumors were staged according to the 2002 American Joint Committee on Cancer TNM classification and graded according to the 1998 WHO/International Society of Urological Pathology consensus classification. Lymphovascular invasion was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls. The presence of concomitant carcinoma in situ was also assessed in every representative section. Patients' clinical characteristics, including age and sex, were extracted from medical charts. The body mass index (BMI) was defined as individual body weight divided by the square of the body height.

Follow-up regimen

Immediate postoperative intravesical chemotherapy was not performed in all patients. Surveillance cystoscopy and voided urine cytology were typically performed at least every 6 months for the first 5 years after nephroureterectomy and annually thereafter. Patients suspected of IVR underwent cystoscopic biopsy and/or subsequent transurethral resection of the bladder tumor if needed. We defined IVR as any pathologically confirmed urothelial carcinoma in the bladder on cystoscopic biopsy or transurethral resection of the bladder tumor. Chest radiography and abdominopelvic CT scan were also typically performed every 6 months for the first 2 years and annually thereafter. EVR was defined as any local recurrence or distant metastasis after surgery except IVR. Adjuvant chemotherapy and radiotherapy were generally recommended for patients with locally advanced disease, except for those who could not tolerate treatment or refused treatment.

Statistical analysis

Patients were divided into 2 groups according to the tumor location (distal ureter or renal pelvis). We compared the clinicopathological features of patients who underwent ONU and

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MINU in each group using Pearson's chi-squared test for categorical variables and Student's *t*-test for continuous variables. Quantitative data were expressed as means ± standard deviation, and qualitative data were expressed using a frequency table. Kaplan–Meier analysis and a log-rank test were performed to evaluate and compare the effect of surgical approach on IVR and EVR-free survival and OS rates in each group. Predictive factors of IVR and EVR-free survival and OS in patients with distal ureteral and renal pelvic tumors were also separately assessed using Cox's proportional hazards model. Factors with $p < 0.2$ in the univariate analysis were entered into the multivariate models. Statistical Package for Social Science for Windows Version 21 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. $p < 0.05$ was considered statistically significant.

Results

Among 270 patients, ONU and MINU were performed in 115 (42.6%) and 155 (57.4%) patients. The median follow-up duration after surgery was 67 and 58.4 months in the ONU and MINU groups, respectively. The mean age of all patients was 62.2 years, and 201 (74.4%) patients were men (Table 1). The tumor was located within the distal ureter in 100 (37.0%) patients and the renal pelvis in 170 (63.0%) patients. Although there were more patients with renal pelvic tumors in the MINU group than in the ONU group (70.3% vs. 53.0%, p=0.004), the clinical characteristics were not significantly different between the 2 groups. More patients underwent lymph node dissection during surgery in the ONU group than in the MINU group (48.7% vs. 20.0%, p<0.001). The UTUC pathological T stage was as follows: Ta or T1 disease in 146 (54.1%) patients, T2 disease in 43 (15.9%), and T3 disease in 81 (30.0%); 16 (5.9%), 133 (49.3%), and 120 (44.4%) patients had pathological grade 1, 2, and 3 tumors, respectively. No significant differences were observed in the pathological T stage and grade between the 2 groups. Carcinoma in situ was detected in 29 (10.7%) patients.

Table 1. Patient characteristics according to surgical approach

	Surgical approach			
	Total	ONU	MINU	p
Number of patients, n (%)	270 (100)	115 (42.6)	155 (57.4)	
Age, year, mean ± SD	62.2±10.6	61.8±11.0	62.6±10.2	0.103
Sex, n (%)				0.695
Male	201 (74.4)	87 (75.7)	114 (73.5)	
Female	69 (25.6)	28 (24.3)	41 (26.5)	
Body mass index, kg/m^2 ± SD	24.7±3.3	24.1±3.3	25.1±3.3	0.435
Side, n (%)				0.851
Right	125 (46.3)	54 (47.0)	71 (45.8)	
Left	145 (53.7)	61 (53.0)	84 (54.2)	
Tumor location, n (%)				0.004
Distal ureter	100 (37.0)	54 (47.0)	46 (29.7)	
Renal pelvis	170 (63.0)	61 (53.0)	109 (70.3)	
Lymph node dissection ,n (%)	87 (32.2)	56 (48.7)	31 (20.0)	<0.001
Pathologic T stage, n (%)				0.431
Ta or T1	146 (54.1)	67 (58.3)	79 (51.0)	
T2	43 (15.9)	18 (15.7)	25 (16.1)	
T3	81 (30.0)	30 (26.1)	51 (32.9)	
Tumor grade, n (%)				0.712
1	16 (5.9)	7 (6.1)	9 (5.8)	

