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Original Article

Comparative effectiveness of neoadjuvant chemotherapy in bladder and upper urinary tract urothelial carcinoma

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Objective

To assess the differential response to neoadjuvant chemotherapy (NAC) in patients with urothelial carcinoma of the bladder (UCB) compared to upper tract urothelial carcioma (UTUC) treated with radical surgery.

Patients and Methods

Data from 1299 patients with UCB and 276 with UTUC were obtained from multicentric collaborations. The association of disease location (UCB vs UTUC) with pathological complete response (pCR, defined as a post-treatment pathological stage ypT0N0) and pathological objective response (pOR, defined as ypT0-Ta-Tis-T1N0) after NAC was evaluated using logistic regression analyses. The association with overall (OS) and cancer-specific survival (CSS) was evaluated using Cox regression analyses.

Results

A pCR was found in 250 (19.2%) patients with UCB and in 23 (8.3%) with UTUC ($P < 0.01$). A pOR was found in 523 (40.3%) patients with UCB and in 133 (48.2%) with UTUC ($P = 0.02$). On multivariable logistic regression analysis, patients with UTUC were less likely to have a pCR (odds ratio [OR] 0.45, 95% confidence interval [CI] 0.27–0.70; $P < 0.01$) and more likely to have a pOR (OR 1.57, 95% CI 1.89–2.08; $P < 0.01$). On univariable Cox regression analyses, UTUC was associated with better OS (hazard ratio [HR] 0.80, 95% CI 0.64–0.99, $P = 0.04$) and CSS (HR 0.63, 95% CI 0.49–0.83; $P < 0.01$). On multivariable Cox regression analyses, UTUC remained associated with CSS (HR 0.61, 95% CI 0.45–0.82; $P < 0.01$), but not with OS.

Conclusions

Our present findings suggest that the benefit of NAC in UTUC is similar to that found in UCB. These data can be used as a benchmark to contextualise survival outcomes and plan future trial design with NAC in urothelial cancer.

Keywords

neoadjuvant chemotherapy, response, survival, upper tract urothelial carcinoma, bladder cancer, #BladderCancer, #blcsm, #utuc, #uroonc

Introduction

Urothelial carcinoma (UC) is the 10th most common cancer worldwide, with an estimated 550 000 new cases in 2018 [1]. UC of the bladder (UCB) and upper tract UC (UTUC) account for ~95% and 5% of UCs, respectively [1,2]. Due to the relative rarity of UTUC most clinical decision-making with resulting therapeutic approaches for patients with UTUC are extrapolated from the UCB literature [3].

The standard treatment for muscle-invasive UCB (MIBC) is cisplatin-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) and pelvic lymphadenectomy [4]. Radical nephroureterectomy (RNU) with excision of the ipsilateral bladder cuff and is the standard of care for high-risk UTUC, followed by adjuvant chemotherapy in locally advanced disease [5,6]. Although NAC has not yet become standard of care in high-grade invasive UTUC, multimodal treatment has consistently been shown to improve survival in retrospective series [7–10].

Patho-epidemiological and molecular analyses suggest that both diseases have biological dissimilarities [11]. Despite originating from the same tissue, UCB and UTUC seem to have different stage-specific survival, different aetiologies, and different rate of alterations in mutations that are common for both [12–14]. Recently, a whole exome sequencing analysis of 37 UTUCs showed that the majority of tumours had high fibroblast growth factor receptor 3 (FGFR3) expressions and were molecularly classified as luminal-papillary. Overall, UTUC had a lower total mutational burden compared to the UCB cohort of The Cancer Genome Atlas (TCGA) [15,16]. These differences in staging, molecular and clinical behaviour suggest that NAC may have a differential effect in UCB and UTUC. However, only a little is known about the differential response and survival of patients with UCB and UTUC treated with a multimodal approach.

One might hypothesise that patients with UCB would have a higher rate of pathological response after NAC as they might benefit from the surgical effect of transurethral resection of the bladder (TURB). Conversely, UTUC may not be adequately resected endoscopically. However, patients with UTUC may have non-invasive disease at the onset. Therefore, having post-treatment pathological stage yp≤T1 after NAC is not due to any benefit from the systemic chemotherapy. There is an unmet need for clinical data comparing these two diseases in order to better understand the differential benefit of NAC.

To evaluate these issues, in the present study, we compared the response to NAC and survival of patients with UCB vs UTUC treated with NAC and radical surgery.

