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Impact of adjuvant chemotherapy on oncologic outcomes following radical nephroureterectomy for patients with pT3NanyM0 upper tract urothelial carcinoma: A retrospective cohort study

Wan Song[a], Jae Yong Jeong[b], Hwang Gyun Jeon[c], Seong Il Seo[c], Seong Soo Jeon[c], Han Yong Choi[b], Hyun Moo Lee[c], Hyun Hwan Sung[c,*]

[a] Department of Urology, Ewha Womans University School of Medicine, Seoul, South Korea
[b] Department of Urology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea
[c] Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

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ABSTRACT

Objective: We investigated the impact of cisplatin-based adjuvant chemotherapy (AC) on oncologic outcomes including recurrence-free survival (RFS), cancer-specific survival (CSS) and overall survival (OS) after radical nephroureterectomy (RNU) for patients with pT3NanyM0 upper tract urothelial carcinoma (UTUC).

Methods: We retrospectively reviewed 293 patients who underwent RNU for UTUC between 1995 and 2017. Clinicopathologic characteristics of patients were examined and compared according to the use of AC. Kaplan-Meier survival analysis was used to illustrate RFS, CSS and OS. Cox proportional hazard models were applied to identify factors predicting oncologic outcomes.

Results: Among the 293 total patients, 127 (43.3%) patients received AC. During a mean follow-up of 59.7 months, recurrence and/or distant metastasis were identified in 124 (42.3%) patients, and 106 (36.2%) patients died overall, of which 93 (31.7%) died from UTUC. The 5-year RFS, CSS and OS rates of overall patients were 51.3%, 68.0% and 64.7%, respectively. In multivariate analysis, AC was inversely associated with tumor recurrence (HR = 0.74, $P = 0.028$) but not significantly associated with death from UTUC ($P = 0.237$) and death from all-cause ($P = 0.433$). The 5-year RFS of patients who had received AC was 58.0%, while 44.0% for patients who had only been observed after RNU.

Conclusion: AC improved RFS, but did not have a significant effect on CSS and OS in patients with pT3NanyM0 UTUCs following RNU. Further efforts are needed to identify reliable criteria in the clinic for patients that would benefit from AC.

1. Introduction

Upper tract urothelial carcinomas (UTUCs) are uncommon in that they only account for 5–10% of all urothelial malignancies [1,2]. Radical nephroureterectomy (RNU) with bladder cuff excision is the therapeutic standard of care for the vast majority of UTUCs, regardless of tumor location [3]. However, despite the development of imaging modalities, approximately 35% of patients are diagnosed with pathologic T3 (pT3) or greater and/or lymph node (LN) involvement after RNU due to the aggressive characteristics of UTUC and/or deferred diagnosis [4,5]. As a result, it has been reported that 5-year cancer-specific survival (CSS) is less than 45% in patients with ≥ pT3 [6] and 35% in patients with positive LN involvement even after surgical intervention [7]. Consequently, RNU alone is not sufficient and multimodal treatment strategies, including chemotherapy, are required.

Over the past decade, several studies [8–10] have examined the benefit of perioperative chemotherapy on improving the oncologic outcomes of patients with locally advanced UTUCs. However, there is no clear recommendation on the use of perioperative chemotherapy in the treatment of locally advanced UTUCs. The UTUCs are generally chemo sensitive but the most frequent adverse effect of cisplatin-based regimen is inherent nephrotoxicity [11]. Therefore, neoadjuvant chemotherapy has the advantage of being able to perform treatment in better renal function state but there is concern for selection bias and/or overtreatment due to the lack of definitive pathologic results preoperatively. On the other hand, despite a decline in renal function,

* Corresponding author. Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, 135-710, South Korea.
E-mail address: hyunhwan.sung@samsung.com (H.H. Sung).

