Original Article

Effect of neoadjuvant chemotherapy on locally advanced upper tract urothelial carcinoma: a pooled analysis

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Background: The outcome of neoadjuvant chemotherapy (NAC) has been established in bladder cancer but remains controversial in upper tract urothelial carcinoma (UTUC). In this work, we explored the therapeutic effect of NAC in patients with locally advanced UTUC.

Methods: We conducted a literature search on articles published from 1995 up to April 2020 in PubMed/Medline, the Cochrane Library, Embase, Google Scholar. A total of 19 eligible studies with 6,283 patients were identified, from which the overall survival (OS), cancer-specific survival (CSS), progression-free survival (PFS), disease-free survival (DFS), pathological complete response (pCR) rate and pathological partial response (pPR) rate were extracted. All analyses were conducted using Review Manager 5.3 and Stata statistical software (version 15).

Results: In total, 6,283 UTUC patients were included from 19 eligible studies out of which 1,474 patients received NAC and subsequent radical nephroureterectomy (RNU), whereas 4,809 patients received RNU only. Compared with single RNU, patients with NAC and subsequent RNU exhibited longer OS, CSS, PFS, DFS by hazard ratio (HR) 2.14 [95% confidence interval (CI): 1.75–2.63; P<0.001], HR 2.07 (95% CI: 1.49–2.87; P<0.001), HR 2.00 (95% CI: 1.42–2.83; P<0.001), and HR 3.76 (95% CI: 2.16–6.56; P<0.001). pCR rate and pPR rate of NAC are 0.10 (0.07–0.13) and 0.40 (95% CI: 0.32–0.49, P <0.001) respectively.

Conclusions: This work revealed that NAC and subsequent RNU provided better survival outcomes in patients with locally advanced UTUC when compared with single RNU.

Keywords: Upper tract urothelial carcinoma (UTUC); neoadjuvant chemotherapy (NAC); survival outcomes; effect; pooled analysis

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Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively rare disease and the proportion is only 5–10% in urothelial carcinomas, about 2 cases in 100,000 residents in Western countries (1,2). Overall, compared with 15–25% cases of bladder tumors, 60% of UTUCs are invasive diagnosis (1,3). Following the EAU guideline, UTUC is recommended in radical nephroureterectomy (RNU) with excision of ipsilateral bladder cuff (1), however, high recurrence rate of advanced UTUC after standard has been reported to cause an unsatisfying prognosis and inaccurate treatment (3,4). Fortunately, increasing assessments have revealed that both neoadjuvant chemotherapy (NAC) and adjuvant chemotherapy (AC) may improve the survival in advanced UTUC (5,6).

Moreover, the effect of NAC in advanced bladder cancer has been affirmed through randomized clinical trials (7). Due to the infrequency of UTUC, clinical trials of NAC in UTUC may be associated with drawbacks, among them, difficulty in enrollment and longtime follow-up. A published prospective study that enrolled 30 patients revealed pathological complete response (pCR) without any prognosis indicators (8). Several retrospective studies have also confirmed high overall survival (OS) and disease-free survival (DFS) by examining the influence of perioperative chemotherapy for UTUCs. Compared with AC, NAC may offer additional benefits. For example, for patients whose renal function is damaged by RNU, chemotherapy or higher doses of chemotherapy may be unsuitable compared with NAC (9-11). A phase 3, open-label, randomized controlled trial with 126 participants showed that AC significantly improved DFS (HR 0.45, 95% CI: 0.30–0.68; P=0.0001) (12), but 44% patients developed acute grade 3 or worse treatment-emergent adverse events (P<0.0001). Additionally, some UTUC patients are excluded from AC because of insufficient recovery after surgery, this might underestimate the incidence rate of adverse events. By 1995, Igawa *et al.* began to adopt cisplatin-based NAC to manage 15 advanced UTUC patients. Notably, the patients showed a 13% pathologic complete response (pCR) rate, a 40% pathological partial response (pPR) rate, and an overall response rate of 53% (13). Several studies also proved that NAC potentially exerted pPR and pCR. Besides, numerous investigations demonstrated that NAC provided better survival outcomes than when surgery is used alone (14). On the contrary, other studies found no differences in survival outcomes when they compared patients who underwent NAC plus RNU with those subjected to surgery without NAC (15,16). Therefore, the treatment efficacy of NAC in advanced UTUC remains elusive, and whether NAC could serve as a more suitable management tool deserves further in-depth studies.

Recently findings published by Kim and his colleagues that investigated the effect of NAC on locally advanced UTUC patients indicate that patients subjected to NAC plus RNU showed better survival outcomes (17). But they pooled only 4 studies in their analysis, which rendered their results inaccurate and incomplete. This work, therefore, purposed to provide a more comprehensive and up to date report that evaluates the efficacy of NAC in advanced UTUC patients. We present this article in accordance with the PRISMA reporting checklist (available at http://dx. doi. org/10. 21037/tau–20–933).

Methods

Search strategy

All the related articles were identified from PubMed, Embase, Cochrane Library, and Google Scholar until April 2020. The selection criterion is highlighted in *Figure 1*. The search terms included: (((neoadjuvant chemotherapy) OR (perioperative chemotherapy) OR (preoperative chemotherapy))) AND ((upper tract urothelial carcinoma) OR (Ureteral Neoplasms) OR (kidney pelvis carcinoma)) AND ((Prognosis) OR (Prognostic Factors) OR (Prognostic Factor) OR (Factors, Prognostic)). To complete the search, these terms were either searched separately or in a combinational manner. All identified studies were reviewed, original studies listed as references, and examined through a manual search by different authors, independently.

