Adjuvant chemotherapy vs. observation for locally advanced upper tract urothelial carcinoma following radical nephroureterectomy

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ABSTRACT

Introduction: Although a single randomized trial demonstrated improved survival with adjuvant chemotherapy (AC) for locally advanced (pT2-4 or N+) upper tract urothelial carcinoma (UTUC) after radical nephroureterectomy (RNU), this survival benefit was not observed in pT2 or N+ patients, and real-world data are lacking. We therefore emulated the completed POUT trial using a large, nationwide cancer registry.

KEY MESSAGES

- Using a nationwide cohort and a target-trial emulation of POUT, adjuvant chemotherapy after radical nephroureterectomy was not associated with improved overall survival vs. observation.
- No survival benefit for adjuvant chemotherapy was observed across any pathologic T stage (pT2–pT4) or nodal category (pN).
- These real-world findings contrast with POUT and suggest the need for further comparative effectiveness on adjuvant chemotherapy in locally advanced UTUC.

Methods: We identified patients aged 50−79 years with pT2−4 or pN+, non-metastatic UTUC treated with RNU from 2006−2020 in the National Cancer Database (NCDB). A propensity score for receipt of multiagent AC within three months of RNU was estimated using logistic regression, and the associations of AC with overall survival (OS) were evaluated after reweighting by stabilized inverse probability of treatment weights (sIPW).
Results: The study cohort comprised 3206 patients, of whom 802 (25%) received AC. pT stage was £pT2 in 954 (30%) patients, and 167 (5%) patients had pN+ disease. Median followup was 47.0 (interquartile range 24.0−86.0) months. After IPW-reweighting, AC was not associated with improved OS compared to observation, with five-year OS of 60% vs. 58%, respectively (hazard ratio 0.92, 95% confidence interval 0.79−1.08, p=0.30). When examining treatment effects across baseline characteristics, AC was not associated with improved survival for any pT or pN category.
Conclusions: In analyses designed to emulate the POUT trial, we did not observe improved OS with AC in the overall cohort, nor in specific pT or pN categories. These findings suggest the need to examine the real-world comparative effectiveness of AC in locally advanced UTUC in further studies.

INTRODUCTION

Radical nephroureterectomy (RNU) remains the gold standard for treatment for localized UTUC.[1,2] However, patients with locally advanced UTUC are at increased risk for recurrence,[3] and adjuvant chemotherapy (AC) has been proposed to improve both disease-specific and overall survival. Historically, the role of AC in UTUC was uncertain due to the lack of robust evidence supporting its efficacy, coupled with the potential harm of administering nephrotoxic agents in patients with a newly solitary kidney.[1,2] Earlier observational studies noted improved overall (OS) and disease-free survival (DFS) in patients who received AC compared to patients who were observed after RNU.[4-12] In a 2014, meta-analysis of 10 observational studies reported that AC was associated with improved DFS,[4] results were mixed when assessing OS. In an updated meta-analysis published in 2021, which included 29 studies, AC was associated with an improvement in DFS, and cancer-specific survival (CSS), and OS.[13] In addition, the recent Ambassador trial demonstrated improved DFS with adjuvant pembrolizumab, an immunotherapy currently approved for locally advanced urothelial carcinoma.[14]

The phase III POUT trial is the landmark the randomized clinical trial that examined the role of AC in patients with locally advanced UTUC.[15,16] In that trial, the patients with pT2–T4 pN0–N3 M0 or pTany N1–3 M0 UTUC were randomized to AC with cisplatin or carboplatin combined with gemcitabine versus observation following RNU. The POUT trial demonstrated improved DFS, which was the primary endpoint, in patients receiving AC, with 5-year DFS of 62% vs 45% compared to observation.[15] A later publication also reported improved OS (66% vs

47%), although this finding was based on a univariable analysis, and the survival benefit was not observed in pT2 or N+ patients.[16]

Although the POUT trial provides randomized evidence to support improved DFS with AC for locally advanced UTUC, it was not powered to examine disease subgroups, and real-world data are lacking. Given these evidence gaps, we emulated the POUT trial using a large, nationwide cancer registry to evaluate the role of AC after RNU in UTUC. In doing so, we provide real-world evidence on the oncologic efficacy of AC, and data for patient subgroups that were limited in the POUT trial.