2	133 (49.3)	60 (52.2)	73 (47.4)	
3	120 (44.4)	48 (41.7)	72 (46.8)	
Lymphovascular invasion, n (%)	49 (18.1)	26 (22.6)	23 (14.8)	0.101
Carcinoma in situ, n (%)	29 (10.7)	9 (7.8)	20 (12.9)	0.183
Adjuvant chemotherapy, n (%)	18 (6.7)	6 (5.2)	12 (7.7)	0.411
Adjuvant radiotherapy, n (%)	13 (4.8)	3 (2.6)	10 (6.5)	0.145
Follow-up duration, months, mean ± SD	62.4±32.9	66.6±35.6	59.2±30.5	0.340

ONU = open nephroureterectomy; MINU = minimally invasive nephroureterectomy; SD = standard deviation

When patients were stratified according to tumor location, a greater number of patients with carcinoma in situ underwent MINU than did those who underwent ONU (26.1% vs. 7.4%, p=0.011) among the patients with distal ureteral tumors (Table 2). However, there were no differences in age, BMI, pathological T stage, tumor grade, and presence of lymphovascular invasion in the patients with distal ureteral tumors according to surgical approach. Among the patients with renal pelvic tumors, more patients underwent lymph node dissection during surgery in the ONU group than in the MINU group (57.4% vs. 14.7%, p<0.001), but no other differences were observed.

IVR and EVR occurred in 120 (44.4%) and 51 (18.9%) patients, and 81 (30.0%) patients died during follow-up. In patients with distal ureteral tumors, there were no significant differences in 5-year IVR-free survival (ONU 37.3% vs. MINU 41.4%, p=0.242), EVR-free survival (63.9% vs. 71.1%, p=0.606), and OS (66.1% vs. 73.8%, p=0.166) rates according to surgical approach in the Kaplan–Meier analysis (Fig. 1). However, in patients with renal pelvic tumors, the 5-year IVR-free survival rate was lower in the ONU group than in the MINU group (45.1% vs. 69.4%, p=0.001), while the 5-year EVR-free survival (89.1% vs. 87.0%, p=0.738) and OS (83.5% vs. 83.8%, p=0.256) rates did not differ.

In patients with renal pelvic tumors, surgical approach (MINU vs. ONU, hazard ratio [HR] 0.50, p=0.006) and BMI (HR 0.90, p=0.015) were significant risk factors for IVR, although surgical approach was not associated with IVR in patients with distal ureteral tumors (Table 3). Risk factors for EVR in patients with distal ureteral tumors included pathological T stage (3 vs. ≤2, HR 2.83, p=0.015) and tumor grade (3 vs. ≤2, HR 3.97, p=0.041), whereas no significant risk factor for EVR was identified in the patients with renal pelvic tumors. A surgical approach (MINU vs. ONU, HR 0.46, p=0.032), carcinoma in situ (HR 2.66, p=0.020), and pathological T stage (3 vs. ≤2, HR 2.30, p=0.034) were also significant risk factors for overall mortality in patients with distal ureteral tumors. In patients with renal pelvic tumors, age (HR 1.06, p=0.001) and BMI (HR 0.88, p=0.013) were the only risk factors of overall mortality.

