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Adjuvant chemotherapy after radical nephroureterectomy does not improve survival in patients with upper tract urothelial carcinoma: a joint study by the European Association of Urology–Young Academic Urologists and the Upper Tract Urothelial Carcinoma Collaboration

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Objective

To analyse the outcomes of adjuvant chemotherapy vs observation in a multicentre cohort of patients with upper tract urothelial carcinoma (UTUC) in order to clarify whether such patients benefit from adjuvant chemotherapy after radical nephroureterectomy (RNU).

Patients and Methods

Data from 15 centres were collected for a total of 1544 patients, treated between 2000 and 2015. Criteria for patient selection included pT2–4N0/x stage, or lymph node-positive disease, and prior RNU. The standardized difference approach was used to compare subgroup characteristics. Overall survival (OS) was the primary endpoint. The primary analysis used 1:1 propensity score matching, with inverse probability of treatment weighting in addition to this in the secondary analysis. The latter was also performed with the inclusion of covariates, i.e. with 'doubly robust' estimation. A 6-month landmark analysis was performed to exclude early events.

Results

A total of 312 patients received adjuvant chemotherapy and 1232 underwent observation. Despite differences between the two groups, the standardized difference was generally <10% after matching. In the matched analysis no difference was observed in OS between adjuvant chemotherapy and observation (hazard ratio [HR] 1.14, 95% confidence inverval [CI] 0.91–1.43; $P = 0.268$). In the doubly robust estimate-adjusted comparison, adjuvant chemotherapy was significantly associated with shorter OS (HR 1.26, 95% CI 1.02–1.54; $P = 0.032$). Similar findings were confirmed in subgroup analyses stratified by pathological stage, and after landmark analysis. Results should be interpreted with consideration given to the inherent limitations of retrospective studies.

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Conclusion

Adjuvant chemotherapy did not improve OS compared with observation in the present study. These results contribute to the uncertainties regarding postoperative chemotherapy in UTUC, and suggest dedicated prospective trials, new more potent therapies, and the identification of enhanced patient selection criteria are required.

Keywords

adjuvant chemotherapy, nephroureterectomy, propensity scores, upper tract, urothelial carcinoma

Introduction

Upper urinary tract urothelial carcinoma (UTUC) is an uncommon disease, accounting for ~5% of all diagnoses of urothelial carcinoma (UC) [1,2]. Better management and improved outcomes are needed in patients with UTUC, in particular in patients presenting with non-metastatic disease. Outcomes of patients undergoing radical nephroureterectomy (RNU) primarily depend on the degree of locoregional extent. Consequently, effective control of systemic disease, particularly for tumours with adverse pathological features, is required. There is also substantial uncertainty regarding the role and extent of retroperitoneal lymph node dissection in patients with UTUC [3–6]. The few available studies on combined treatments are limited by their heterogeneity with regard to patient characteristics and treatments, as well as by small patient numbers, so that it is not possible to generalize their results [7]. The chemotherapy regimens currently used for UTUC are the same as those offered for bladder UC. Despite large variations in the proportion of patients who are administered adjuvant chemotherapy after RNU, as reflected in surveys of urologists and oncologists, very few patients receive peri-operative systemic therapy [8,9]. Huge efforts have been made to develop better risk assessment tools before and after RNU, but it is still unclear as to how to identify the patients with true high-risk disease who would benefit from systemic therapy [10–13]. Additionally, the likelihood of receiving optimum chemotherapy is often limited by the reduction in renal function post-RNU [14–16]. Until recently, the evidence obtained with regard to adjuvant chemotherapy use in UTUC has led to contradictory overall survival (OS) results, owing to the retrospective nature of the studies [7]; however, a hazard ratio (HR) of 0.43 favouring adjuvant cisplatin-based chemotherapy was observed in a trial-level meta-analysis [17], in addition to the 12-month median OS improvement reported by a retrospective analysis conducted on data from the US National Cancer Database (NCDB) [18].