METHODS

Target clinical trial

We conducted observational analyses designed to emulate a completed target trial of adjuvant chemotherapy (AC) vs observation after RNU for patients with locally advanced UTUC using the emulation framework described by Hernan and Robins.[17] The components of the target trial to be emulated were specified, a priori, as summarized in Supplementary Table 1. This study obtained a determination that this work does not constitute human subjects research from our institutional review board (IRB).

Patient population, clinicopathologic features and outcomes

Based on the eligibility criteria in Supplementary Table 1, we identified adults age 50-79 years with Charlson comorbidity index 0-1 who were diagnosed with pT2-4 pNany or pTany pN+, M0 urothelial carcinoma of the upper tract treated with RNU between 2006-2020 in the National Cancer Database (NCDB). Patients who received neoadjuvant chemotherapy or single-agent postoperative chemotherapy were excluded (Supplementary Figure 1).

We defined two treatment strategies for the target trial based on those in the POUT trial. In the intervention arm, patients received multiagent AC within 3 months of RNU (defined as zero time). In the observation arm, patients did not receive any chemotherapy within 3 months of RNU, but were allowed (though not required) to receive chemotherapy beyond 3 months (considered "deferred" chemotherapy herein).

The following clinicopathological characteristics were recorded from the NCDB: age, gender, Charlson index, year of diagnosis, race, Hispanic status, insurance status, geographic location, facility type, distance from the hospital, rurality, income level, educational level, pathological TN stage, tumor grade, surgical margin status, number of lymph nodes removed, number of positive lymph nodes, and average annual hospital RNU volume. The primary outcome was overall survival (OS).

Statistical methods

Baseline characteristics were summarized using medians and interquartile ranges (IQR) or frequency counts and percentages and compared across treatment groups using the Wilcoxon rank sum or chi-square tests.

We utilized a propensity score (PS) based approach to adjust for differences in baseline characteristics between treatment groups.[18] We estimated a PS for receipt of AC using a flexible logistic regression model, with all pre-treatment covariates listed in Supplementary Table 2 included in the model. We conducted a complete case analysis. Model fit was assessed by standardized differences (SDs) after re-weighting by stabilized inverse probability of treatment weights (sIPWs). We revised the PS model until covariate balance was obtained. Categorical variables were modeled as specified in Supplementary Table 2, while continuous variables were modeled as linear covariates.

After covariate balance was obtained, we then estimated absolute and relative measures of treatment effects after reweighting with sIPWs. We estimated OS, stratified by receipt of AC, using the Kaplan-Meier method with reweighting by sIPWs. We also estimated the association of AC with OS using a Cox regression model with reweighting by sIPWs. Results are reported using hazard ratios (HR's) with 95% confidence intervals (95% CI). We examined heterogeneity of treatment effects in separate Cox regression models using treatment-covariate interaction terms to examine how treatment effects varied across clinically relevant covariates. These covariates were specified a priori, and included pT stage, pN stage, age, Charlson index, race, gender, income level, educational level, insurance status, number of lymph nodes removed, and distance from the hospital.

Statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and P-values <0.05 were considered statistically significant.