Table 2. Clinicopathological characteristics stratified by tumor location

	Distal ureter			Renal pelvis		
	ONU	MINU	p	ONU	MINU	p
Number of patients, n (%)	54 (54.0)	46 (46.0)		61 (35.9)	109 (64.1)	
Age, year, mean ± SD	62.5±9.1	63.9± 9.4	0.653	61.1±12.4	62.4±10.6	0.443
Sex, n (%)			0.437			0.719
Male	38 (70.4)	29 (63.0)		49 (80.3)	85(78.0)	
Female	16 (29.6)	17 (37.0)		12 (19.7)	24 (22.0)	
Body mass index, kg/m^2 ± SD	24.3±3.4	25.0±3.5	0.497	23.9±3.1	25.1±3.3	0.246
Side, n (%)			0.759			0.536
Right	23 (42.6)	21 (45.7)		31 (50.8)	50 (45.9)	
Left	31 (57.4)	25 (54.3)		30 (49.2)	59 (54.1)	
Lymph node dissection,,n (%)	21 (38.9)	15 (32.6)	0.514	35 (57.4)	16 (14.7)	<0.001
Pathologic T stage, n (%)			0.365			0.254
Ta or T1	29 (53.7)	19 (41.3)		38 (62.3)	60 (55.0)	
T2	7 (13.0)	10 (21.7)		11 (18.0)	15 (13.8)	
T3	18 (33.3)	17(37.0)		12 (19.7)	34 (31.2)	
Tumor grade, n (%)			0.219			0.584
1	3 (5.6)	4 (8.9)		4 (6.6)	5 (4.6)	
2	22 (40.7)	11 (24.4)		38 (62.3)	62 (56.9)	
3	29 (53.7)	30 (66.7)		19 (31.1)	42 (38.5)	
Lymphovascular invasion, n (%)	13 (24.1)	11 (23.9)	0.985	13 (21.3)	12 (11.0)	0.069
Carcinoma in situ, n (%)	4 (7.4)	12 (26.1)	0.011	5 (8.2)	8 (7.3)	0.840

Adjuvant chemotherapy, n (%)	5 (9.3)	7 (15.2)	0.361	1 (1.6)	5 (4.6)	0.422
Adjuvant radiotherapy, n (%)	2 (3.7)	6 (13.0)	0.138	1 (1.6)	4 (3.7)	0.655
Follow-up duration, months, mean ± SD	62.1±35.8	58.2±28.1	0.166	70.6±35.2	59.7±31.6	0.707

ONU = open nephroureterectomy; MINU = minimally invasive nephroureterectomy; SD = standard deviation