Patients and Methods

Study Population

We performed a retrospective analysis of 1830 patients treated with NAC followed by RC for UCB or RNU for UTUC from two established multicentre databases arising from international cooperation [9,17]. Patients with clinically distant metastatic disease (cM status) and those lost to follow-up were not included in the analysis, leaving 1575 patients for the final analyses. A flow diagram for the patient selection is shown in Fig. S1.

Chemotherapy

NAC regimens consisted in general of platin-based combination chemotherapy such as methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) or gemcitabine and cisplatin. Patients were grouped as cisplatin-based NAC or other, according to the NAC regimen that they received. Chemotherapy regimen and number of cycles was administered at clinician discretion in accordance with institutional standards and guidelines recommendation at the time [4,6,18].

Radical Surgery

All RC and RNU procedures were performed using standard techniques [4,6,18]. The decision for the approach (open, laparoscopic or robotic) and the extent of lymphadenectomy were at the discretion of individual surgeons based on patient and disease characteristics and preoperative imaging. All surgical specimens were processed according to standard

pathological procedures and staged according to the 1998 TNM classification.

Outcome Measurement

The primary endpoint was the association of disease location (UCB vs UTUC) with pathological complete response (pCR) defined as ypT0N0 status. The secondary endpoints included association of disease location with pathological objective response (pOR), defined as ypT0-Ta-Tis-T1N0 status, and the association of the disease with overall survival (OS) and cancer-specific survival (CSS).

On exploratory subgroup analyses we investigated the association of pathological stages and NAC response between UCB and UTUC with OS and CSS.

OS and CSS were calculated from the date of surgery until the last follow-up. Cause of death was recorded from patients' charts and/or death certificates.

Statistical Analysis

We performed a stepwise approach to the statistical analyses. First, we performed multiple imputations by using chained equations to handle missing data that were assumed to be missing at random. Five imputed data sets were generated using predictive mean matching for numeric variables, logistic regression for binary variables and Bayesian polytomous regression for factor variables. Second, uni- and multivariable logistic regression analyses were used to investigate the association of disease location with pCR and pOR. Third, we investigated the association of disease location with OS and CSS using uni- and multivariable Cox proportional hazard regression analysis and estimated the hazard ratios (HRs) with their 95% CIs. Fourth, we compared OS and CSS between groups using Kaplan–Meier curves and estimated difference in survival using the log-rank test. Fifth, we performed pre-planned subgroups analyses using Kaplan–Maier curves and Cox proportional hazard regression analyses to investigate the association of pathological stage and response to NAC with OS and CSS between UCB and UTUC. Sixth, we introduced interaction terms between disease location and postoperative pathological features to explore the synergistic effects of these combined predictors. Finally, we compared the predictive power of the additive and the interaction survival models by calculating the respective concordance indexes. Statistical significance was considered at $P < 0.05$. All tests were two-sided and performed with R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall, 1299 (82.5%) patients had UCB and 276 (17.5%) had UTUC. The clinicopathological features of the patients, stratified by disease location, are shown in Table 1.

A pCR after NAC was found in 250 (19.2%) patients with UBC and in 23 (8.3%) patients with UTUC ($P < 0.01$). A pOR after NAC was found in 523 (40.3%) patients with UBC and in 133 (48.2%) with UTUC ($P = 0.02$).

On univariable logistic regression analysis there was a statistically significant association of disease location with pCR (for UTUC: odds ratio [OR] 0.38, 95% CI 0.24–0.58; $P < 0.01$) and pOR (for UTUC: OR 1.38, 95% CI 1.06–1.79; $P = 0.01$) after NAC. On multivariable logistic regression, which adjusted for patient's sex, cisplatin-based NAC, number of NAC cycles and clinical N stage, disease location remained significantly associated with pCR (for UTUC: OR 0.45, 95% CI 0.27–0.70; $P < 0.01$) and pOR (for UTUC: OR 1.57, 95% CI 1.19–2.08; $P < 0.01$). The C-indexes for the models were 0.62 and 0.57, respectively (Table 2). On subgroups analyses in patients with clinically nodal positive stage, disease location was neither associated with pOR (for UTUC: OR 0.95, 95% CI 0.55–1.62; $P = 0.85$) nor with pCR (for UTUC: OR 0.73, 95% CI 0.28–1.64; $P = 0.47$).

The overall median (interquartile range [IQR]) follow-up for patients still alive was 18 (7–42) months. Within a median (IQR) follow-up of 18 (6.6–39) months in the UCB cohort,

Table 1 Clinicopathological features of 1575 patients treated with NAC and radical surgery with lymphadenectomy for UCB or UTUC.