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adjuvant chemotherapy (AC) following RNU could be performed based on pathologic risk stratification and thus more precisely predict the efficacy of AC in patients with locally advanced UTUCs. However, conflicting results have been reported for oncologic outcomes, which include recurrence-free survival (RFS), CSS, and overall survival (OS) of AC [8,12–14].

The appropriate selection of patients could increase efficacy and reduce unnecessary adverse effects of AC. Therefore, the aim of this study is to investigate the impact of cisplatin-based AC on oncologic outcomes after RNU in patients with pT3NanyM0 UTUCs.

2. Materials and methods

2.1. Study population

This study was approved by the institutional review boards of our institution. The need for informed consent was waived due to the retrospective study design. We retrospectively reviewed a prospectively maintained database of 820 patients who underwent RNU for UTUC between February 1995 and May 2015 at a single institution by 8 surgeons. Of the 820 patients, we excluded patients who previously underwent radical cystectomy (n = 52), had bilateral UTUCs (n = 25), and were pathologically diagnosed with pTa (n = 109), pTis (n = 12), pT1 (n = 179), pT2 (n = 131), or pT4 (n = 10) UTUCs. In addition, 9 patients who received less than 3 cycles of AC were also excluded. Ultimately, 293 patients with pT3NanyM0 UTUC following RNU were analyzed in this study (Fig. 1). RNU included a radical nephrectomy and the entire removal of the ureter with a cuff of bladder. LN dissection was performed for possible cancerous lesions on radiologic images preoperatively, or for suspected, enlarged LNs intraoperatively. No patients had evidence of distant metastasis at the time of surgery or had a history of neoadjuvant chemotherapy and/or radiotherapy.

This study was registered (UIN: researchregistry4575) and has been reported in line with the strengthening the reporting of cohort studies in surgery (STROCSS) criteria [15].

2.2. Data collection

Clinicopathologic characteristics of patients, including age at surgery, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, operation side, tumor location and multifocality, surgical approach and type, tumor size and grade, presence of micropapillary urothelial carcinoma (MPUC), surgical margin status, LN involvement, concomitant *carcinoma in situ* (CIS), and lymphovascular invasion (LVI) were obtained from the medical charts at the time of surgery. Pathologic staging and grading were determined according to the 2010 TNM classification from the American Joint Committee on Cancer (AJCC) and 2004 World Health Organization (WHO)/International Society of Urologic Pathology consensus classification.

In general, after RNU, patients were scheduled for a follow-up at 1 month postoperatively and then every 3 months for 2 years, every 6 months for 3 years, and annually thereafter. During the follow-up, physical examinations with laboratory tests, urine analysis with urine cytology, chest radiography, cystoscopy, and radiologic evaluation, which included computed tomography (CT) and/or bone scan, were performed at every visit to identify local recurrence and/or distant metastasis. AC was performed approximately 1 month after RNU, and the three to six courses of combined gemcitabine/cisplatin (GC) regimen (1000 mg/m^2 gemcitabine on days 1, 8, and 15 and 70 mg/m^2 cisplatin on day 2) was used every 4 weeks. AC was performed in consideration of pathologic characteristics, surgeons` and patients` preference to AC or renal function. RFS was defined as time from RNU to local recurrence and included the surgery site, reginal LNs, and/or distant metastasis. Recurrence in the bladder or contralateral upper tract was not considered in the analysis of RFS. The CSS and OS were defined as time from RNU to final follow-up or death due to UTUC and death due to any cause, respectively.

2.3. Statistical analysis

Descriptive analyses were used to compare clinical and pathological characteristics of patients who had or had not received AC. Means and standard deviation (SD) were reported for continuous variables and categorical variables were presented as absolute values and percentages. An independent *t*-test was used to compare the continuous variables and Pearson's chi-square test or Fisher's exact test was used to compare categorical clinicopathologic characteristics. The influence of AC on oncologic outcomes was analyzed using a Kaplan-Meier survival analysis, and differences were assessed with a log-rank test.