Inclusion and exclusion criteria

A total of 19 articles were selected based on the following 5 criteria (PICOS principle): (I) population (P), patients pathologically diagnosed as advanced UTUC; (II) intervention (I): treated with NAC with subsequent RNU; (III) comparison (C): treated with RUN only; (IV) outcomes (O): prognosis indicators including OS (periods from the start of treatment to death from any cause), cancer-specific survival (CSS) (cancer survival in the absence of other causes of death), progression-free survival (PFS) (periods from the start of treatment to disease progression or death from any cause), DFS (periods from the start of treatment to disease recurrence or death from any cause), pCR rate (achieve pT0N0 disease condition after treatment) and pPR rate (achieve ≤pT2N0 disease condition after treatment); (V) study design (S), both randomized controlled trials and retrospective trials relative to this subject. Eligible studies were identified as follows: (I) accurately defines prognosis indicators. (II), Have data in pathological response rate, the hazard ratio (HR) with 95% confidence interval (CIs), or sufficient original data to calculate pathological response rate or HR and 95% CI. (III) Patients pathologically diagnosed as advanced UTUC. (IV) Reliable quality evaluated by Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. (V) Published article in English language on a human subject. Studies on bladder urothelial cancer, UTUC treated with AC and unsuitable forms such as reviews, case series, case reports, editorials, letters, among others were excluded.

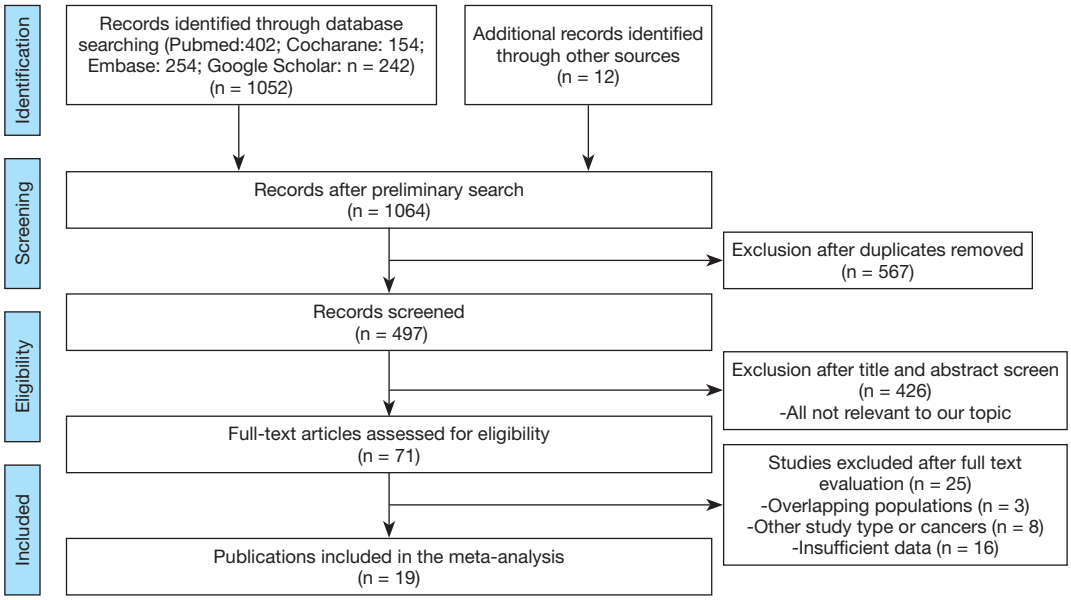


Figure 1 Flowchart for article selection.

Data extraction and quality assessment

In extracting data from the enrolled studies, 3 authors (Dongxu Qiu, Jiao Hu, and Tongchen He) reviewed each article and independently collected data from the 19 published studies. Any emerging conflict was resolved through debate. Extracted items from those articles included author, year, country, study design, tumor stage, NAC regimen, and oncologic outcomes (OS, CSS, PFS, DFS, pCR, pPR). The effective percentage of available HRs and 95% CIs provided by articles were directly extracted. Then, using originally recorded statistical data, the HRs and 95% CIs were calculated.

The quality of the articles was evaluated by 3 authors (Dongxu Qiu, Jiao Hu, and Tongchen He) using methodology, precision of results, consistency of results, directness, and risk of publication bias according to GRADE system. As a result, all studies were classified into one out of 4 evidence quality levels (high, moderate, low, and very low). In addition, publication bias was evaluated through visual inspection of funnel plots, whereas to determine the reliability of each result, a sensitivity analysis was conducted using the leave-one-out cross-validation

Statistical analysis

HRs, 95% CIs of OS, CSS, PFS, and DFS were extracted or calculated from enrolled studies. The I^2 test estimated study variance. If the I^2<50%, a fixed-effect model would be used, If the I^2>50%, a random effect model would be applied. Publication bias was evaluated by funnel plots. As mentioned above, a sensitivity analysis was performed to assess the stability of each result. All the analyses were performed with Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) (including OS, PFS, DFS, CSS) and Stata statistical software (version 15) (including pCR and pPR rate). All P-values were two-sided, and P<0.05 was considered statistically significant.