Clinicopathological feature	UCB	UTUC	*P*
n	1299	276	
Male sex, *n* (%)	1002 (77.1)	189 (68.5)	<0.01
Age, years, median (IQR)	64 (57–71)	68 (61.7–74)	<0.01
Variant histology, *n* (%)	125 (9.6)	9 (3.3)	<0.01
Cisplatin-based NAC, *n* (%)	1077 (82.9)	212 (76.8)	0.02
NAC cycles, *n* (%)			
1	33 (2.5)	5 (1.8)	0.34
2–4	1153 (88.8)	240 (87)	
5–8	113 (8.7)	31 (11.2)	
ypT, *n* (%)			
ypT0	283 (21.8)	32 (11.6)	<0.01
ypTis/Ta	154 (11.9)	57 (20.7)	
ypT1	86 (6.6)	44 (15.9)	
ypT2	240 (18.5)	30 (10.9)	
ypT3/T4	532 (41)	112 (40.6)	
ypTx	4 (0.3)	1 (0.4)	
Pathological grade (WHO 2004), *n* (%)			
No malignancy	284 (21.9)	32 (11.6)	<0.01
High Grade	1011 (77.8)	231 (83.7)	
Low Grade	4 (0.3)	13 (4.7)	
ypN, *n* (%)			
ypN0	900 (69.3)	175 (63.4)	<0.01
ypNpos	350 (26.9)	64 (23.2)	
ypNx	49 (3.8)	37 (13.4)	
Nodes removed, *n* (%)	19 (12–31)	12 (5–20)	<0.01
Number of positive nodes, median (IQR)	2 (1–5.25)	1 (1–3)	0.01
STSM, *n* (%)			
Negative	1078 (83)	247 (89.5)	0.01
Positive	115 (8.9)	21 (7.6)	
Not evaluable	106 (8.2)	8 (2.9)	
Adjuvant chemotherapy, *n* (%)	0 (0)	24 (8.7)	<0.01

STSM, soft tissue surgical margin.

462 (36%) patients died from all causes and 372 (29%) died from UCB. Within a median (IQR) follow-up of 28 (11–59) months in the UTUC cohort, 102 (37%) patients died from all causes and 64 (23%) died from UTUC (Fig. 1).

On univariable Cox regression analyses UTUC was associated with better OS (HR 0.80, 95% CI 0.64–0.99; $P = 0.04$) and CSS (HR 0.63, 95% CI 0.49–0.83; $P < 0.01$). On multivariable Cox regression analyses, which adjusted for established pathological features, UTUC remained associated with CSS (HR 0.60, 0.45–0.81; $P < 0.01$), but not with OS (Table 3).

On subgroup analyses we investigated the association of pathological stage and response to NAC with survival. On univariable analyses, there was a difference in OS and CSS between patients with UCB and UTUC with ypT3/T4 disease (HR 0.71, 95% CI 0.53–0.94, $P = 0.02$; and HR 0.67, 95% CI 0.49–0.91, $P = 0.01$, respectively), as well as for CSS in patients with ypT1 disease (HR 0.17, 95% CI 0.04–0.72, $P = 0.01$; Fig. 2).

There was no difference in OS or CSS between patients with UCB and UTUC who achieved no response or pCR status after NAC. However, there was statistically significant difference in CSS between patients with UCB and UTUC with pOR after NAC ($P = 0.02$, Fig. 3). Specifically, the 5-year OS was 36% (95% CI 31–41) for UCB and 46% (95% CI 38–56) for UTUC. The 5-year CSS was 43% (95% CI 39–48) for UCB and 60% (95% CI 51–69) for UTUC. On multivariable Cox regression analyses disease location, pOR and pCR remained independently associated with OS and CSS (all $P < 0.05$). Interaction terms between disease location and response to NAC showed a causal association of pCR and disease location with OS ($P = 0.01$; Tables 4 and 5).

The multivariable Cox regression model, which investigated the prognostic value of pOR and pCR, had a lower discrimination compared to the model including ypT and ypN stage (Tables 3–5).