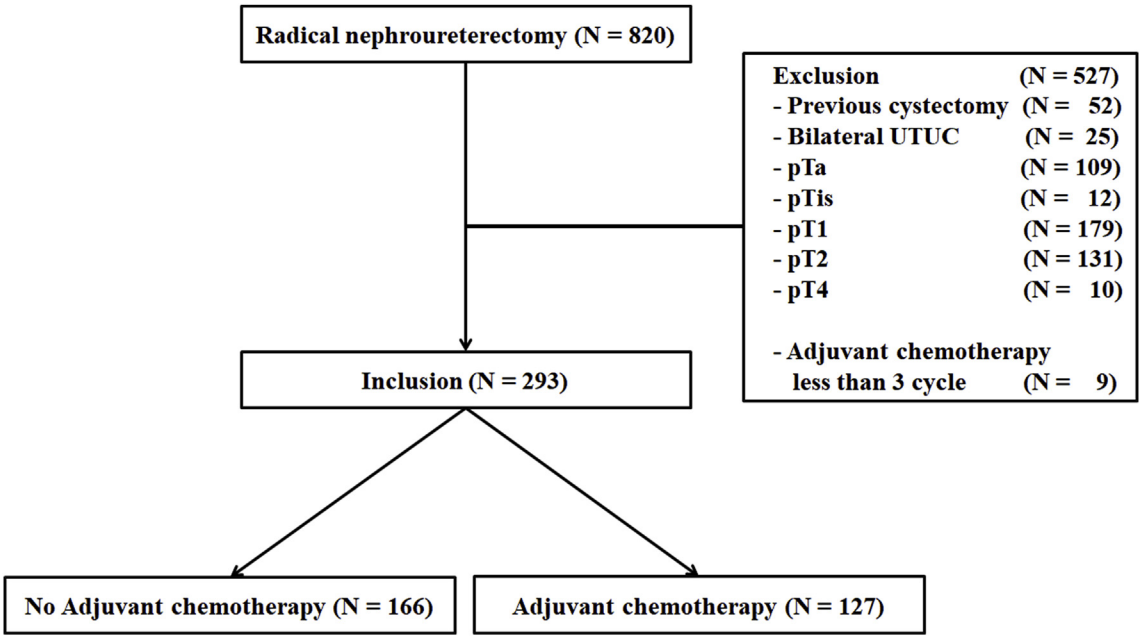

Fig. 1. Study flow diagram.

Table 1
Baseline clinicopathologic characteristics.