RESULTS

A total of 3,206 patients were included in the study cohort, including 802 (25%) who received multiagent AC within 3 months of RNU. Baseline characteristics are summarized in Table 1. Median age at diagnosis was 69 (IQR 62-74) years, and 59% of the cohort was male. A total of 1,128 (35%) patients were treated at an academic/research facility. Pathological tumor stage was £pT2 in 954 (30%) patients, pT3 in 2,079 (65%) patients, and pT4 in 173 (5%) patients. A total of 167 (5%) patients had pN+ disease. Compared to patients who did not receive AC, those who received AC were younger (67 vs 69 years, p<0.01), less comorbid (78% vs 73% Charlson 0, p<0.01), more likely to be privately insured (41% s 28%, p<0.01), and more likely to reside in a higher education level area (31% vs 25% Q4, p<0.01). Furthermore, patients who received AC were more likely to have higher pT stage (88% vs 64% pT3/T4, p<0.01), have pN+ disease (13% vs 2%, p<0.01), and have positive surgical margins (16% vs 6%, p<0.01). Median follow-up for the cohort was 47.0 (IQR 24.0-86.0) months. The percentage of missing data for each covariate is shown in Supplementary Table 3.

After sIPW-adjustment, the treatment groups were well balanced with regards to all available pre-treatment characteristics (Supplementary Table 2). After IPW-reweighting, AC was not associated with improved OS compared to observation, with 5-year OS of 60% vs 58%, respectively (HR 0.92, 95% CI 0.79-1.08, p=0.30; Figure 1; Table 2). When examining treatment

effects across baseline characteristics, AC was not associated with improved survival for any pT or pN category, nor across age, Charlson, race, income, insurance status, education level, or number of LNs removed categories (Figure 2). The only group noted to have a benefit with AC was female gender (HR 0.76; 95% CI 0.59 – 0.98; p=0.03).

DISCUSSION

In observational analyses designed to emulate the POUT trial, we did not observe improved OS with AC compared to observation. Moreover, there was no observed OS benefit for AC across pT or pN stage, suggesting that AC may not provide an oncologic benefit even in higher risk disease. Female patients appeared to derive an OS benefit from AC in subgroup analysis, although this observation should be interpreted cautiously, as subgroup findings may be prone to chance associations, particularly in the absence of an obvious biological explanation. Although these results contrast with the findings of the POUT trial, it is important to acknowledge the limitations of observational analyses, and that our observed findings should be interpreted with caution. However, our findings provide real-world data on the oncologic role of AC in patients with locally advanced UTUC following RNU.

The POUT trial is the landmark randomized trial to examine the efficacy of AC in locally advance RNU. In the initial results, AC was associated with improved DFS compared to observation (HR 0.45, 95% CI 0.30-0.68; p=0.0001), although OS data was not mature yet.[15] In the final results,[16] published in 2024, AC was associated with improved OS, with 5-year OS of 66% vs 57% (HR 0.68, 95% CI 0.46-1.00; p=0.049). Although treatment effects were consistent across chemotherapy regiments (cisplatin vs carboplatin), there appeared to be no benefit to OS in patients with T2 or N+ disease.[16] The present results clearly differ from the OS data in the POUT trial, and several potential explanations may exist. While there is always the possibility of residual confounding in observational study designs, it is also possible that the OS benefit of AC in real-world settings may be of smaller magnitude, or may not be present altogether. It is possible that secondary therapies at the time of disease progression, including immunotherapy, may reduce the potential impact of AC on OS. Of note, a smaller, single-center randomized study reported improved OS (HR 1.39; p=0.0397) in high-risk UTUC.[19]

A number of prior studies have examined oncologic outcomes following AC. In one systematic review,[4] the authors analyzed 10 observational studies and reported that AC was not associated with a statistically significant benefit in OS (pooled HR 0.65; p=0.17) or DSS (pooled HR 0.77; p=0.318). However, AC was associated with improved DFS (pooled HR 0.49; p=0.048). In a more recent systematic review and meta-analysis that included 29 studies,[13] the authors reported that AC was associated with a statistically significant improvement in DFS (pooled HR 0.52; p < 0.001), CSS (pooled HR 0.79; p= 0.001), and OS (pooled HR 0.77; 95% CI 0.64-0.92; p = 0.004). In another systematic review that examined the efficacy of AC after RNU in patients with UTUC of variant histology (VH), the authors reported that AC was associated with improved CSS (pooled HR 0.46; 95% CI 0.25-0.84; p = 0.01) and OS (pooled

HR 0.61; 95% CI 0.42-0.87; p = 0.007).[20] It should be noted that these meta-analyses did not examine treatment effects across pathological stages within the cohorts.