Fig. 1-1. Oncological outcomes according to surgical approach in patients with distal ureteral tumors. (A) Intravesical recurrence-free survival (p=0.242); (B) Extravesical recurrence-free survival (p=0.606); (C) Overall survival (p=0.166) (blue line, ONU; green line, MINU)
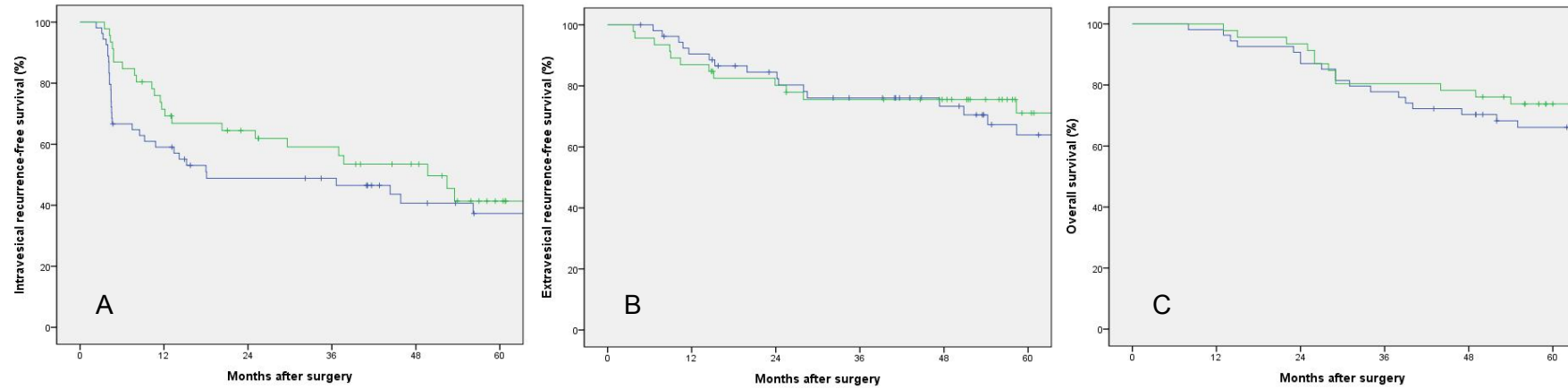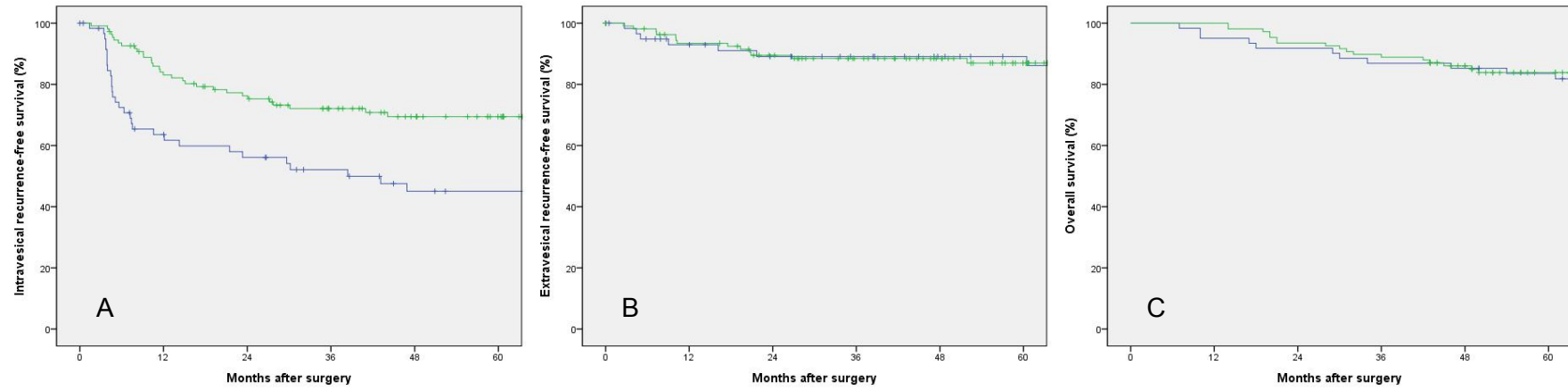

ONU = open nephroureterectomy; MINU = minimally invasive nephroureterectomy

Fig. 1-2. Oncological outcomes according to surgical approach in patients with renal pelvic tumors. (A) Intravesical recurrence-free survival (p=0.001); (B) Extravesical recurrence-free survival (p=0.738); (C) Overall survival (p=0.256) (blue line, ONU; green line, MINU)

ONU = open nephroureterectomy; MINU = minimally invasive nephroureterectomy

Table 3-1. Cox regression analysis of factors that influence the intravesical recurrence according to tumor location

	Distal ureter				Renal pelvis			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)		HR (95% CI)	p
Surgical approach (MINU vs. ONU)	0.73 (0.42-1.25)	0.245			0.43 (0.26-0.70)		0.50 (0.30-0.82)	0.006
Age (continuous)	0.99 (0.96-1.02)	0.319			1.02 (1.00-1.04)	0.114	1.01 (0.99-1.04)	0.270
Body mass index (continuous)	0.98 (0.91-1.06)	0.636			0.88 (0.81-0.95)	0.001	0.90 (0.83-0.98)	0.015
Lymph node dissection (yes vs. no)	0.83 (0.47-1.46)	0.517			1.07 (0.62-1.83)	0.812		
Lymphovascular invasion (yes vs. no)	1.36 (0.74-2.51)	0.318			1.32 (0.71-2.49)	0.382		
Carcinoma in situ (yes vs. no)	1.00 (0.47-2.12)	0.999			1.08 (0.43-2.69)	0.874		
Pathologic T stage (T3 vs. ≤T2)	1.27 (0.72-2.22)	0.414			0.62 (0.34-1.14)	0.125		
Tumor grade (3 vs. ≤2)	1.23 (0.71-2.14)	0.464			0.70 (0.41-1.21)	0.206	0.69 (0.37-1.29)	0.240