Variables	Total	Adjuvant chemotherapy		*P*
		No	Yes	
No. of patients, n (%)	293 (100.0)	166 (56.7)	127 (43.3)	
Age at surgery, years	64.3 ± 10.6	65.9 ± 11.9	62.2 ± 8.2	0.002
Sex, n (%)				0.298
Male	210 (71.7)	115 (69.3)	95 (74.8)	
Female	83 (28.3)	51 (30.7)	32 (25.2)	
Body mass index, kg/m^2	24.0 ± 3.2	23.9 ± 3.5	24.1 ± 2.8	0.462
Hospital stay, day	9.3 ± 3.4	9.3 ± 3.6	9.4 ± 3.0	0.725
ASA score, n (%)				0.221
1	86 (29.4)	44 (26.5)	42 (33.1)	
2-3	207 (70.6)	122 (73.5)	85 (66.9)	
Laterality, n (%)				0.203
Right	137 (46.8)	83 (50.0)	54 (42.5)	
Left	156 (53.2)	83 (50.0)	73 (57.5)	
Location, n (%)				0.117
Renal pelvis	163 (55.7)	102 (61.4)	61 (48.0)	
Ureter	91 (31.0)	44 (26.5)	47 (37.0)	
Both	39 (13.3)	20 (12.1)	19 (15.0)	
Multifocality, n (%)				0.663
No	216 (73.7)	124 (74.7)	92 (72.4)	
Yes	77 (26.3)	42 (25.3)	35 (27.6)	
Approach, n (%)				0.530
Transperitoneal	196 (66.9)	116 (69.9)	80 (63.0)	
Retroperitoneal	97 (33.1)	50 (30.1)	47 (37.0)	
Operation type, n (%)				0.098
Open	115 (39.2)	72 (43.4)	43 (33.9)	
Laparoscopic	178 (60.8)	94 (56.6)	84 (66.1)	
Bladder cuffing, n (%)				0.804
Intravesical	157 (53.6)	90 (54.2)	67 (52.8)	
Extravesical	136 (46.4)	76 (45.8)	60 (47.2)	
Grade[a], n (%)				0.138
1-2	99 (34.0)	60 (36.1)	39 (30.7)	
3	192 (66.0)	104 (62.7)	88 (69.3)	
Concomitant CIS, n (%)				0.597
No	266 (90.8)	152 (91.6)	114 (89.8)	
Yes	27 (9.2)	14 (8.4)	13 (10.2)	
Pathologic N+, n (%)				0.014
No	242 (82.6)	145 (87.3)	97 (76.4)	
Yes	51 (17.4)	21 (12.7)	30 (23.6)	
Tumor size, mm	4.8 ± 3.2	4.9 ± 3.6	4.6 ± 2.6	0.460
Surgical margin, n (%)				0.923
Negative	275 (93.9)	156 (94.0)	119 (93.7)	
Positive	18 (6.1)	10 (6.0)	8 (6.3)	
MPUC, n (%)				0.046[b]
No	287 (98.0)	165 (99.4)	122 (96.1)	
Yes	6 (2.0)	1 (0.6)	5 (3.9)	
Lymphovascular invasion, n (%)				0.031
No	204 (69.6)	124 (74.7)	80 (63.0)	
Yes	89 (30.4)	42 (25.3)	47 (37.0)	
Post-RNU eGFR, ml/min/1.73m^2	54.7 ± 14.9	53.6 ± 16.3	56.0 ± 12.8	0.158
Clinical progression, n (%)				0.512
No	169 (57.7)	93 (56.0)	76 (59.8)	
Yes	124 (42.3)	73 (44.0)	51 (40.2)	
Death, n (%)				0.470
Overall	106 (36.2)	63 (38.0)	43 (33.9)	
Due to UTUC	93 (31.7)	56 (33.7)	37 (29.1)	
Follow up, month	59.7 ± 52.5	62.7 ± 57.5	55.9 ± 45.1	0.261

ASA, American Society of Anesthesiologists; CIS, *carcinoma in situ*; MPUC, micropapillary urothelial cancer; RNU, radical nephroureterectomy; eGFR, estimated glomerular filtration rate; UTUC, upper tract urothelial cancer.

[a] n = 291.

[b] Fisher's exact test.

Multivariate Cox proportional hazard models were used to identify predictive factors associated with RFS, CSS, and OS after RNU. All statistical analyses were performed using IBM SPSS statistics for Windows, version 23.0 (IBM Corp. Armonk, NY, USA). Two-sided *P* values < 0.05 were considered statistically significant.

3. Results

The baseline clinicopathological characteristics of 293 patients who underwent RNU for UTUC and were diagnosed with pT3NanyM0 are summarized in Table 1. Among the 293 total patients, mean (SD) age was 64.3 (10.6) years and 210 (71.7%) patients were male. Mean (SD) tumor size was 4.8 (3.2) mm and, in about two-thirds of patients, the tumor was located in the renal pelvis. AC was administered to 127 (43.3%) patients. When patients were divided into two groups depending on AC (no versus yes), significant differences were noted for age (65.9 vs. 62.2 years), positive LN involvement (12.7% vs. 23.6%), MPUC (0.6% vs. 3.9%), and LVI (25.3% vs. 37.0%) (each $P < 0.05$). However, no significant differences were noted for sex, BMI, ASA score, tumor side, location and multifocality, surgical type and approach, type of bladder cuffing, tumor size and grade, concomitant CIS, surgical margin status and contralateral renal function.