Discussion

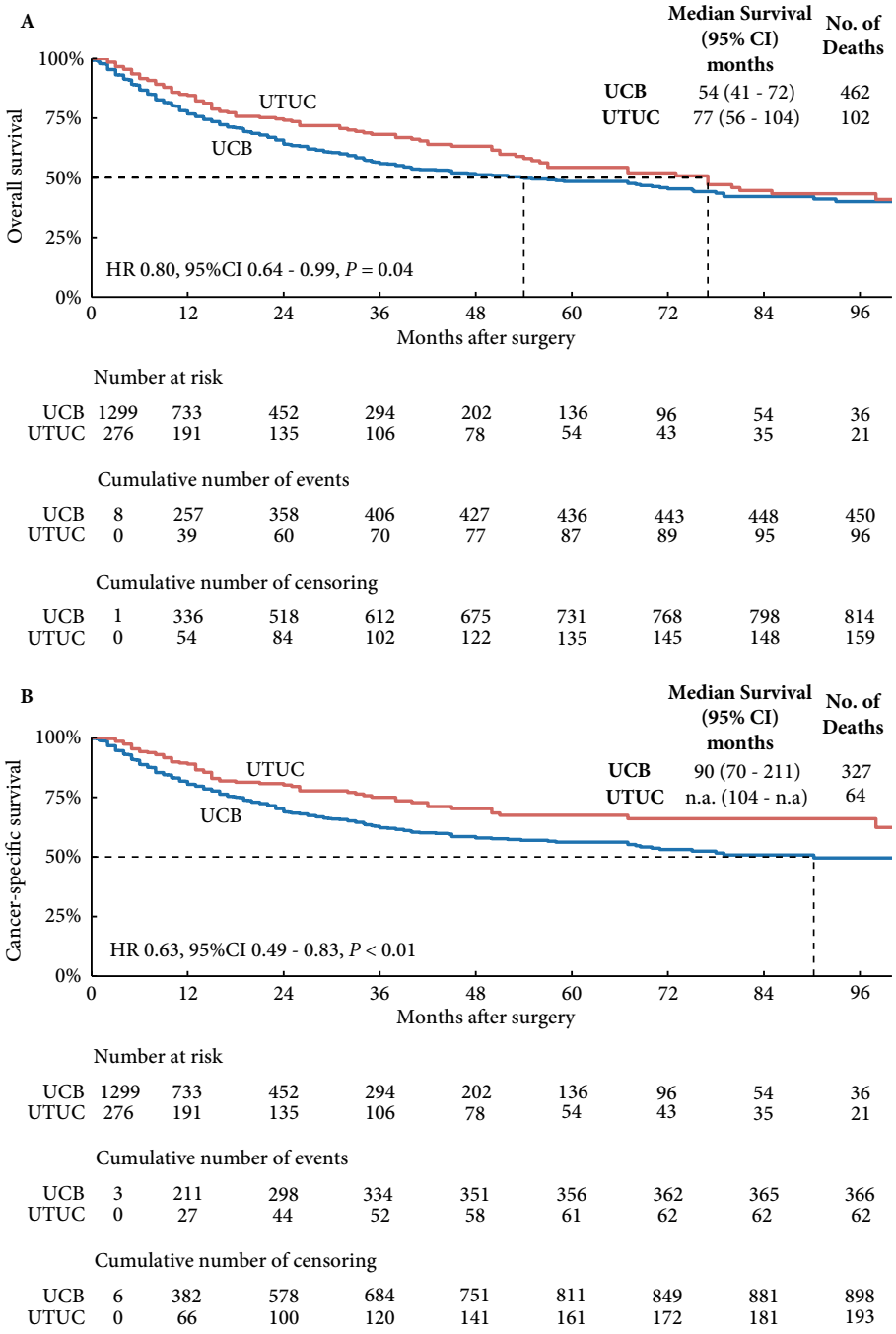
We used data from a large multicentre cooperation programme to assess the response to NAC in patients with UCB vs UTUC and found higher rates of pCR in patients with UCB, as well as an independent association of UCB with pCR. There are several explanations for these findings. First and foremost, these results highlight the challenge of an accurate preoperative clinical staging, which could have potentially led to the selection of patients with lower stage UTUC [19]. Multi-detector CT, for example, has an excellent diagnostic performance in the detection of UTUC [20]. However, its staging accuracy is very low in UTUC, as well as in UCB [21,22]. Endoscopic stage assessment of UTUC using ureteroscopy is notoriously difficult and the information obtained by biopsies is mainly limited to the tumour grade [23]. Moreover, discrepancies between clinical and pathological staging underscore the challenge in outcome measurement and lead to dissimilar results [19]. This mirrors the predictive ability of the model investigated in our present study, which is slightly better than a toss of a coin. Second, it has to be considered that patients with UCB undergo TURB before NAC and RC. TURB allows a better clinical staging [4,24], but also reduces the tumour burden, which could potentially bias response to NAC [25]. On the other hand, the endoscopic management of UTUC is generally limited to diagnostic purposes. Third, anatomical differences between UCB and UTUC lead to different treatment strategies [4], which can potentially delay definitive treatment and influence outcomes [25]. Indeed, adjuvant therapies such as BCG and mitomycin-C can be easily administered in UCB; however, the retrograde or percutaneous administration of these drugs is difficult and relatively ineffective in UTUC [6]. Furthermore, in a recent genomic analysis of 288 patients with MIBC treated with cisplatin-based NAC followed by RC, the authors found that patients with secondary MIBC had lower pathological response rates and worse survival