ONU = open nephroureterectomy; MINU = minimally invasive nephroureterectomy; HR = hazard ratio; CI = confidence interval

Table 3-2. Cox regression analysis of factors that influence the extravesical recurrence according to tumor location

	Distal ureter				Renal pelvis			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)		HR (95% CI)	p
Surgical approach (MINU vs. ONU)	0.82 (0.39-1.73)	0.607			0.86 (0.36-2.08)	0.738		
Age (continuous)	1.02(0.98-1.06)	0.327			1.04 (1.00-1.09)	0.047	1.04 (0.99-1.08)	0.110
Body mass index (continuous)	1.01 (0.91-1.12)	0.880			0.89 (0.77-1.02)	0.096	0.90 (0.78-1.04)	0.159
Lymph node dissection (yes vs. no)	1.00 (0.46-2.15)	0.994			1.07 (0.42-2.76)	0.888		
Lymphovascular invasion (yes vs. no)	1.64 (0.75-3.61)	0.218			1.86 (0.68-5.07)	0.228		
Carcinoma in situ (yes vs. no)	2.58 (1.14-5.85)	0.024	1.98 (0.85-4.59)	0.114	2.16 (0.64-7.34)	0.217		
Pathologic T stage (T3 vs. ≤T2)	4.87 (2.26-10.50)	<0.001	2.83 (1.23-6.52)	0.015	2.65 (1.13-6.24)	0.026	2.24 (0.94-5.33)	0.070
Tumor grade (3 vs. ≤2)	7.87 (2.38-26.05)	0.001	3.97 (1.06-14.84)	0.041	2.20 (0.93-5.18)	0.072	2.14 (0.89-5.16)	0.089

ONU = open nephroureterectomy; MINU = minimally invasive nephroureterectomy; HR = hazard ratio; CI = confidence interval

Table 3-3. Cox regression analysis of factors that influence the overall mortality according to tumor location

	Distal ureter				Renal pelvis			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)		HR (95% CI)	p
Surgical approach (MINU vs. ONU)	0.61 (0.31-1.23)	0.171	0.46 (0.22-0.94)	0.032	0.70 (0.37-1.30)	0.259		
Age (continuous)	1.02 (0.99-1.06)	0.206			1.07 (1.03-1.10)	<0.001	1.06 (1.02-1.09)	0.001
Body mass index (continuous)	0.98 (0.89-1.07)	0.605			0.86 (0.78-0.94)	0.001	0.88 (0.79-0.97)	0.013
Lymph node dissection (yes vs. no)	0.79 (0.39-1.60)	0.507			0.89 (0.47-1.69)	0.720		
Lymphovascular invasion (yes vs. no)	2.04 (1.03-4.04)	0.040	1.61 (0.78-3.31)	0.194	1.83 (0.90-3.69)	0.094	2.25 (1.00-5.04)	0.050
Carcinoma in situ (yes vs. no)	2.52 (1.16-5.51)	0.020	2.66 (1.16-6.08)	0.020	0.96 (0.30-3.11)	0.946		
Pathologic T stage (T3 vs. ≤T2)	3.62 (1.86-7.04)	<0.001	2.30 (1.07-4.97)	0.034	1.68 (0.90-3.14)	0.104	1.09 (0.54-2.21)	0.809
Tumor grade (3 vs. ≤2)	4.16 (1.78-9.69)	0.001	2.62 (1.00-6.89)	0.051	1.62 (0.89-2.94)	0.115	1.54 (0.81-2.90)	0.186

ONU = open nephroureterectomy; MINU = minimally invasive nephroureterectomy; HR = hazard ratio; CI = confidence interval

Discussion

In the present study, we evaluated the associations between surgical approach and oncological outcomes in patients with UTUC stratified by tumor location. We hypothesized that MINU would have a poorer IVR or EVR and a decreased OS rate in patients with distal ureteral tumors. To compare the efficacy of ONU and MINU in distal ureteral tumors, we included 100 patients with pathological T1-3/N0-x UTUC that was confined to the distal ureter, with 170 patients with renal pelvic tumors as a control group. In contrast to our hypothesis, we found that MINU had equivalent IVR and EVR-free survival rates compared with ONU in patients with distal ureteral tumors. Even in the OS analysis, patients who underwent MINU showed significantly better results compared with those who underwent ONU. Patients with renal pelvic tumors showed similar results, with equivalent EVR-free survival and OS rates and a significantly better IVR-free survival rate in the MINU group.