During a mean follow-up of 59.7 months, local recurrence and/or distant metastasis were identified in 124 (42.3%) patients and 106 (36.2%) patients died overall, of which 93 (31.7%) died from UTUC. The 5-year RFS, CSS and OS rates of overall patients were 51.3%, 68.0% and 64.7%, respectively. Fig. 2 shows the survival outcomes of patient using the Kaplan-Meier estimation method. When stratified according to AC, there was a significant difference in RFS ($P = 0.021$) but not in CSS and OS ($P = 0.461$ and $P = 0.699$, respectively). The 5-year RFS of patients who had received AC was 58.0%, while 44.0% for patients who had only been observed after RNU.

Of the 127 patients who received AC, the median number of cycle was 4 (range 3–6). When patients were divided into two groups according to the number of AC cycles (3 Vs. 4–6) there was no significant difference in RFS ($P = 0.212$, Fig. 3).

The outcomes of Cox proportional hazard regression analysis on the prognostic factors for tumor recurrence, death from UTUC, and death from all-cause after RNU are presented in Table 2. Multivariate Cox regression analyses revealed that tumor grade 3 (hazard ratio [HR] = 1.76, $P = 0.015$), positive LN involvement (HR = 2.27, $P = 0.001$), and LVI (HR = 1.67, $P = 0.013$) were independently associated with a significantly increased risk of tumor recurrence. Positive LN involvement was a significant risk factor for death from UTUC (HR = 1.87, $P = 0.019$). Age (HR = 1.02, $P = 0.040$) and positive LN involvement (HR = 1.86, $P = 0.014$) were independent predictive factors for all-cause death. AC was inversely associated with tumor recurrence (HR = 0.74, $P = 0.028$) but was not significantly associated with death from UTUC ($P = 0.237$) and death from all-cause ($P = 0.433$).

4. Discussion

Locally advanced UTUCs showed a high chance of recurrence and poor oncologic prognosis and hence it is reasonable to consider perioperative chemotherapy to improve oncologic outcomes. However, results of bladder cancer treatment could not always be extrapolated to those of UTUCs because of phenotypic and genotypic differences between the two cancers [16,17]. In addition, due to the low incidence of UTUC, there have been no large, randomized controlled clinical trials that evaluate the efficacy of perioperative chemotherapy. Collectively, substantial uncertainties persist as to when (neoadjuvant vs. adjuvant), which regimen (cisplatin based vs. others), and to whom perioperative chemotherapy should be given in patients with locally advanced UTUCs.

Therefore, we retrospectively identified 293 patients with pT3NanyM0 UTUCs following RNU and evaluated the efficacy of cisplatin-based AC in terms of oncologic outcomes, which included RFS, CSS, and OS. Our results showed that AC was significantly associated with improved RFS but not CSS and OS in these patient groups. To the best of our knowledge, this is the largest study performed at a single institution to analyze the impact of AC on survival in this particular