Table 2 Multivariable logistic regression predicting the association with pCR and pOR in 1575 patients treated with NAC and radical surgery for UCB or UTUC.

Variable	pCR			pOR		
	OR	95% CI	P	OR	95% CI	P
UTUC vs UCB	0.45	0.27–0.70	<0.01	1.57	1.19–2.08	<0.01
Male vs female sex	1.06	0.78–1.46	0.71	1.09	0.86–1.39	0.47
Cisplatin-based NAC	1.62	1.11–2.43	0.01	1.67	1.27–2.20	<0.01
Number of NAC cycles						
1 NAC cycle				Ref		
2–4 NAC cycles	1.18	0.52–3.19	0.71	1.37	0.71–2.80	0.37
5–8 NAC cycles	1.05	0.40–0.86	0.92	1.35	0.64–2.94	0.44
Clinical N stage						
cN0				Ref		
cNpos	0.60	0.40–0.86	<0.01	0.79	0.60–1.03	0.08
cNx	0.69	0.46–1.03	0.08	0.78	0.58–1.05	0.1
C-index			0.62			0.57

pCR, pathological complete response defined as ypT0N0; pOR, pathological objective response defined as ypT0-Ta-Tis-T1N0.

Fig. 1 OS (**A**) and CSS (**B**) of 1575 patients treated with NAC and radical surgery for UCB or UTUC.



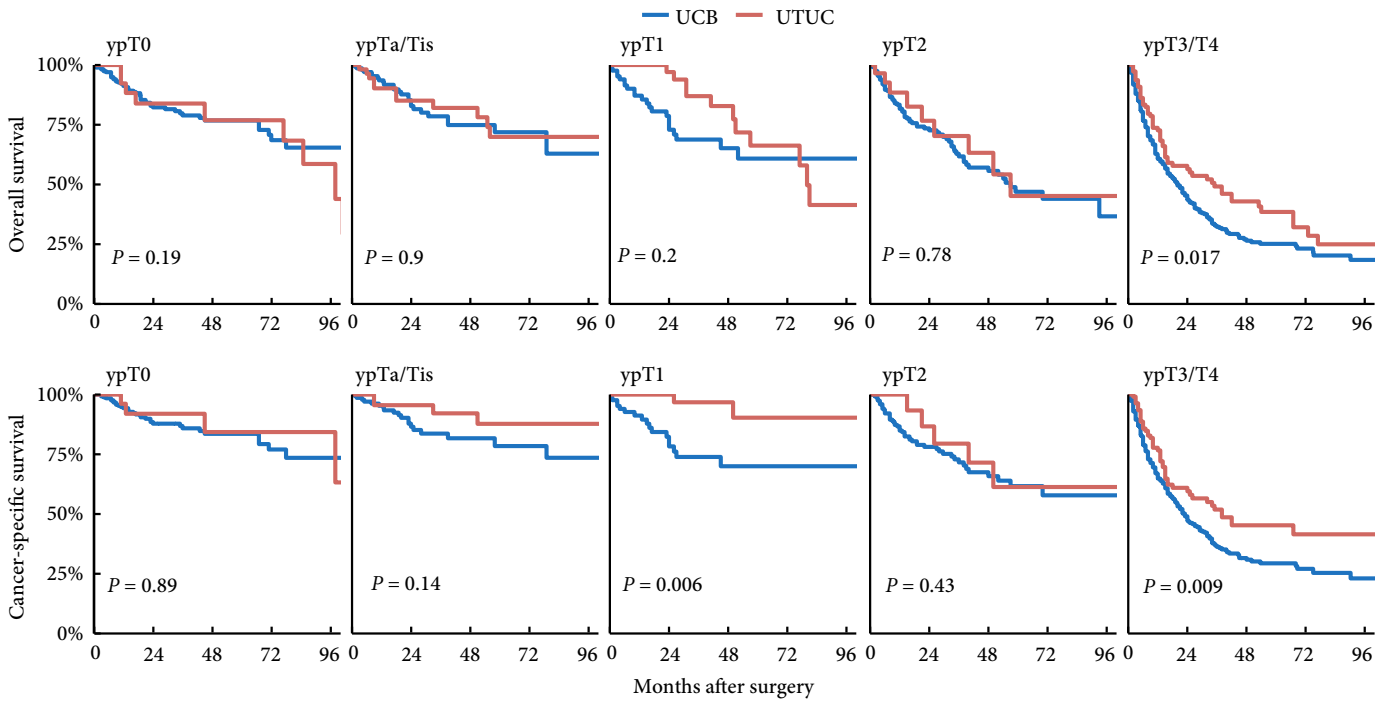
outcomes compared to patients with primary MIBC [26]. In our present analysis, an undefined proportion of patients in the UCB cohort had recurrent disease, while all patients in UTUC cohort had a primary diagnosis and were treated with upfront NAC. Finally, it has been shown that UTUC has a predominant luminal expression and is characterised by a lower total mutational burden and higher percentage of FGFR3 alterations compared to UCB [27]. These genetic differences between UCB and UTUC may be responsible for the differential response to NAC and survival found in our present study. Indeed, it is known that UCB with luminal subtype has better oncological outcomes compared to UCB with basal subtype [28], which derives more clinical benefit from NAC compared to luminal UCB [29]. Pathological tumour downstaging after NAC has been investigated in UCB and UTUC by several working groups [9,30–34] and is