We have previously reported no difference in outcomes between adjuvant chemotherapy and observation in a study from the Upper Tract Urothelial Carcinoma Collaboration [19]. To increase the sample size of the present study, to allow us to perform subgroup analyses on the OS differences between adjuvant chemotherapy and observation, we proposed an international collaborative study sponsored by the Young Academic Urologists (YAU) group of the European Association of Urology (EAU).

Patients and Methods

Patient Selection

The aim of the present study was to compare the outcomes of patients who underwent adjuvant chemotherapy or observation after RNU. The database included data from 15 academic centres and hospitals in Europe and the USA. Inclusion criteria for this study were: RNU performed between the year 2000 and 2015; disease in the renal pelvis or ureter; predominant UC histology; high-risk disease, defined as ≥pT2 and/or pN1–3 (according to the local pathology report); and the administration of adjuvant chemotherapy or follow-up initiation after RNU. To meet the criteria for adjuvant chemotherapy, treatment must have been started within 90 days of RNU. The surgical procedure and indication for adjuvant chemotherapy administration were based on the clinical judgement of each treating physician. Patients who had received neoadjuvant chemotherapy were excluded from the study. The study was approved by the by the ethics committees at each participating institution.

Statistical Methods

The main series characteristics were summarized using conventional statistics, with median and interquartile range (IQR) for continuous variables, and absolute or relative frequencies for categorical data. Covariates used in the analyses included pathological grade and stage, age, preoperative Eastern Cooperative Oncology Group Performance Status (ECOG-PS), tumour location; and gender [12,19]. Analyses relied on the standardized difference approach to compare covariates between patients who received adjuvant chemotherapy vs those who did not [20].

The primary endpoint of the study was OS, and the secondary endpoint was cancer-specific survival (CSS). The OS time for each patient was computed as the interval

between the date of surgery and the date of death for any reason, with censoring at the date of last follow-up in alive patients. The reverse Kaplan–Meier method, described by Schemper and Smith, was used for follow-up quantification [21]. The association between OS and treatment group was investigated with the use of Cox regression models using several propensity score techniques, and summarized with HRs and 95% CIs.

The propensity scores were adopted to control for pretreatment imbalances on observed covariates and in order to establish the marginal causal effects of intervention. Propensity score building relied on the inclusion of all available covariates into a generalized boosted model (GBM) [22]. This machine-learning method has been shown to outperform simple logistic regression in the context of case-mix adjustment. The primary analysis relied on OS with 1:1 propensity score matching. In addition, we performed secondary analyses based on inverse probability of treatment weighting (IPTW). Regarding the first approach, we created a matched sample by matching treated and untreated subjects in a 1:1 ratio based on the logit of the propensity score and using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score. A greedy, nearest-neighbour matching algorithm was used to form pairs of treated and untreated subjects. This sample was then analysed with a Cox model including treatment as the only predictor. The second approach consisted of fitting a Cox model to the overall sample, including treatment as a predictor and propensity score weighting, thus obtaining the average treatment effect [23]. Because some covariate imbalance remained after weighting, the IPTW analysis was also performed with the inclusion of the covariates, i.e. with 'doubly robust' estimation. Given the presence of missing data for some covariates, we resorted to 10-fold multiple imputations and used the Rubin rules for obtaining the doubly robust estimates of Cox regression coefficients. Adjusted survival curves were provided, as described by Colea and Hernan [24]. As the number of chemotherapy cycles was not available for the majority of cases, we used 6-month conditional landmark analysis to remove the bias of early events. Furthermore, subgroup analyses were carried out to assess whether the propensity score-matched HR of adjuvant chemotherapy vs observation was affected by prognostic characteristics. For such an analysis, propensity score calculation, balance checks and matching were carried out within each subgroup. Results are reported both in tabular form and graphically by means of a forest plot. Statistical analyses were performed using SAS version 9.2, the R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) and the following R packages, all accessible at http://cran.r-project.org/web/packages/: *twang* for propensity score building, *nonrandom* for matching, *mice* for multiple imputation. All tests were two-sided and P values <0.05 were taken to indicate statistical significance.