A prior NCDB study similarly examined the association of AC with OS.[5] In that study, which included patients with pT3/T4 or pN+ disease following RNU from 2004-2012, the authors reported improved 5-year OS with AC of 44% versus 36% with observation (adjusted HR 0.77; p<0.001). While these results differ from the present analyses, several differences warrant emphasis. The present study emulated the POUT trial and therefore included patients with pT2 disease. In addition, we included patients who underwent surgery from 2006-2020, which reflects more contemporary treatment paradigms.

This study is not without limitations. It is observational, and despite using a framework for conducting observational analyses to emulate a pragmatic target trial, it is subject to unmeasured confounding and selection bias. In addition, we performed a complete case analysis, which may introduce bias if data are not missing at random. Also, relatively few patients with pT2 disease received AC, and there may be residual selection bias in such patients. Furthermore, we were unable to adjust for features not captured in the NCDB, such as radiographic findings, renal function, or specific chemotherapy regimen administered. In addition, while OS may be an adequate surrogate for CSS in the absence of substantial competing causes of mortality, it must be acknowledged that we were not able to assess DFS or CSS.

CONCLUSIONS

In analyses designed to emulate the POUT trial, we did not observe improved OS with AC in the overall cohort, nor in specific pT or pN categories. Notwithstanding potential limitations related to lack of data regarding specific chemotherapy agents utilized and unmeasured confounding, these findings should be considered hypothesis-generating, and suggest the need to examine the real-world comparative effectiveness of AC in locally advanced UTUC in further studies.

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Data Statement: The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

FIGURES AND TABLES

Figure 1. Adjusted associations of adjuvant chemotherapy vs. observation after radical nephroureterectomy (RNU) with overall survival stratified (main and marginal treatment effects).