Results

Search results

In total, 19 eligible studies were enrolled in the pooled analysis from which a total of 6,283 UTUC patients were recruited. Among them, 1,474 UTUC patients accepted NAC and subsequent RNU, while 4,809 patients underwent RUN only. The process of enrolling studies was documented in *Figure 1*. Extracted information for each enrolled study is presented in *Table 1*. The outcomes of each included study are provided in *Table S1*. The final pooled results of all studies are displayed in *Table 2*.

Table 1 Characteristics and details of included studies

Author	Year	Country	Type	NAC regimen	UTUC stage	Period of follow-up	Patient number	Extracted prognosis indicators
Foerster *et al.*	2020	Austria	Retrospective multicenter	MVAC GC GCb and others	NA	NA	NAC + surgery: 267	pCR pPR
Pelcovits *et al.*	2020	USA	Retrospective single center	NA	N+ M0	39.5 months	NAC + surgery: 60; surgery only: 734	OS
Margulis *et al.*	2020	USA	Prospective multi-institution	MVDC	NA	NA	NAC + surgery: 30	pCR
Meng *et al.*	2019	USA	Retrospective multicenter	cisplatin-based	T0-T3 N0-Nx	NAC + surgery: 21 months; surgery only: 24 months	NAC + surgery: 25; surgery only: 36	OS PFS pCR pPR
Martini *et al.*	2019	USA	Retrospective multicenter	NA	T1-T4	28 months	NAC + surgery: 264	pCR pPR
Chakiryan *et al.*	2019	Portland	Retrospective single center	NA	N+M0	NA	NAC + surgery: 113; surgery only: 607	OS pPR
Chen *et al.*	2020	China	Retrospective multicenter	GC	T2-T4a	36 months	NAC + surgery:37; surgery only: 37	OS DFS
Liao *et al.*	2018	USA	Retrospective single center	GC d-MVDC	T0-T4	NA	NAC + surgery:32	pCR
Almassi *et al.*	2018	USA	Retrospective single center	NA	Ta-T4 p	NA	NAC + surgery: 260	pCR pPR
Hosogoe *et al.*	2018	Japan	Retrospective single center	GC GCb	T3-4 or N+	NAC + surgery: 24 months; surgery only: 34 months	NAC + surgery: 51; surgery only: 51	OS CSS PFS pPR
Cohen *et al.*	2017	USA	Retrospective	Emcitabine, carboplatin, cisplatin, and paclitaxel	Ta-T4 N0-Nx	35 months	NAC + surgery: 62; surgery only: 2,965	CSS
Kubota *et al.*	2017	Japan	Retrospective multicenter	GC GCb	T3-4 or N+	NA	NAC + surgery: 101; surgery only: 133	OS PFS CSS
Kobayashi *et al.*	2016	Japan	Retrospective single center	MEP MVAC GC	Tany and N+	NAC + surgery: 33 months; surgery only: 12 months	NAC + surgery: 24 surgery only: 31	OS CSS PFS DFS pPR
Porten *et al.*	2014	USA	Retrospective single center	Ifosfamide Cisplatin	T1-4 N0-N2	NA	NAC + surgery: 31; surgery only: 81	OS DFS
Kitamura *et al.*	2012	Japan	Retrospective single center	NA	Tany and N+	81 months	NAC + surgery: 15; surgery only: 14	OS pCR pPR

Table 1 (*Continued*)

Table 1 (*Continued*)

Author	Year	Country	Type	NAC regimen	UTUC stage	Period of follow-up	Patient number	Extracted prognosis indicators
Youssef *et al.*	2011	USA	Retrospective multicenter	MVAC GC	T0-T4 N0-N2	NA	NAC + surgery: 18; surgery only: 120	DFS
Rajput *et al.*	2011	USA	Retrospective single center	Methotrexate, vinblastine, doxorubicin, and cisplatin	T0-T4	NA	NAC + surgery: 26	pCR
Matin *et al.*	2010	USA	Retrospective single center	MVAC GC/GCI others	T0-T4 N+	NA	NAC + surgery: 43	pCR pPR
Igawa *et al.*	1995	Japan	Retrospective single center	MVAC MVEC MEC	T2-T4	NA	NAC + surgery: 15	pCR pPR

OS, overall survival; CSS, cancer-specific survival; PFS, progression-free survival; DFS, disease-free survival; pCR, pathological complete response pPR, pathological partial response. NA, not available GCarbo , gemcitabine and carboplatin; MVAC, methotrexate; vinblastine; doxorubicin; and cisplatin; GC, gemcitabine and cisplatin; MEP, methotrexate, etoposide, and cisplatin; MEC, methotrexate, etoposide and etoposide; MVEC, methotrexate, vinblastine, etoposide and cisplatin; GCI, gemcitabine and cisplatin, and ifosfamide; d-MVDC, dose dense methotrexate, vinblastine, doxorubicin and cisplatin.

OS

In total, 9 included studies reported the OS results (14,18-25). After pooling the data across the 9 studies, we obtained the results were HR 2.14 (95% CI: 1.75–2.63; P<0.001), which represented a 2.14 times OS benefit in UTUC patients undergoing NAC following surgery compared to surgery alone (*Figure 2A*). Notably, there was no significant heterogeneity among studies based on Cochran Q statistics (P<0.001) and I^2=8%. Heterogeneity (I^2<50%) was low in OS analyses. Hence, this study used a fixed-effect model.