Results

Characteristics of the Study Groups

The study flow chart is shown in Fig. 1. Of 2714 patients registered as having undergone RNU, 1147 were excluded because of their pathological stage or receipt of adjuvant chemotherapy later than 90 days after RNU and 23 were excluded because they had received neoadjuvant chemotherapy. The remaining 1544 patients, from 15 contributing centres, treated between January 2000 and October 2015, were analysed. Of these patients, 312 (20.2%) received adjuvant chemotherapy and 1232 (79.8%) did not. After a median (IQR) follow-up duration of 58 (27–103) months, 609 patients (39.4%) experienced a relapse, 542 patients (35.1%) died from the disease and 179 (11.6%) died from other causes. Table 1 shows the distribution of main patient and disease characteristics, and includes the standardized difference values for each baseline characteristic, according to the type of propensity score-based analysis. Standardized differences obtained for the matched samples

Fig. 1 Study flow chart, with counts and reasons for patient selection. ACT, adjuvant chemotherapy; EAU–YAU, European Association of Urology–Young Academic Urologists; NACT, neoadjuvant chemotherapy; RNU, radical nephroureterectomy.

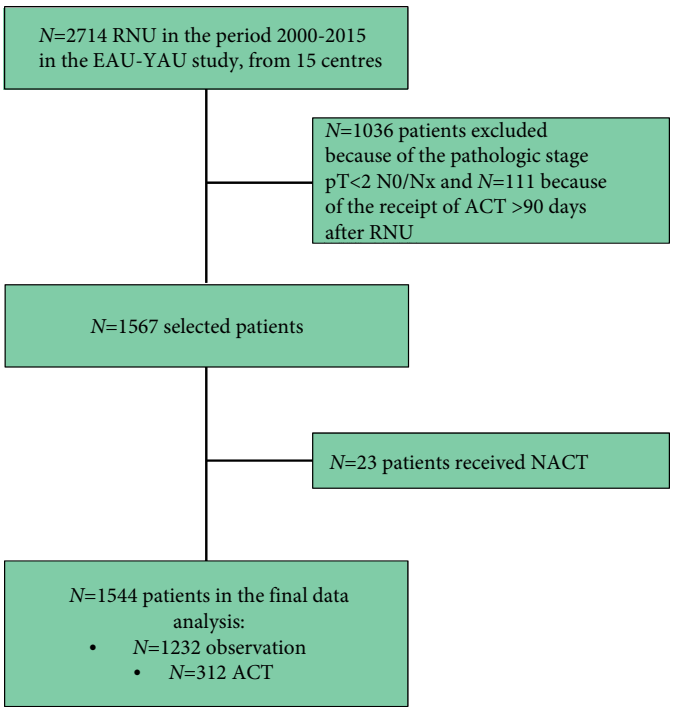


Table 1 Characteristics of patients in the study population and according to subgroup, and comparison of the standardized difference values according to the type of analysis.

Characteristic	Overall *N* = 1544	ACT *N* = 312	Observation *N* = 1232	Unweighted standardized difference, % *N* = 1544	Standardized difference after IPTW, % *N* = 1544	Standardized difference after 1:1 matching (%) *N* = 570
Median (IQR) age at surgery, years	68 (61–75)	65 (58–72)	69 (62–76)	34.1	10.5	3.7
Gender, *n* (%)						
Male	1039 (67.3)	231 (74.0)	808 (65.6)	19.3	7.1	1.6
Female	505 (32.7)	81 (26.0)	424 (34.4)	19.3	7.1	1.6
ECOG-PS*, *n* (%)						
0	752 (68.7)	197 (73.5)	555 (67.1)	37.5	15.4	3.3
1	276 (25.2)	58 (21.6)	218 (26.4)	2.3	0.9	1.8
2	67 (6.1)	13 (4.9)	54 (6.5)	1.1	3.5	3.4
Missing	449	44	405	53.9	19.6	9.1
Primary tumour location, *n* (%)						
Renal pelvis	994 (64.4)	202 (64.7)	792 (64.3)	0.9	2.9	2.9
Ureter	535 (34.6)	105 (33.7)	430 (34.9)	2.6	1.3	2.2
Both	15 (1.0)	5 (1.6)	10 (0.8)	6.3	5.7	3.2
Pathological stage, *n* (%)						
pT2N0	162 (10.9)	15 (5.2)	147 (12.2)	33.3	2.2	0.0
pT2Nx	308 (20.7)	15 (5.2)	293 (24.3)	88.7	18.0	10.5
pT3–4N0	265 (17.8)	68 (23.8)	197 (16.3)	14.1	4.2	4.1
pT3–4Nx	490 (32.9)	76 (26.6)	414 (34.4)	21.5	0.6	1.6
pTanyN+	266 (17.8)	112 (39.2)	154 (12.8)	48.8	8.0	4.5
Missing	53	26	27	22.2	2.5	3.8
Tumour grade, *n* (%)						
Low	29 (2.0)	3 (1.2)	26 (2.2)	–	–	–
High	1436 (98.0)	245 (98.8)	1191 (97.8)	–	–	–
Chemotherapy regimen, *n* (%)						
Cisplatin-based	148 (75.1)	148 (75.1)	–	–	–	–
Carboplatin-based	27 (13.7)	27 (13.7)	–	–	–	–
Non platinum-based	22 (11.2)	22 (11.2)	–	–	–	–
Missing	115	115	–	–	–	–