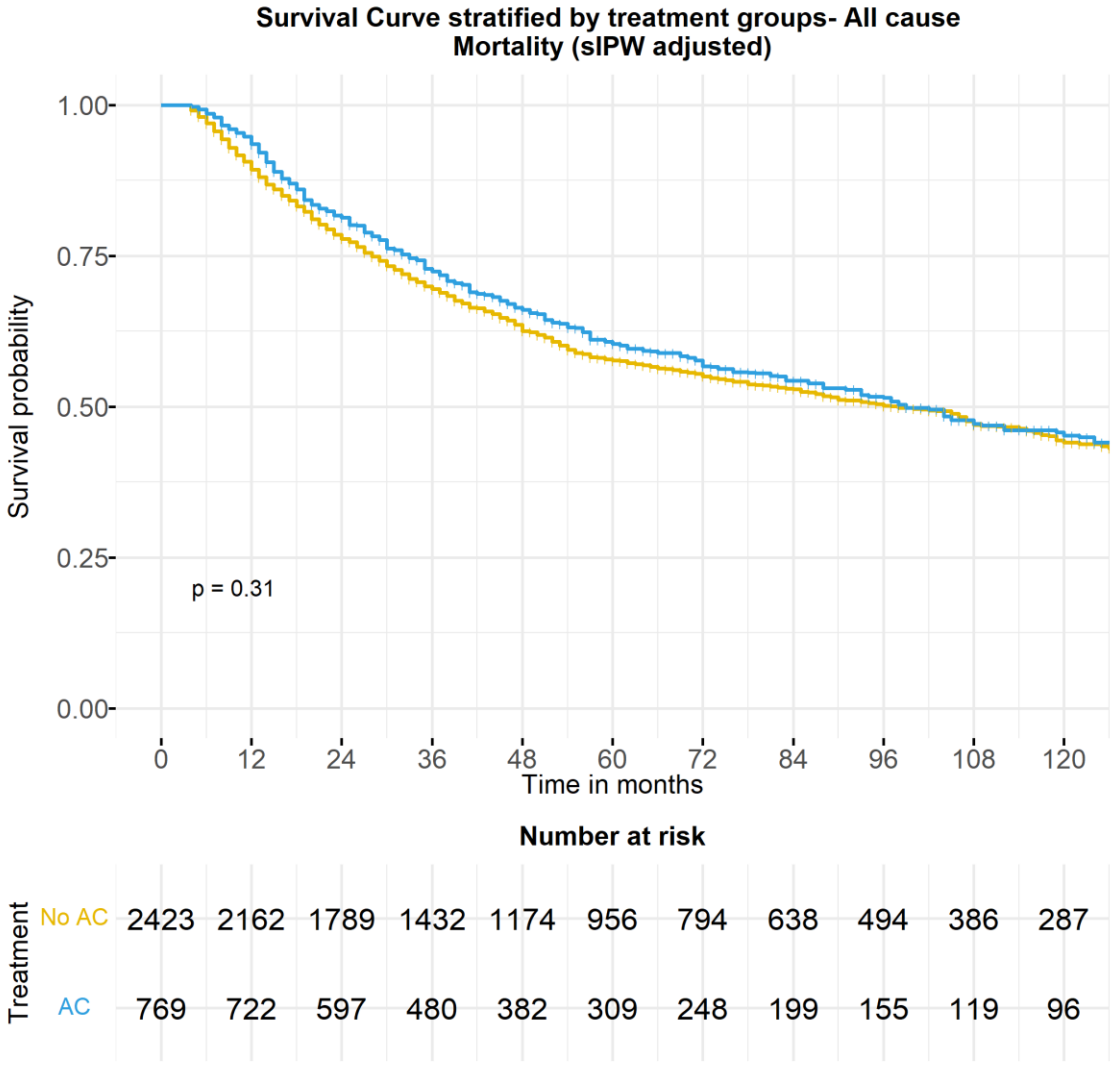

Figure 2. Adjusted associations of adjuvant chemotherapy vs observation after radical nephroureterectomy (RNU) with overall survival stratified (main and marginal treatment effects).