Reports of tumor implantation after laparoscopic procedures in patients with intra-abdominal malignancies are concerning. Upon manipulation of large tumors in a pneumoperitoneal environment, early experiences have reported retroperitoneal metastatic dissemination and dissemination along the trocar pathway. However, only 12 cases of port-side seeding during laparoscopy are reported to date[29]. Experimental and clinical studies of tumor seeding indicate that the gravitational migration of tumor cells and subsequent implantation in the bladder can occur due to tumor manipulation during MINU[16]. Furthermore, the high-pressure environment of laparoscopic procedures may lead to the spread of tumor cells[30]. It is well known that the rate of IVR after RNU can be up to 50%. However, the impact of surgical approach on these risks remains controversial.

In accordance with several previous comparative studies, we found that MINU was not associated with worse oncological outcomes compared with ONU[14,17,19,22,31,32]. After stratification according to tumor location, MINU also showed equivalent recurrence and survival rates, particularly for distal ureteral tumors. In one large, multicenter collaborative study, no difference was observed between patients who underwent ONU and LNU in terms of cancer-specific survival and recurrence-free survival[12]. Similarly, the long-term follow-up study also showed the oncological equivalence of LNU to ONU in terms of progression-free survival, cancer-specific survival, and OS[21]. The only randomized prospective study that compared ONU and LNU did not report any differences in IVR and survival between the 2

approaches, although it included a small sample size[24]. Although one study demonstrated a trend toward an independent association between LNU and poorer recurrence-free survival[15], the heterogeneity of cohorts, including lymph node metastasis, pathological T4 disease, and positive surgical margins represents a limitation that complicates comparison with the present study.

To our knowledge, our study is the first to compare the oncological outcomes of ONU and MINU according to tumor location. Some studies have shown the effect of tumor location on recurrence after RNU for UTUC. Our previous study reported that ureteral tumors are associated with local recurrence in the form of surgical bed recurrence[28]. A population-based analysis in the United States also showed that ureteral tumors were predictors of poor cancer-specific survival compared with renal pelvic tumors[33]. Moreover, because distal ureter dissection during MINU has proved technically challenging, especially in patients with distal ureteral tumors, various procedures to control distal ureter and bladder cuff excision have been suggested[34-36]. Based on those studies, we hypothesized poorer oncological outcomes in MINU than in ONU for distal ureteral tumors because of the difficulty of distal ureter dissection. Because bladder cuff excision was performed extravesically in all patients, including those who underwent ONU, we focused on the feasibility of MINU for distal ureter dissection. However, as mentioned above, our study showed oncological equivalence between ONU and MINU for patients with distal ureteral tumors, with a superior OS rate in patients who underwent MINU for distal ureteral tumors. These results support the feasibility of MINU for distal ureteral tumors.

Several risk factors for recurrence after nephroureterectomy were demonstrated including sex, BMI, pathological T stage, nodal metastasis, tumor grade, surgical margin, previous history of bladder tumor, concomitant carcinoma in situ, and tumor location[37-45]. However, the conclusions based on previous comparative studies between ONU and MINU are underpowered because of the heterogeneity of the cohorts. In our study, the factors predictive of oncological outcomes were included and analyzed, and patients with previous or concomitant bladder cancer at the time of RNU and those with pathological T4, node-positive disease, or positive resection margins on pathologic reports were excluded. Clinical and pathological characteristics, including factors predicting oncological outcomes, were similar between the ONU and MINU groups, thus preventing selection bias. Additionally, all

patients underwent extravesical bladder cuff excision, and the standardization of this approach precluded the presence of confounding factors when analyzing recurrence rates.