CSS

Four studies were pooled in the CSS subgroup (21-23,26). Pooled HR was calculated as 2.07 (95% CI: 1.49–2.87; P<0.001), representing 2.07 times benefit in CSS (*Figure 2B*). Based on Cochran Q statistics (P<0.001), there was no heterogeneity among studies when I^2=0%. Hence, we used a fixed-effect model.

PFS

PFS results were reported in 4 studies (19,21-23). After data were pooled across 4 studies, it was found that HR 2.00 (95% CI: 1.42–2.83; P<0.001), which represents a 2 times PFS benefit in UTUC patients after using NAC following RNU compared with surgery alone (*Figure 2C*). No heterogeneity existed among studies based on Cochran Q statistics (P<0.001) and I^2=0%. Heterogeneity (I^2<50%) was low in PFS analyses, thus, adopting a fixed-effect model.

DFS

Here, a total of 4 included studies were pooled in the DFS subgroup (14,21,23,27). Pooled HR was calculated 3.76 (95% CI: 2.16–6.56; P<0.001), representing 3.76 times benefit in DFS (*Figure 2D*). Based on Cochran Q statistics (P<0.001), there was no heterogeneity among studies when I^2=0%, therefore, we used a fixed-effect model.

pCR rate and pPR rate

pCR rate was reported in 10 studies (8,13,16,19,25,28-32). After pooling data across the 10 studies, the pooled pCR rate was 11% (95% CI: 0.07, 0.14; P=0.058), implying that about one in ten patients with UTUC treated with

Table 2 Summary of pooled survival outcomes (NAC + surgery versus surgery alone in UTUC) and efficiency rate of NAC in UTUC

Outcomes	No. of participants (studies)	No. of patients (events)		Effect relative (95% CI)	P value	I^2	Effect model
		NAC + surgery	Surgery only				
OS	9	457	1724	HR 2.14 (1.75–2.63)	<0.001	8%	Fixed
CSS	4	238	3180	HR 2.07 (1.49–2.87)	<0.001	0%	Fixed
PFS	4	201	251	HR 2.00 (1.42–2.83)	<0.001	0%	Fixed
DFS	4	110	269	HR 3.76 (2.16–6.56)	<0.001	0%	Fixed
pCR	10	977	NA	0.11 (0.07–0.14)	0.058	45.3%	NA
pPR	10	939	NA	0.40 (0.31–0.49)	<0.001	86.60%	NA

OS, overall survival; CSS, cancer-specific survival; PFS, progression-free survival; DFS, disease-free survival; pCR, pathological complete response; pPR, pathological partial response; NA, not available; HR, hazard ratio; CI, confidence interval.

NAC can achieve pCR (*Figure 3A*). Heterogeneity existed among studies based on Cochran Q statistics (P=0.036) and I^2=34.7%. In addition, pPR rate was displayed in 10 studies (13,19-21,23,25,28,29,31,32). After analyzing data from the 10 studies, the pooled pPR rate was 40% (95% CI: 0.32–0.49; P<0.001), which revealed that about 4 in ten patients with UTUC treated with NAC can achieve pPR (*Figure 3B*). In subgroup analysis, pCR rate of patients with stage TxN0 was 0.11 (95% CI: 0.05–0.16; P=0.014) (*Figure 4A*), and pCR rate of patients with stage TxNx was 0.12 (95% CI: 0.03–0.21; P=0.200) (*Figure 4B*). In subgroup analysis of pPR rate, patients with stage TxN0 was 0.27 (95% CI: 0.23–0.31; P=0.339) (*Figure 4C*), and patients with stage TxNx was 0.36 (95% CI: 0.29–0.42; P=0.520) (*Figure 4D*).

Quality assessment, sensitivity, and publication bias

To evaluate how individual studies impacted the pooled results, a sensitivity analysis was performed by eliminating one study at a time. However, there were no significant changes thus, this verified the reliability of the pooled results. GRADE quality assessments of each outcome are shown in *Table S2*. The certainty of 4 comparisons and 2 response rates was extremely low. Funnel plots of each outcome are displayed in *Figure S1*.

Discussion

Urothelial cancers that transpire in the upper (including ureteral neoplasms or kidney pelvis carcinoma) or lower tracts (bladder cancer) , exhibit similar biological, practical, anatomical features and other aspects, but also have some differences (33). At diagnosis, about 15% to 25% of bladder cancer cases are reported, whereas more than 60% of UTUC cases are diagnosed at advanced stages. This implies that UTUC is more invasive and with worse prognosis (9). The EAU guideline [2020] on UTUC recommends RNU plus excision of ipsilateral bladder cuff for high-grade UTUC (34). For patients with advanced UTUC, a higher prognosis benefit is achieved when chemotherapy and RNU are combined that when chemotherapy is used alone (35). With the recent advancement and increasing utilization of NAC in bladder cancer, increasing NAC utilization in high-grade UTUC aroused our interests. NAC utilization is currently more frequent compared to previous reports (32). It is worth noting that adjuvant therapy after RNU is restricted especially when there is decreasing renal function. In phase 3, open-label, randomized controlled trial (a POUT trial), better DFS outcome was reported in patients subjected to AC compared to the surveillance group (HR 0.45, 95% CI: 0.30–0.68; P=0.0001) (12). However, the side effects of AC could not be ignored at the same time. After AC, 44% of patients developed acute grade 3 or worse treatment-emergent adverse events, compared with 4% in the surveillance group (P<0.0001). Furthermore, some UTUC patients were excluded from the AC group due to the unsatisfactory recovery after RNU, which potentially underestimate the incidence rate of adverse events. On the other hand, NAC is not associated with a similar side effect and may play a more indispensable role in managing advanced UTUC (36,37). Elsewhere, a retrospective study reported no difference in prognosis between NAC plus RNU and RNU plus AC in high-grade UTUC patients, and the study hypothesized that patients who responded to NAC showed better survival compared with AC (38).