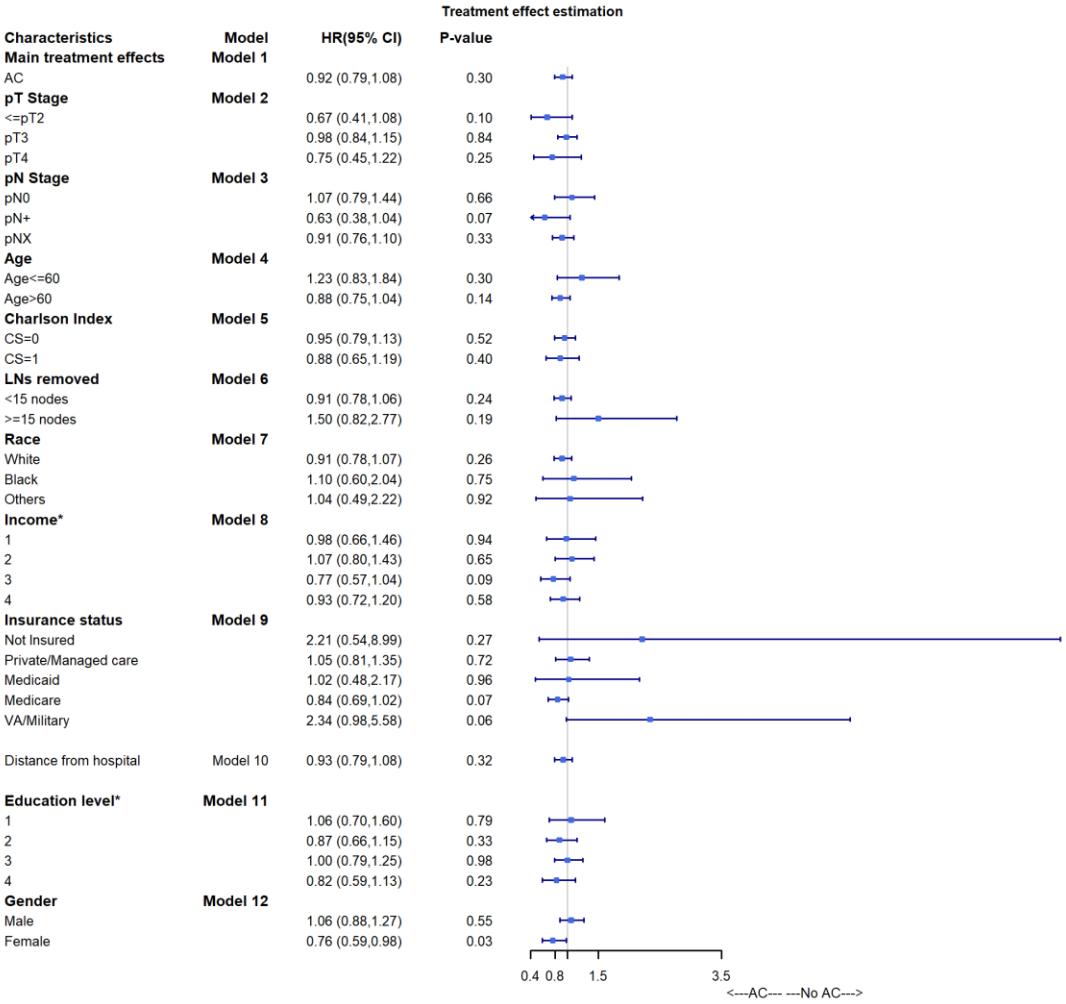

Table 1. Baseline characteristics				
		Adjuvant chemotherapy		
Characteristic	**Overall** (n=3206)[1]	**No multiagent AC within 3 months** 2404 (75%)[1]	**Multiagent AC within 3 months** 802 (25%)[1]	**p**[2]
Age, years	69 (62, 74)	69 (63, 74)	67 (61, 73)	<0.01
Gender				0.75
Male	1,882 (59)	1,415 (59)	467 (58)	
Female	1,324 (41)	989 (41)	335 (42)	
Charlson index				<0.01
0	2,383 (74)	1,756 (73)	627 (78)	
1	823 (26)	648 (27)	175 (22)	
Year of diagnosis				0.04
2006	64 (2)	46 (2)	18 (2)	
2007	83 (3)	65 (3)	18 (2)	
2008	155 (5)	121 (5)	34 (4)	
2009	171 (5)	129 (5)	42 (5)	
2010	244 (8)	192 (8)	52 (6)	
2011	230 (7)	180 (7)	50 (6)	
2012	251 (8)	199 (8)	52 (6)	
2013	257 (8)	193 (8)	64 (8)	
2014	299 (9)	236 (10)	63 (8)	
2015	276 (9)	207 (9)	69 (9)	
2016	264 (8)	198 (8)	66 (8)	
2017	235 (7)	172 (7)	63 (8)	
2018	217 (7)	152 (6)	65 (8)	
2019	259 (8)	180 (7)	79 (10)	
2020	201 (6)	134 (6)	67 (8)	
Race				0.15
White	2,925 (91)	2,182 (91)	743 (93)	
Black	161 (5)	131 (5)	30 (4)	
Others	120 (4)	91 (4)	29 (4)	
Hispanic				0.91
No	3,084 (96)	2,312 (96)	772 (96)	
Yes	122 (4)	92 (4)	30 (4)	
Insurance status				<0.01
Not insured	54 (2)	49 (2)	5 (1)	