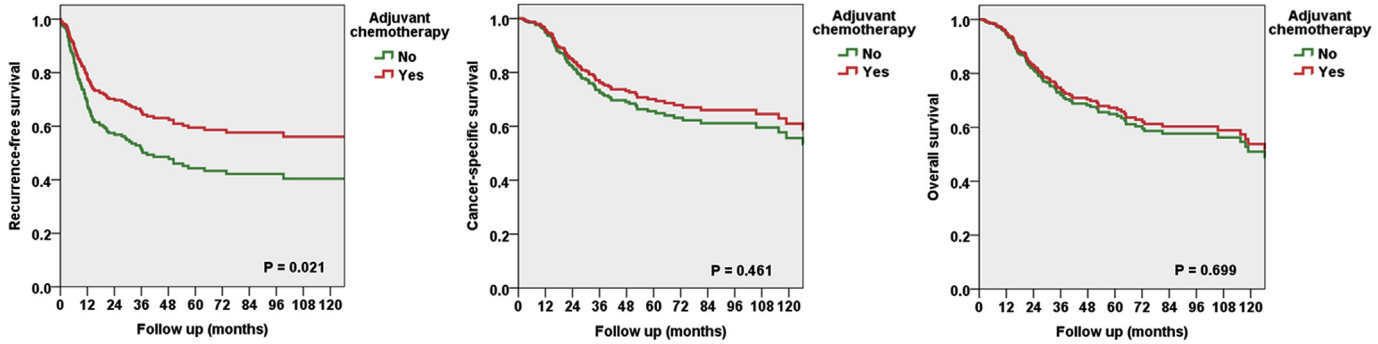

Fig. 2. Kaplan-Meier analyses for (A) recurrence-free survival, (B) cancer-specific survival, and (C) overall survival according to adjuvant chemotherapy for patients with. pT3NanyM0 upper tract urothelial carcinoma following radical nephroureterectomy.

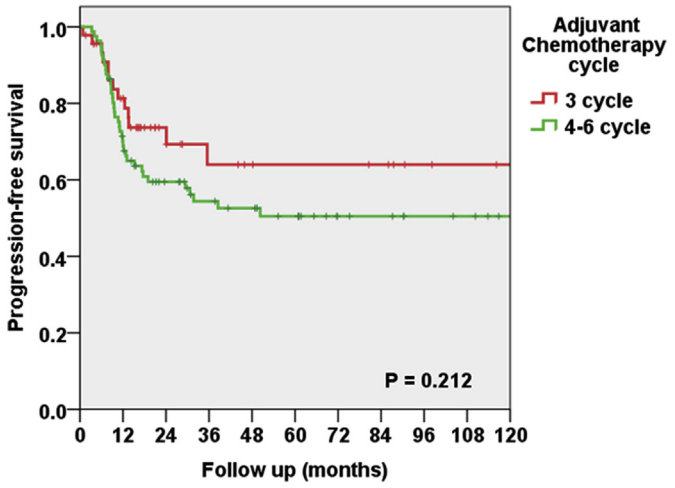

Fig. 3. Kaplan-Meier analysis for recurrence-free survival according to the number of adjuvant chemotherapy cycles.

patient group.

UTUCs are relatively chemo sensitive and cisplatin-based AC could provide improved RFS by killing microscopic residual cancer cells [14]. However, removal of residual cancer cells does not always lead to an increase in CSS and OS. Furthermore, CSS and OS are presumably influenced by several clinicopathological factors [14]. Therefore, recently published studies [8,13,18–20] that examined the role of AC in locally advanced UTUCs have reported contradictory results.

In a recent systematic review study [8], three studies [21–23] on cisplatin-based AC were included for meta-analysis and the pooled hazard ratio for OS compared with those who underwent RNU only was 0.43 (95% CI 0.21–0.89, $P = 0.023$). In addition, to compensate for the limitations in the previous study, for example selection bias and a relatively small sample size, Seisen T et al. [13] retrospectively analyzed 3253 patients and used an inverse probability of treatment weighting (IPTW)-adjusted Kaplan-Meier curve to compare OS of patients with pT3/T4 and/or pN + UTUCs who had received AC (N = 762, 23.4%) or had only been observed (N = 2,491, 76.6%) after RNU. They reported that the median OS of patients who had received AC was significantly longer than the median OS of patients who had only been observed after RNU (47.4 vs. 35.8 months, $P < 0.001$) [13].