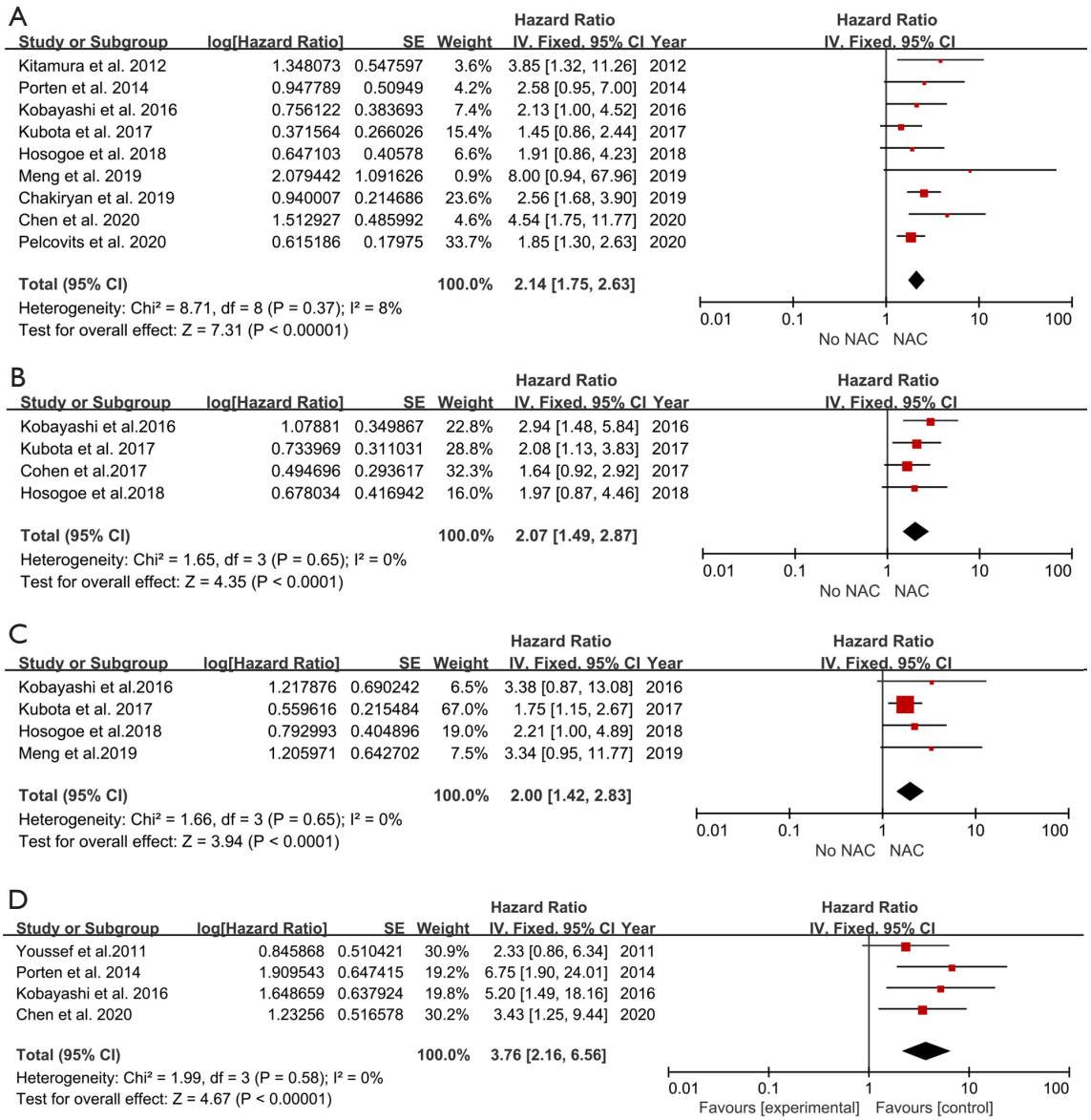


Figure 2 Pooled survival outcomes of UTUC patients treated with NAC plus RNU compared to RNU alone. (A) Overall survival (OS); (B) cancer-specific survival (CSS). (C) progression-free survival (PFS); (D) disease-free survival (DFS). UTUC, upper tract urothelial carcinoma; NAC, neoadjuvant chemotherapy; RNU, radical nephroureterectomy.