Table 3 Multivariable Cox regression analyses predicting OS and CSS in 1575 patients treated with NAC and radical surgery for UCB or UTUC.

Variable	OS		CSS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
UTUC vs UBC	0.81 (0.64–1.02)	0.08	0.60 (0.45–0.81)	<0.01
Male vs female sex	0.95 (0.78–1.15)	0.60	0.95 (0.76–1.18)	0.64
Cisplatin-based NAC	0.76 (0.62–0.92)	<0.01	0.83 (0.66–1.05)	0.12
Pathological T stage				
ypT0	Ref		Ref	
ypTa/Tis	0.9 (0.6–1.35)	0.61	0.96 (0.57–1.63)	0.89
ypT1	1.24 (0.81–1.91)	0.33	1.26 (0.72–2.2)	0.43
ypT2	1.86 (1.34–2.59)	<0.01	2.02 (1.34–3.06)	<0.01
ypT3/T4	2.96 (2.21–3.95)	<0.01	4.2 (2.93–6.02)	<0.01
Pathological N stage				
ypN0	Ref		Ref	
ypNpos	2.27 (1.88–2.74)	<0.01	2.45 (1.98–3.02)	<0.01
ypNx	2.47 (1.78–3.44)	<0.01	2.58 (1.74–3.83)	<0.01
STSM				
Negative	Ref		Ref	
Positive	1.54 (1.21–1.97)	<0.01	1.39 (1.06–1.83)	0.02
Not evaluable	1.06 (0.76–1.47)	0.75	1.18 (0.83–1.68)	0.36
Adjuvant chemotherapy	0.6 (0.32–1.13)	0.11	0.93 (0.48–1.79)	0.82
C-index		0.74		0.77

STSM, soft tissue surgical margin

Fig. 2 OS and CSS of 1575 patients treated with NAC and radical surgery for UCB or UTUC.



indeed accepted as a surrogate marker for survival in retrospective series. However, to the best of our knowledge, none of the previous studies have performed a direct comparison of UCB vs UTUC.

We found a significant difference in survival between UCB vs UTUC. There is only a little evidence comparing oncological outcomes of UCB vs UTUC, with controversial results [12,13,35,36]. To the best of our knowledge, the present study is the first comparing response rates and survival outcomes of patients with these two diseases treated in a multimodal setting.

To date, the largest series reported on the stage-specific survival of 4335 patients with UCB and 2492 patients with UTUC treated with RC and RNU, respectively. NAC was not administered. Overall, authors found that patients with UCB were more likely

Fig. 3 OS and CSS of 1575 patients treated with NAC and radical surgery for UCB UTUC, stratified by patients with no response (n = 919), pOR (n = 656, defined as ypT0-Ta-Tis-T1N0) and pCR (n = 273, defined as ypT0N0) after NAC.