On the other hand, in a study from Yafi FA et al. [19], the authors had retrospectively identified 1029 patients across 10 Canadian academic centers who had received RNU. Of the 312 patients with ≥pT3 and/or pTxN+, only 19% of patients with an estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m^2 had received AC. However, AC was not significant prognostic factor for CSS ($P = 0.963$) and OS ($P = 0.836$). In addition, results from an international collaborative database of 542 patients with pT3/T4 and/or positive LN involvement had indicated that AC confers minimal impact on CSS ($P = 0.129$) and OS ($P = 0.687$) [20]. Furthermore, a joint study by the European Association of Urology-Young Academic Urologists (EAU-YAU) and the UTUC Collaboration group had identified 1544 patients with ≥pT2 and/or pN1-3 and reported that AC did not improve OS after RNU when compared to observation alone ($P = 0.268$) [18].

In a study from Vassilakopoulou M et al. [24], the authors had suggested possible explanations for the minimal impact of AC on survival outcomes observed in patients with high-risk UTUCs. They had proposed that these patients already have limited expectancy of survival, and AC-related toxicity, in particular nephrotoxicity, in patients with already impaired renal function after RNU may be associated with reduced survival in these patients.

In our study, positive LN involvement was significantly associated with increased risk of tumor recurrence, death from UTUC, and death from all-cause. However, when sub-group analysis was performed in patients with positive LN, AC showed minimal impact on RFS ($P = 0.496$), CSS ($P = 0.757$), and OS ($P = 0.588$).

Current studies [10,20,25] on the role of AC in patients with LN-positive UTUCs have also reported inconsistent findings. In a study by Fujita K et al. [25], they retrospectively reviewed 74 LN-positive UTUCs patients and reported that the estimated 5-year CSS was 42.5% in patients with RNU plus AC, but 12.0% in patients with RNU alone (HR = 0.36, $P = 0.0003$). In addition, a recent study analyzed 263 patients with LN-positive UTUCs and reported that AC had no significant impact on CSS in all LN-positive UTUCs patients ($P = 0.49$) but, in patients with pT3-4 disease, AC decreased CSS by 34% ($P = 0.019$) that the absolute difference of CSS after 1-year and 5-years were 10% and 23%, respectively [10]. However, Hellental et al. [20] had reported no benefit of AC on CSS (HR = 0.85, $P = 0.516$) and OS (HR = 0.80, $P = 0.353$) in a sub-group analysis of 127 patients with LN-positive UTUC.

There are several potential explanations for the conflicting findings of these studies. First, since pathologic tumor stage is one of the major prognostic factors in patients with UTUCs [26], the impact of AC in patients with LN-positive UTUCs could be affected by the pathologic tumor stage. Second, since surgical procedure were not standardized for the anatomical templates of LN dissection, the adequacy of LN dissection was not verified, thereby there is a chance that positive LNs were missed and that may have affected the clinical outcome.

Recently, the phase III POUT trial [27] reported that adjuvant platinum-based chemotherapy improved disease-free survival (DFS) in patients with pT2-4N0-3M0 UTUCs. In this randomized trial, 248 patients (123 surveillance, and 125 chemotherapy) were recruited between May 2012 and Sep 2017. The 2-year DFS was 51% for surveillance and 70% for chemotherapy, respectively. Metastasis-free survival favored chemotherapy (HR = 0.49, $P = 0.003$) that the trial was terminated early due to efficacy favoring the chemotherapy arm. The follow-up data for overall survival is still ongoing.

This study has several limitations to consider. First, the

Table 2
Multivariate Cox proportional hazard regression analyses to predict postoperative tumor recurrence, death from upper tract urothelial carcinoma, and death from all-cause after radical nephroureterectomy.