Whether NAC would achieve a better outcome than AC should be intensively explored. After reviewing published articles in PubMed/Medline, the Cochrane Library, Embase and Google Scholar, we identified most included articles to be retrospective. For keeping pace with research actuality of NAC in UTUC patients, we deeply analyzed about launching clinical trials about this subject. The recruitment status of NCT01663285 was terminated because it did not enroll enough participants. Besides, the recruitment status of NCT01261728 is active, not recruiting, without relevant published articles. Notably, one prospective article of NCT02412670 enrolled 30 patients in the study and showed pathologic complete response without other prognosis indicators (8). To ensure completeness and persuasiveness of our study, we included this article in the analysis. Other clinical trials such as NCT02876861,

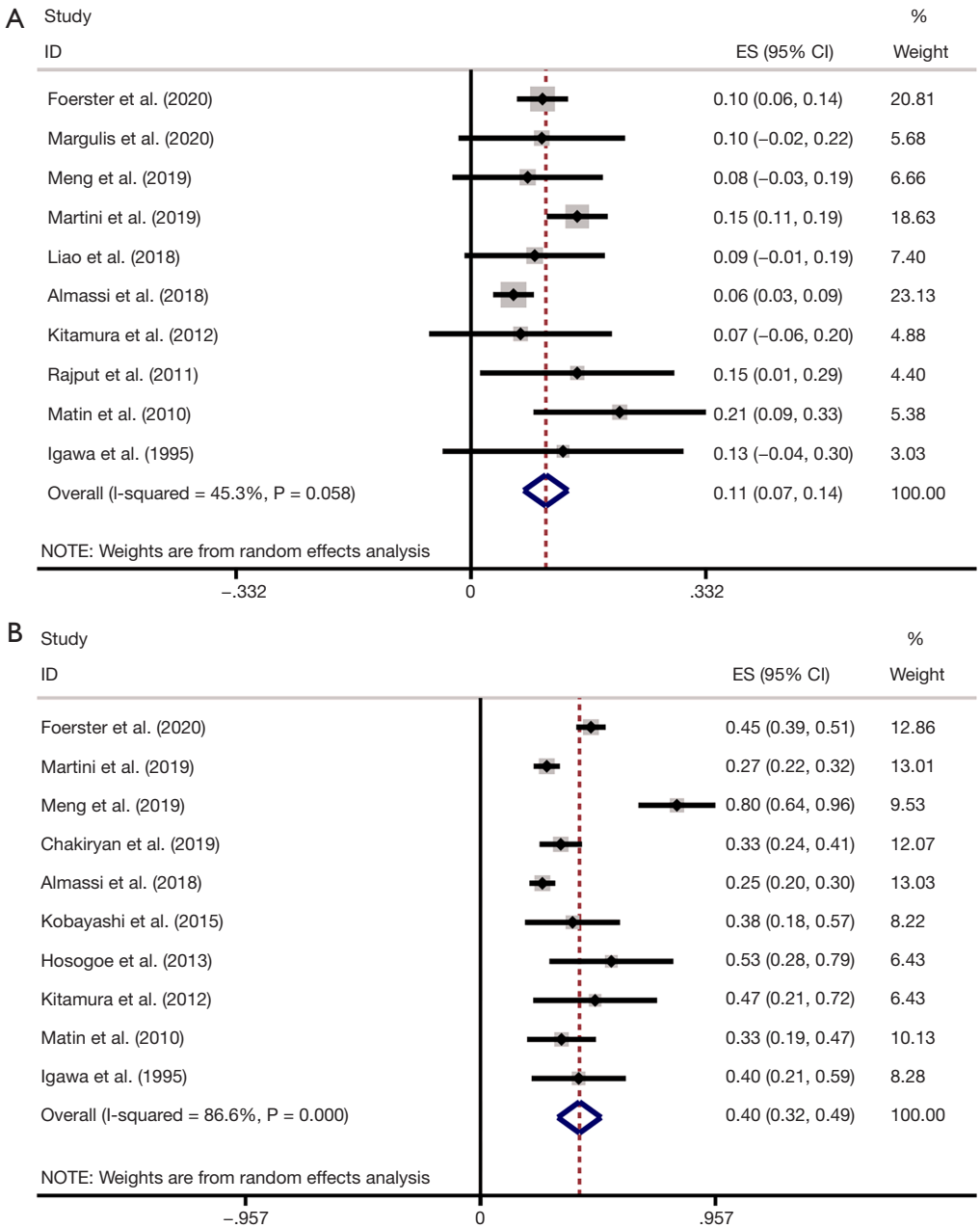
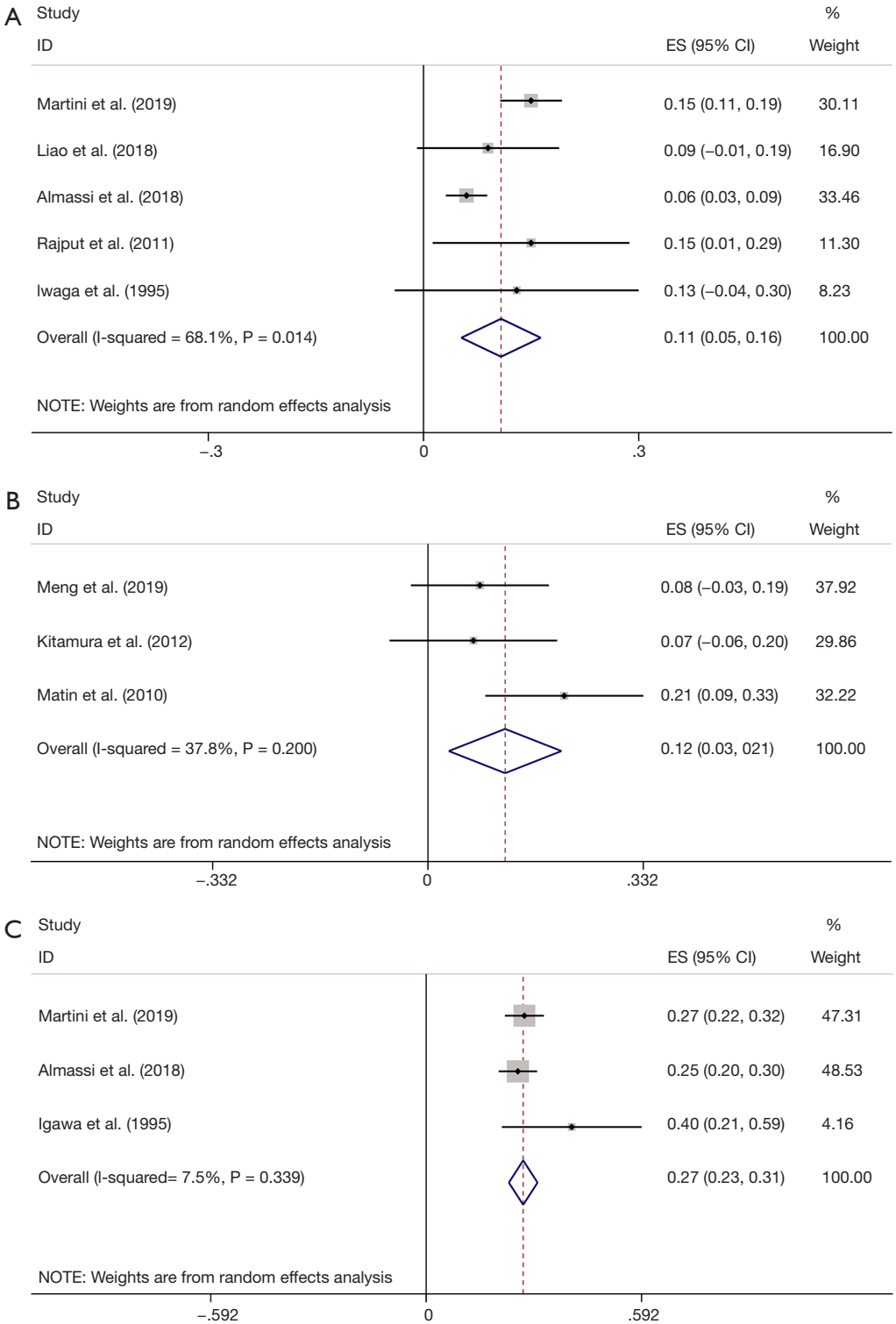