ACT, adjuvant chemotherapy; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; IPTW, inverse probability of treatment weighting; IQR, interquartile range.
**Assessed before radical nephroureterectomy.*

were generally below 10%. The results of the GBM analysis are shown in Table S1. Most of the imbalances between the treated and untreated groups were relative to the pathological staging, whereas no influence was observed for the primary tumour site and gender. Results of the GBM were used to select the variables to use in the multivariate propensity score-adjusted models.

Results of the Cox Proportional Hazards Regression Models

Results of the primary analysis are shown in Table 2, while those of the secondary analyses are shown in Table 3. In the unadjusted comparison between treated and control patients, a significant difference was observed in OS favouring observation, and the HR of adjuvant chemotherapy was 1.44 (95% CI 1.21–1.72; $P < 0.0001$).

The treatment effect estimated with the Cox model in the matched sample was much less strong (HR 1.14, 95% CI 0.91–1.43) and no longer statistically significant ($P = 0.268$). The propensity score-adjusted OS curves of the matched population are shown in Fig. 2. The apparently significant detrimental effect of adjuvant chemotherapy on OS was confined to the subgroups of pT2N0 ($P = 0.049$) and pT3–4Nx ($P = 0.033$), whereas OS results were overlapping in the remaining subgroups (Table 2). Forest plots and the corresponding interaction tests of the treatment effect for OS endpoint across the subgroups are shown in Fig. S1. In

Table 2 Results of the Cox model analyses on overall survival outcomes, after 1:1 matching, in the total population and in the pathological stage subgroups.

Covariate	HR	Lower 0.95	Upper 0.95	*P*
Matched analysis, total population (*N* = 570)				
ACT vs No ACT	1.14	0.91	1.43	0.268
pT2N0 (*N* = 26)				
ACT vs No ACT	4.01	1.00	16.04	0.049
pT2Nx (*N* = 30)				
ACT vs No ACT, *n* (%)	1.15	0.36	3.62	0.817
pT3-4N0 (*N* = 128)				
ACT vs No ACT	1.47	0.85	2.56	0.172
pT3-4Nx (*N* = 146)				
ACT vs No ACT	1.67	1.04	2.68	0.033
pTanyN+ (*N* = 150)				
ACT vs No ACT	0.84	0.56	1.25	0.390
Missing (*N* = 36)				
ACT vs No ACT	0.98	0.39	2.48	0.966