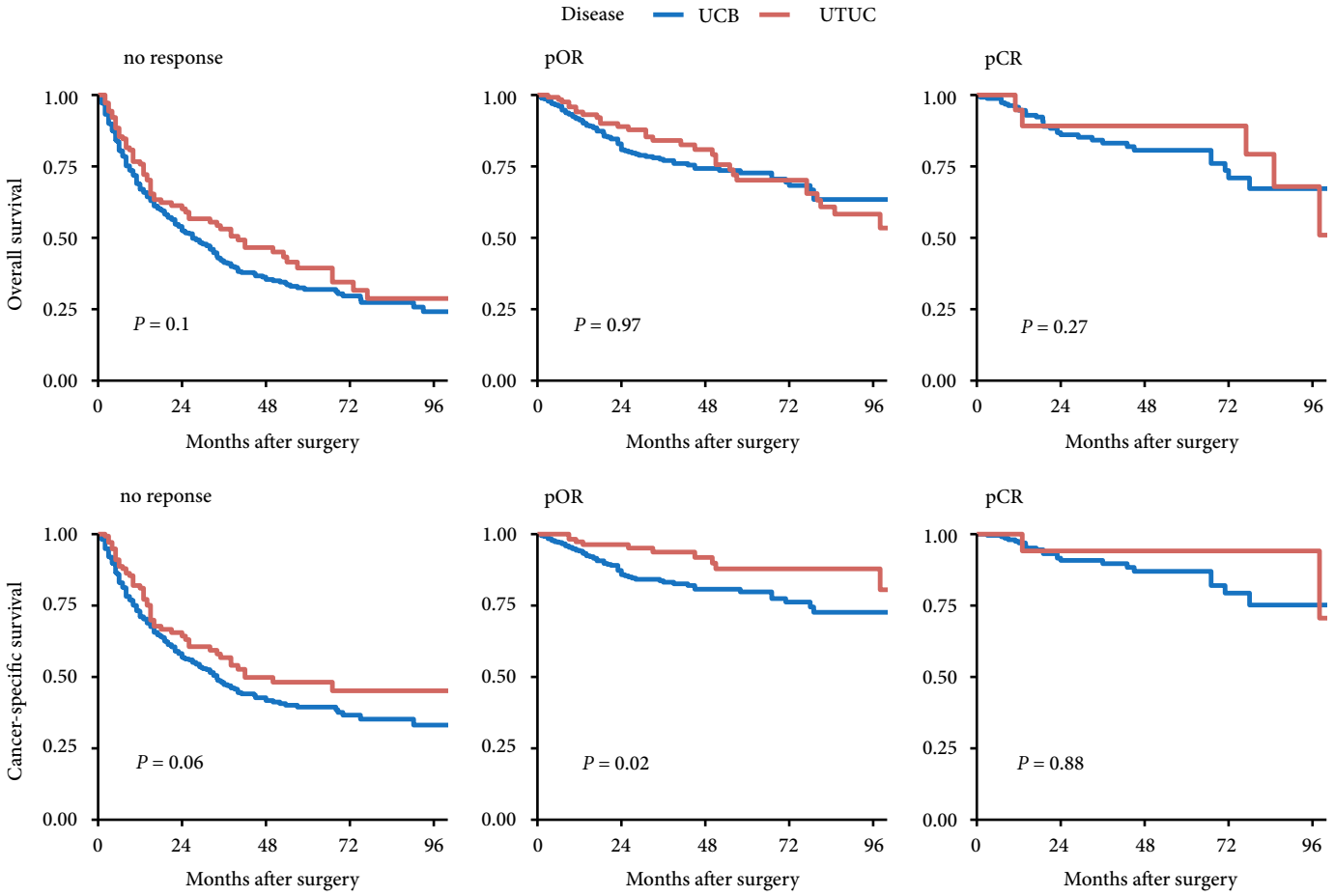


Table 4 Multivariable Cox regression analyses investigating the association of pOR after NAC with OS and CSS in 1575 patients treated with NAC and radical surgery for UCB or UTUC.

Variable	OS		CSS	
	HR (95% CI)	P	HR (95% CI)	P
pOR vs no response	0.33 (0.27–0.41)	<0.01	0.25 (0.19–0.32)	<0.01
UTUC vs UCB	0.89 (0.71–1.12)	0.33	0.68 (0.51–0.91)	<0.01
Male vs female sex	0.94 (0.78–1.14)	0.54	0.93 (0.74–1.15)	0.48
Cisplatin-based NAC	0.76 (0.62–0.93)	<0.01	0.84 (0.67–1.06)	0.14
STSM				
Negative				
Positive	2.05 (1.62–2.61)	<0.01	2 (1.53–2.61)	<0.01
Not evaluable	1.19 (0.86–1.64)	0.29	1.26 (0.89–1.79)	0.19
Adjuvant chemotherapy	0.78 (0.41–1.47)	0.44	1.24 (0.65–2.39)	0.51
pOR : UTUC*	1.28 (0.8–2.07)	0.30	0.69 (0.34–1.4)	0.30
C-index		0.69		0.71