Figure 3 Pooled efficiency rates of UTUC patients treated with NAC. (A) Pathological complete response (pCR) rate; (B) pathological partial response (pPR) rate. UTUC, upper tract urothelial carcinoma; NAC, neoadjuvant chemotherapy.

NCT02969083 and NCT04099589 were conducted to assess the significance of NAC in UTUC, the status of 3 clinical trials is recruiting. The status of another clinical trial (NCT00696007) is withdrawn because the study did not recruit subjects meeting the inclusion criteria. We found no published article on the above 4 clinical trials. Additional details of clinical trials are displayed in the *Table S3*.

From the included studies, we revealed a smaller proportion of UTUC patients treated with NAC, but these patients exhibited a better prognosis compared to those who received surgery alone. After pooling data from 19 studies, we reported 2.14 times benefit in OS, 2.07 times benefit in CSS, 2 times benefit in PFS, and 3.76 times benefit in DFS, as well as, 10% pCR rate and 40% pPR



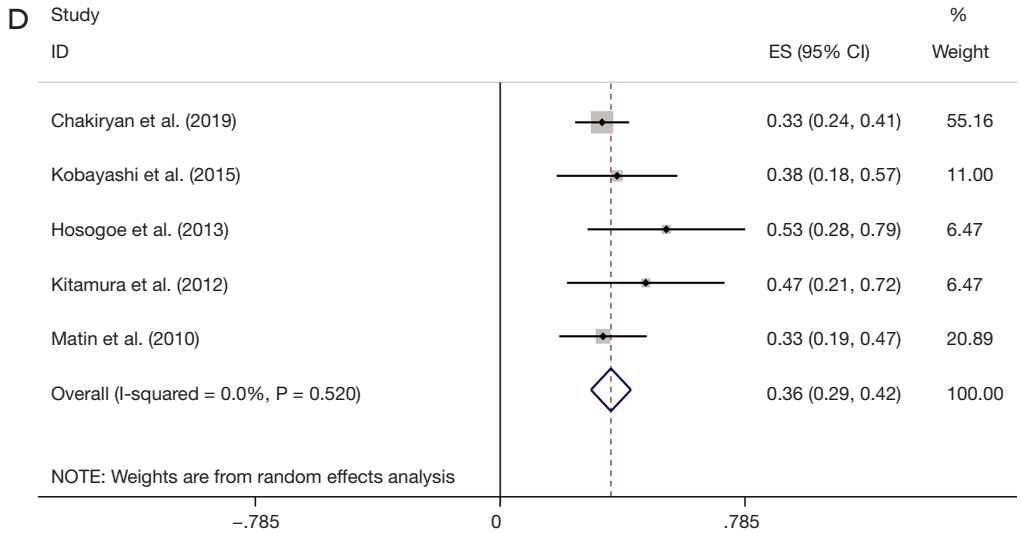


Figure 4 Subgroup analysis of pathological complete response (pCR) rate and pathological partial response (pPR) rate. (A) pCR rate of patients with stage TxN0; (B) pCR rate of patients with stage TxNx; (C) pPR rate of patients with stage TxN0; (D) pPR rate of patients with stage TxNx.