Among factors associated with the oncological outcomes found in this study, the results that a lower BMI was associated with poorer IVR-free survival and OS in patients with renal pelvic tumor are interesting. This finding is contrary to that stated in a recent study that a higher BMI was associated with worse recurrence-free, cancer-specific, and overall survival in patients treated with RNU for UTUC in United States[45]. Explanations for this discrepant finding are unclear but may include differences in the median BMI between Asians and Westerners. Actually, the median BMI of patients in this study was 24.6 kg/m2, which is much lower than that in a previous study in United States (median BMI : 27.9 kg/m2). Furthermore, the BMI of 30.4% of patients in the present study was less than 23 kg/m2, which is underweight and normal range in World Health Organization criteria for the Asia-Pacific population. We supposed that some of the cachexic patients accounted for this result, although further investigation of this result is warranted.

This study has several limitations including its retrospective design. The MINU group included patients who underwent either LNU or HALNU, as opposed to only one method. Nevertheless, the distal ureter dissection procedure was similar in both methods, and bladder cuff excision was always performed extravesically. Other limitations include possible selection bias, lack of control for comorbidity status, and lack of standardized follow-up. The low incidence of the disease would complicate the completion of a well-designed randomized trial.

Conclusions

MINU was not associated with poorer IVR and EVR-free survival or overall survival, even in patients with distal ureteral tumors. Further prospective evaluation according to surgical approach is warranted.

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국문 요약

서론 : 상부요로의 요로상피세포암 환자에서 종양의 위치를 계층화시킨 후 개복 신요관절제술 및 최소침습 신요관절제술의 종양학적 결과를 비교하였다.

연구대상 및 방법 : 1998 년부터 2012 년까지 본 기관에서 상부요로의 요로상피세포암으로 근치적 신요관절제술을 시행받은 514 명의 환자 중 원위부 요관 또는 신우에 종양이 국한된 환자들을 대상으로 하였다. 원격전이가 동반된 환자, 병리학적 T4 또는 림프절 전이가 있는 환자, 수술 전 또는 수술 당시 방광암이 동반된 환자, 병리검사 결과 절제면 양성인 환자는 제외하였다. 결과적으로 270 명의 환자 (원위부 요관, n = 100; 신우, n = 170)가 이번 연구에 포함되었다. 생존 자료를 분석하기 위해 Kaplan-Meier 생존분석 및 Cox 회귀분석이 사용되었다.

결과 : 개복수술군보다 최소침습수술군에서 신우암 환자의 비율이 높았으나 (53.0% vs. 70.3%, p=0.004), 양 군간에 임상적 및 병리학적 특성에는 유의한 차이가 없었다. 최소침습수술군에 비해 개복수술군에서 더 많은 환자가 수술 시 림프절 절제술을 시행받았다 (20.0% vs. 48.7%, p<0.001). 원위부 요관암 환자에서 개복수술군 및 최소침습수술군 간에 5 년 방광내 무재발 생존율 (37.3% vs. 41.4%, p=0.242), 방광외 무재발 생존율 (63.9% vs. 71.1%, p=0.606), 전체 생존율 (66.1% vs. 73.8%, p=0.166)에 유의한 차이가 없었다. 하지만 신우암 환자에서는 개복수술군에서 최소침습수술군에 비해 5 년 방광내 무재발 생존율이 낮았으며 (45.1% vs. 69.4%, p=0.001), 방광외 무재발 생존율 (89.1% vs. 87.0%, p=0.738)과 전체 생존율 (83.5% vs. 83.8%, p=0.256)은 유의한 차이가 없었다. Cox 회귀 분석 결과 수술방법은 신우암 환자에서는 방광내 재발의 예측 인자로 나타났으며 (최소침습수술군 vs. 개복수술군, 위험비 0.50, p=0.006), 원위부 요관암 환자에서는 전체 사망률의 예측 인자로 나타났다 (최소침습수술군 vs. 개복수술, 위험비 0.46, p=0.032).

결론 : 상부요로의 요로상피세포암 환자 중 원위부 요관에 암이 국한된 경우에도 최소침습 신요관절제술은 개복 수술에 비해 방광내 및 방광외 무재발 생존율, 전체 생존율에서 더 불량한 결과를 보이지 않았다.

중심 단어 : 요로상피세포암, 신요관절제술, 생존율