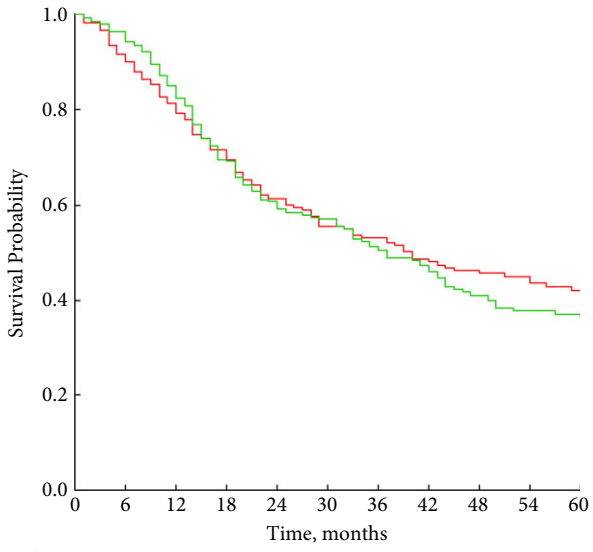
ACT, adjuvant chemotherapy; HR, hazard ratio; OS, overall survival.

Table 3 Results of the additional secondary Cox analyses for the overall survival endpoint.

Covariate	HR	Lower 0.95	Upper 0.95	*P*
Unadjusted comparison (N = 1544)				
Group				
ACT vs no ACT	1.44	1.21	1.72	<0.001
IPTW (ATE approach, N = 1544)				
Group				
ACT vs no ACT	1.31	1.08	1.58	0.005
Doubly-robust procedure (ATE approach, N = 1544)				
Group				
ACT vs no ACT	1.26	1.02	1.54	0.032
Age				
3rd vs 1st quartile (75 vs 61)	1.33	1.18	1.49	<0.001
ECOG-PS				
1 vs 0	1.37	1.18	1.58	<0.001
2 vs 0	1.61	1.20	2.16	
Pathological stage				
pT3-4N0 vs pT2N0	1.30	0.99	1.71	<0.001
pTanyN+ vs pT2N0	2.97	2.26	3.90	
pT2Nx vs pT2N0	0.92	0.69	1.20	
pT3-4Nx vs pT2N0	1.72	1.36	2.19	

ACT, adjuvant chemotherapy; ATE, average treatment effect; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival.

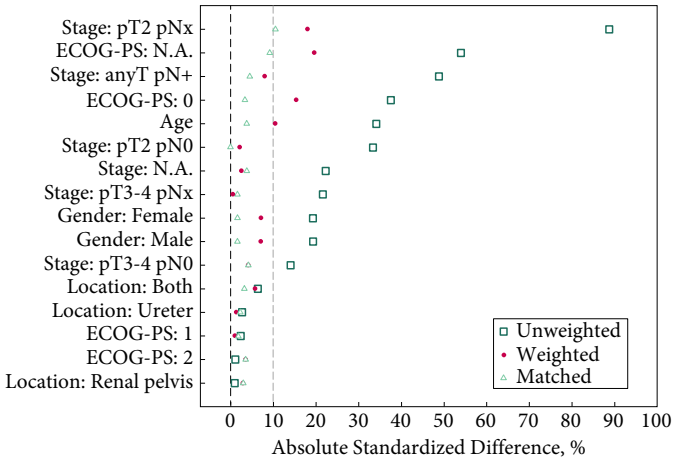
Fig. 2 Propensity score-matched overall survival curves according to the study group in the total population. Adjuvant chemotherapy (ACT): green line; no ACT: red line.



particular, the pathological stage was not significantly associated with adjuvant chemotherapy effect ($P_{interaction}$ = 0.081).

Using the IPTW approach, the negative treatment effect of adjuvant chemotherapy was attenuated (HR 1.31, 95% CI 1.08–1.58; P = 0.005) compared with the raw estimate of the unadjusted model, but not so much as in paired matching. At the same time, compared with the latter, the IPTW approach was slightly less effective in controlling baseline imbalance, as shown in Table 1 and the plot of standardized differences (Fig. 3), with the figures often in the range 20–50% rather than below the more satisfactory 10%. For this reason we also performed doubly robust estimation, whereby we achieved a further correction in the estimated treatment effect, that remained significant against chemotherapy use (HR 1.26, 95% CI 1.02–1.54; P = 0.032; Table 3).

Fig. 3 Effect of inverse probability of treatment weighting (points) and propensity score matching (triangles) on baseline characteristic distribution of the standardized differences (squares) of patients who underwent adjuvant chemotherapy or observation after radical nephroureterectomy for pT2–4 and/or pN+ upper tract urothelial carcinoma. ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; NA, not available.