*pOR, pathological objective response defined as ypT0-Ta-Tis-T1N0; STSM, soft tissue surgical margin. *Interaction term.*

to experience recurrence and cancer-specific mortality compared to patients with UTUC ($P < 0.001$). On subgroup analyses, non-invasive UCB was associated with worse survival outcomes, while in pT4 disease UTUC was associated with worse survival outcomes [12]. We expanded upon that study by comparing the survival in a cohort of patients treated with NAC, which is considered standard of care in MIBC [4] and a generally accepted option in high-grade UTUC.

Table 5 Multivariable Cox regression analyses investigating the association of pCR to NAC with OS and CSS in 1575 patients treated with NAC and radical surgery for UCB or UTUC.

Variable	OS		CSS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
pCR vs no response and pOR	0.34 (0.25–0.46)	<0.01	0.24 (0.16–0.36)	<0.01
UTUC vs UCB	0.73 (0.58–0.91)	<0.01	0.53 (0.4–0.71)	<0.01
Male vs female sex	0.93 (0.77–1.13)	0.49	0.92 (0.74–1.14)	0.43
Cisplatin-based NAC	0.74 (0.6–0.9)	<0.01	0.81 (0.64–1.02)	0.07
STSM				
Negative	Ref		Ref	
Positive	2.41 (1.9–3.05)	<0.01	2.41 (1.85–3.13)	<0.01
Not evaluable	1.15 (0.84–1.58)	0.39	1.21 (0.85–1.72)	0.29
Adjuvant chemotherapy	1.07 (0.57–2.01)	0.83	1.79 (0.93–3.45)	0.08
pCR : UTUC*	2.75 (1.23–6.12)	0.01	2.28 (0.66–7.9)	0.19
C-index		0.66		0.68

*pCR, pathological complete response defined as ypT0N0; pOR, pathological objective response defined as ypT0-Ta-Tis-T1N0; STSM, soft tissue surgical margin. *Interaction term.*

The results of our present study support the use NAC also in UTUC and generate the hypothesis that patients with UTUC who do not respond to NAC may have better CSS compared to UCB if treated in a multimodal setting, particularly in locally advanced stage. However, results from an ongoing randomised trial (NCT02969083) [37] are awaited to shed light on the real benefit of NAC in UTUC.

The results of our present analysis have several implications for clinical practice, translational research and clinical trial design. Indeed, these data reflect real-world clinical cohorts, allowing feasible replication and complementing of clinical trials, and generalisability [38]. Moreover, the reduction in renal function after RNU is the main limitation for the administration of cisplatin-based chemotherapy. Based on our present results, the administration of NAC could represent a better time-point in the multimodal treatment of UTUC.

Despite its strengths our present study is not devoid of limitations, which are mainly inherent to its retrospective design and the significant selection bias. We could not adjust for surgical quality and lymphadenectomy template. Preoperative staging and the administration of NAC were not standardised. We could not account for patients' performance status, renal function and comorbidities, which could have influenced the clinical decisions of giving NAC; leading, therefore, to the selection of patients with a longer life expectancy. We acknowledge the difference in follow-up time between groups. We could not account for the number of previous organ-sparing therapies, the number of recurrences, or the administration of adjuvant or systemic therapies. Despite accounting for missing data, we could not adjust for not measurable confounders.

Conclusion

Our present study generates the hypothesis that, despite stage and genetic specific differences, the benefit of NAC in UTUC is similar to that which is known in UCB. Although pCR rates were lower in patients with UTUC, survival rates between groups were comparable, underscoring the role of consolidative RNU as an essential step in the management of the disease. These data can be used as a benchmark to contextualise survival outcomes and plan future trial design with NAC in UC.

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Conflicts of Interest

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Abbreviations: CSS, cancer-specific survival; HR, hazard ratio; IQR, interquartile range; MIBC, muscle-invasive urothelial carcinoma of the bladder; NAC, neoadjuvant chemotherapy; OR, odds ratio; OS, overall survival; pCR, pathological complete response; pOR, pathological objective response; RC, radical cystectomy; RNU, radical nephroureterectomy; UC(B), urothelial carcinoma (of the bladder); UTUC, upper tract UC.

Supporting Information

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

Fig. S1. Patient selection process.