Variables	Tumor recurrence			Death from UTUC			Death from all-cause		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age[a]	1.01	0.99–1.03	0.203	1.02	0.99–1.04	0.197	1.02	1.00–1.05	0.040
ASA									
1	ref			ref			ref		
2-3	0.85	0.57–1.28	0.434	1.19	0.71–1.97	0.510	1.03	0.64–1.64	0.912
Ureter involvement									
No	ref			ref			ref		
Yes	1.27	0.85–1.90	0.239	1.24	0.78–1.97	0.373	1.17	0.76–1.81	0.478
Multifocality									
No	ref			ref			ref		
Yes	1.29	0.86–1.93	0.215	1.30	0.81–2.07	0.274	1.31	0.85–2.03	0.227
Grade									
1-2	ref			ref			ref		
3	1.76	1.12–2.78	0.015	1.40	0.84–2.33	0.193	1.36	0.85–2.17	0.203
Pathologic N+									
No	ref			ref			ref		
Yes	2.27	1.46–3.52	0.001	1.87	1.11–3.16	0.019	1.86	1.13–3.06	0.014
Surgical margin									
No	ref			ref			ref		
Yes	1.37	0.69–2.75	0.369	1.63	0.77–3.43	0.202	1.68	0.83–3.40	0.152
MPUC									
No	ref			ref			ref		
Yes	1.86	0.77–4.48	0.169	2.38	0.90–6.32	0.081	2.27	0.86–5.97	0.096
LVI									
No	ref			ref			ref		
Yes	1.67	1.11–2.50	0.013	1.41	0.87–2.30	0.167	1.34	0.85–2.11	0.216
Post-RNU eGFR[a]	0.99	0.98–1.01	0.554	0.99	0.98–1.01	0.370	0.99	0.98–1.01	0.388
Adjuvant chemotherapy									
No	ref			ref			ref		
Yes	0.74	0.54–0.94	0.028	0.76	0.48–1.20	0.237	0.84	0.56–1.29	0.433

UTUC, upper tract urothelial cancer; HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; MPUC, micropapillary urothelial cancer; LVI, lymphovascular invasion; RNU, radical nephroureterectomy; eGFR, estimated glomerular filtration rate.
[a] Continuous variable.

retrospective, non-randomized study design performed at a single institution may have introduced inherent selection bias with unequal distribution of clinicopathologic variables. In particular, patients who received AC were younger and had a higher rate of positive LN and/or LVI, which required additional treatment following RNU. Therefore, to adjust for the effects of potential confounders, we performed multivariate analysis using Cox proportional hazard models to identify the efficacy of AC on survival outcomes. Second, multiple factors that may influence survival outcomes, such as treatment-related toxicities were not considered. These methodologic limitations and interpretational bias could not be avoided, which may underestimate the results of our study. Thus, a well-controlled, large, prospective validation study is required to corroborate the findings reported here.

5. Conclusion

Our study indicated that AC improved RFS but did not have a significant effect on CSS and OS in patients with pT3NanyM0 UTUCs following RNU. The limited efficacy of AC in locally advanced UTUCs observed in this retrospective study requires additional verification through prospective, randomized clinical trials. Further efforts are needed to identify reliable criteria in the clinic for patients that would benefit from AC.

Ethical approval

This study was approved by the Institutional Review Board of Samsung Medical Center, Seoul, Korea.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Sources of funding

No funding.

Author contribution

Study design: Wan Song, Hyun Hwan Sung.
Data collection: Wan Song, Jae Yong Jeong.
Data analysis: Wan Song, Jae Yong Jeong, Hyun Hwan Sung.
Writing: Wan Song.
Critical revision of the manuscript: Hwang Gyun Jeon, Seong Il Seo, Seong Soo Jeon, Han Yong Choi, Hyun Moo Lee.
Statistical analysis: Wan Song, Hyun Hwan Sung.
Supervision: Hyun Hwan Sung.

Research registration number

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Guarantor

Hyun Hwan Sung, M.D., PhD.
Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135–710, Korea.
Tel: +82-2-3410-3558; Fax: +82-2-3410-3027.
E-mail: hyunhwan.sung@samsung.com.

Data statement

Due to the sensitive nature of the questions asked in this study, survey respondents were assured that raw data would remain confidential and would not be shared.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Appendix A. Supplementary data

Supplementary data to this chapter can be found online at https://doi.org/10.1016/j.ijsu.2019.04.013.

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