The median (IQR) number of cycles of adjuvant chemotherapy was 4 (3–4), although it was available in only 75/312 cases (24%). The 6-month landmark analysis demonstrated little impact of early events on the treatment effect on OS: the HR of the propensity score-matched analysis was 1.28 (95% CI 1.00–1.64; P = 0.051), whereas the HR of the doubly robust estimate analysis was 1.46 (95% CI 1.16–1.82; P = 0.001). All the remaining covariates (age, ECOG-PS and pathological stage) were statistically significant in the doubly robust estimate-adjusted Cox model (Table S2). The results on CSS endpoint were also significantly against chemotherapy use (Table S3).

Discussion

In the present study, we investigated the impact of adjuvant chemotherapy in an international cohort of patients with UTUC undergoing RNU. We observed that adjuvant chemotherapy was not associated with any survival benefit in high-risk UTUC compared with observation, while its

apparent detrimental effect is probably attributable to clinical or pathological confounders that remained unaccounted for in this analysis. This observation was confirmed for all the study endpoints.

The statistical analyses show that residual important confounders were likely to persist even after using the IPTW and doubly-robust procedure, and that only the primary analysis method, the matched analysis, was able to accommodate the residual biases.

Interestingly, the worst effect of adjuvant chemotherapy on OS was seen in patients with lymph node-negative or unknown disease. The quality of results in these subgroups is limited by potential biases, for example, the lack of standardized indication and templates for lymph node dissection and small numbers. Furthermore, it is possible that the decision to administer adjuvant chemotherapy in these patients was attributable to the presence of negative pathological factors found in the primary tumour specimen, and we were unable to analyse the site of relapses (e.g. local vs distant), which may have been important as guidance for future studies.

In the literature, the existing data on adjuvant chemotherapy effectiveness has a very low level of evidence in high-risk, non-metastatic, UTUC [7,17]. Conversely, analyses from the NCDB robustly favoured adjuvant chemotherapy use in these patients [18]. Co-authors of the present study have reported an analysis of the UTUC Collaborative database that was consistent in reporting minimal impact on both OS and CSS in a population of 1390 treated or observed patients from 1992 to 2006. In that study, high-risk disease was defined as pT3–4 and/or lymph node-positive tumour after RNU [19].

In the present updated analysis, additional patients were included from European centres through the EAU-YAU network, and analyses have focused on a more recent timeframe of surgical performance. We were also able to analyse the effect of treatment in the pathological subgroups. Statistical analyses based the comparison of chemotherapy-treated and untreated patients on the use of multiple propensity score techniques. Indeed, the design and methods used in our study mirror those used in the analyses from the NCDB initiative. The two studies provide the largest patient series comparing adjuvant chemotherapy and observation in UTUC, but had conflicting results. In their study from the USA, Seisen *et al.* [18] analysed 3253 patients with pT3–4 and/or pN+ UTUC who received treatment or observation between 2004 and 2012. A total of 762 patients, compared with 312 in the present study, received adjuvant chemotherapy. Although it is hard to make comparisons between the two studies, mainly because of the different nature of the data (obtained from community oncology vs high-volume centres), some strengths of the present analyses can be noted; in particular, the possibility of adjusting multiple Cox models with clinical covariates of recognized prognostic importance, such as preoperative ECOG-PS, instead of Charlson comorbidity index scores. Preoperative ECOG-PS and age had indirect validation as key predictors of OS and CSS in the present analysis. The apparent detrimental effect of adjuvant chemotherapy on OS and CSS raises huge uncertainties regarding the presence of inherent confounders. It is likely that patients who received adjuvant chemotherapy had a more aggressive disease that was not adjusted for by the pathological staging alone. Conversely, larger sample size and the possibility of evaluating the results at the community oncology practice level may be regarded as distinct qualities of the NCDB data, while the present findings were obtained from a restricted number of high-volume centres, and it is possible that some patient selection biases were not accounted for in the analyses. This is the reason, for example, why we did not record cases with positive surgical margins after RNU, while there were 482 cases (14.8%) in the study by Seisen *et al.* In general, it is possible that the two analyses ultimately mirror different populations, whose heterogeneity precludes the possibility of adjusting the data with the use of advanced statistics, and the two study populations were not overlapping based on the pathological stage selection. Also, the RNU technique (open vs minimally invasive) was not recorded in the present study or in the NCDB study [18]. Theoretically, patients receiving minimally invasive RNU are more likely to receive adjuvant chemotherapy as a result of faster recovery compared with open surgery, and the lack of such information is a bias that could affect interpretation of the results.