Private/managed care	1,005 (31)	674 (28)	331 (41)	
Medicaid	115 (4)	93 (4)	22 (3)	
Medicare	1,993 (62)	1,554 (65)	439 (55)	
VA/military	39 (1)	34 (1)	5 (1)	
Geographic location				0.46
Northeast	744 (23)	545 (23)	199 (25)	
South/Southeast	1,130 (35)	864 (36)	266 (33)	
Midwest	823 (26)	614 (26)	209 (26)	
West	509 (16)	381 (16)	128 (16)	
Facility type				0.58
Community cancer program	234 (7)	182 (8)	52 (6)	
Comprehensive community cancer program	1,268 (40)	958 (40)	310 (39)	
Academic/research program	1,128 (35)	833 (35)	295 (37)	
Integrated network cancer program	576 (18)	431 (18)	145 (18)	
Distance from hospital	11 (5, 27)	11 (5, 29)	11 (5, 24)	0.08
Rurality				0.25
Metropolitan	2,656 (83)	1,985 (83)	671 (84)	
Urban	483 (15)	373 (16)	110 (14)	
Rural	67 (2)	46 (2)	21 (3)	
Income*				0.23
Q1	481 (15)	371 (15)	110 (14)	
Q2	717 (22)	550 (23)	167 (21)	
Q3	797 (25)	596 (25)	201 (25)	
Q4	1,211 (38)	887 (37)	324 (40)	
Education level*				<0.01
Q1	513 (16)	402 (17)	111 (14)	
Q2	839 (26)	651 (27)	188 (23)	
Q3	1,004 (31)	749 (31)	255 (32)	
Q4	850 (27)	602 (25)	248 (31)	
pT stage				<0.01
≤pT2	954 (30)	856 (36)	98 (12)	
pT3	2,079 (65)	1,449 (60)	630 (79)	

pT4	173 (5)	99 (4)	74 (9)	
pN stage				<0.01
pNX	2,314 (72)	1,806 (75)	508 (63)	
pN0	725 (23)	538 (22)	187 (23)	
pN+	167 (5)	60 (2)	107 (13)	
Tumor site				0.10
Renal pelvis	2,205 (69)	1,672 (70)	533 (66)	
Ureter	1,001 (31)	732 (30)	269 (34)	
Surgical margins				<0.01
Negative	2,928 (91)	2,254 (94)	674 (84)	
Positive	278 (9)	150 (6)	128 (16)	
Tumor grade				<0.01
Grade 1−2	310 (10)	271 (11)	39 (5)	
Grade 3−4	2,594 (81)	1,888 (79)	706 (88)	
Unknown	302 (9)	245 (10)	57 (7)	
Annual average hospital RNU volume	22.07 (11.33, 37.87)	22.40 (11.53, 38.00)	20.67 (10.33, 36.07)	0.05
LNs removed	0 (0, 1)	0 (0, 0)	0 (0, 2)	<0.01
LNs positive	0 (0, 0)	0 (0, 0)	0 (0, 1)	<0.01
Missing	2,314	1,806	508	
Followup (months)	47.0 (24.0, 86.0)	48.0 (24.0, 88.0)	44.0 (23.0, 80.0)	0.04

[1]Median (IQR); n (%). [2]Wilcoxon rank sum test; Pearson's Chi-squared test. *Quartile cutoffs for education level and income varied according to year of data. AC: adjuvant chemotherapy; LN: lymph node; RNU: radical nephroureterectomy.

Table 2. Table of overall survival estimates at 1, 3, 5, 7, and 10 years.		
Treatment group	**Time (years)**	**Overall survival**
AC	1	0.93 (0.91, 0.96)
No AC	1	0.89 (0.88, 0.91)
AC	3	0.72 (0.69, 0.77)
No AC	3	0.69 (0.67, 0.72)
AC	5	0.60 (0.56, 0.65)
No AC	5	0.58 (0.55, 0.60)
AC	7	0.54 (0.49, 0.60)
No AC	7	0.53 (0.51, 0.55)
AC	10	0.45 (0.40, 0.52)
No AC	10	0.44 (0.41, 0.47)

AC: adjuvant chemotherapy