An important limitation of the NCDB study is that the details of chemotherapy regimens were not reported, even regarding the platinum used. Such information was available in 63.1% of cases in the present study, 75.1% of them being treated with cisplatin-based chemotherapy. For this reason, it is unlikely that the lack of effectiveness observed for adjuvant chemotherapy is attributable to the use of suboptimal chemotherapy in the present cohort, and outcomes do largely reflect those achieved with the recommended cisplatin-based chemotherapy. Conversely, it is likely that unavoidable biases of patient selection for adjuvant chemotherapy have had an impact on the study endpoints. Influential pathological factors were not fully analysed in the present study, or in other similar studies, and there was no centralized assessment of pathology specimens. These factors include lymphovascular invasion, tumour architecture and the presence of concomitant carcinoma *in situ*. In addition, information on clinical staging was not captured in our database, and it is possible that patients were more likely to receive postoperative treatment if they were thought to harbour advanced disease at first presentation. Similarly, the number of chemotherapy cycles was recorded for a minority of patients in our database, and the availability of such data

might have led to the exclusion of patients who interrupted treatment early because of excess toxicity development or the occurrence or early relapses. Additional lacking data that might have helped in fine-tuning the analyses include race, presence of comorbidities, socio-economic class and hospital characteristics. To obviate the major limitations and exclude early events attributable to stage selection biases, additional analyses were run by applying a 6-month conditional landmark analysis; however, the results of the propensity score-adjusted Cox models were largely overlapping for all the study endpoints.

Finally, the uncertainties of adjuvant chemotherapy should reconcile the benefits of neoadjuvant chemotherapy use in UTUC and in bladder UC alike. In UTUC, in particular, the advantages of neoadjuvant chemotherapy are dependent on the likelihood of post-surgical complications and decline in renal function that prevent most patients from receiving cisplatin-based chemotherapy postoperatively [12,25]. At present, the landscape of possible therapeutic developments in the field is limited by the lack of clinical trials, but the advent of immune-checkpoint inhibitors will probably revolutionize the current therapeutic paradigm of non-metastatic UTUC [26].

In summary, we reported no impact or even inferior survival for adjuvant chemotherapy vs observation after RNU in patients with high-risk UTUC. Taking all retrospective data available in the literature together, substantial uncertainties persist regarding the indication and selection criteria to use in clinical practice and patient counselling. Further efforts should be made, through prospective studies and retrospective analyses, to identify subgroups that do not benefit from adjuvant chemotherapy, focusing on cisplatin chemotherapy regimens and standardized lymphadenectomy templates.

Conflict of Interest

None declared.

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Abbreviations: CSS, cancer-specific survival; EAU, European Association of Urology; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; GBM, generalized boosted model; HR, hazard ratio; IPTW, inverse probability of treatment weighting; IQR, interquartile range; NCDB, US National Cancer Database; OS, overall survival; RNU, radical nephroureterectomy; UC, urothelial carcinoma; UTUC, upper tract urothelial carcinoma; YAU, Young Academic Urologists.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 Forest plot showing the hazard ratios (HR) and p-values of interaction tests of adjuvant chemotherapy versus observation according to the baseline characteristics, evaluated after propensity score-matching within each subgroup.
Table S1 Generalized boosted regression model for propensity score estimation: relative influence measured for each variable.
Table S2 Results of the Cox analyses for the OS endpoint, with 6-month conditional landmark analysis.
Table S3 Results of the Cox analyses for the CSS endpoint.