rate among UTUC patients undergoing NAC followed by compared to patients subjected to surgery alone. Yang *et al.* in their study explored the effect of AC and NAC in UTUC patients, however, only two prognosis indicators of NAC (OS and CSS) were studied in this study (39). Studies published by Leow *et al.* and Gregg *et al.* included only two retrospective studies in their analyses. What's more, the above studies are largely heterogeneous in terms of patient characteristics, because they defined high-risk UTUC based on tumor grade, tumor burden, and architecture, rather than the TNM staging system (5,40). Of note, Kim *et al.* in his studies included 4 articles and added more prognosis indicators (OS, CSS, PFS, and effect of NAC on downstaging) (17), but it evident that the included studies were uncomplete and all were based in one country, which perhaps cannot extend or apply to different ethnic groups. Therefore, evidence on the benefits and prognosis of NAC presented by these studies may not be persuasive. In our study, we included 19 articles and added 3 new effectivity indicators including DFS, pPR and pCR, which advanced the prognosis indicators and provided more meaningful and persuasive evidence to support the use of NAC in advanced UTUC patients.

Concerning pPR and pCR, no previous pooled analyses have explored the 2 outcomes. In total, we included 12 studies, the pooled pCR was 11% (95% CI: 0.07, 0.14; P=0.058), and pooled pPR rate was 40% (95% CI: 0.31–0.49; P<0.001). To further assess the effect in various diseases and whether it lowers the heterogeneity, we conducted a subgroup analysis according to regional nodal metastasis (N0 or Nx). The pCR rate of patients with Stage TxN0 was 0.11(95% CI: 0.05–0.16; P=0.014), whereas the pCR rate of patients with stage TxNx was 0.12(95% CI: 0.03–0.21; P=0.191). Besides, stage TxN0 pPR rate was 0.27 (95% CI: 0.23–0.31; P=0.339), while stage TxNx pCR rate was 0.36 (95% CI: 0.29–0.42; P=0.520). Several possible reasons potentially led to high heterogeneity, including: (I) patients recorded in the included studies adopted different NAC regimens. (II) The number of UTUC patients in the present studies was small, and most studies included were retrospective. After analyzing these results, we found that NAC could improve the curative effect of advanced UTUC. Furthermore, due to the lack of published clinical trials findings on NAC effect in UTUC, this pooled analysis provided strong proof about this treatment for the clinicians.

In addition, the GRADE system was used to validate the accuracy of our findings. Given the methods we used, the pooled results could further validate the benefits of using NAC in advanced UTUC. What's more, findings from this study will provide insights to clinicians on the accurate use of the NAC regimen in managing UTUC patients. Besides, UTUC patients will appreciate better survival with NAC treatment.

However, there were some limitations to this study. Firstly, most studies included were retrospective, this might have led to selection bias. Secondly, types, timing, cycle and disadvantages of using chemotherapy drugs were not included in subgroup analysis due to insufficient data from the included studies. Thirdly, survival endpoint was not clearly defined, and RNU was performed by different surgeons across different institutions and countries, this may influence the survival outcomes. To address these limitations and provide more reliable evidence on why NAC regimen should be adopted as a new treatment, there is a need for larger, more international, well-balanced, and multicenter prospective randomized studies or randomized control trials to demonstrate the actual effect of NAC when used to manage UTUC patients.

Conclusions

NAC treatment for patients with UTUC before RNU may provide better survival outcomes and achieve higher pathological response rate compared to when RNU is used independently. However, additional prospective randomized studies or randomized control trials should be undertaken to verify the benefits of NAC on prognosis in locally advanced UTUC patients are reliable.

Acknowledgments

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx. doi. org/10. 21037/tau-20-933). Dr. XZ served as an unpaid editorial board member of *Translational Andrology and Urology* from Mar 2015 to Feb 2021. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Detailed survival outcomes and efficiency rate of NAC in UTUC extracted from included studies

Author	Year	OS		CSS		PFS		DSS		pCR rate	pPR rate
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI		
Foerster *et al.*	2020	NA	NA	NA	NA	NA	NA	NA	NA	0.101	0.449
Margulis *et al.*	2020	NA	NA	NA	NA	NA	NA	NA	NA	0.108	NA
Chakiryan *et al.*	2019	2.56	1.72–4.00	NA	NA	NA	NA	NA	NA	NA	0.327
Pelcovits *et al.*	2020	1.85	1.30–2.63	NA	NA	NA	NA	NA	NA	NA	NA
Meng *et al.*	2019	8.01	0.94–67.85	NA	NA	3.34	0.95–11.8	NA	NA	0.08	NA
Martini *et al.*	2019	NA	NA	NA	NA	NA	NA	NA	NA	0.15	0.21
Chen *et al.*	2020	4.54	1.75–11.76	NA	NA	NA	NA	3.43	1.25–9.47	NA	NA
Liao *et al.*	2018	NA	NA	NA	NA	NA	NA	NA	NA	0.094	NA
Almassi *et al.*	2018	NA	NA	NA	NA	NA	NA	NA	NA	0.061	0.252
Hosogoe *et al.*	2018	1.91	0.86–4.22	1.97	0.87—4.46	2.21	1.00–4.89	NA	NA	NA	0.533
Kubota *et al.*	2017	1.45	0.86–2.44	2.08	1.13–3.84	1.75	1.1–2.56	NA	NA	NA	NA
Cohen *et al.*	2017	NA	NA	1.64	0.93–2.94	NA	NA	NA	NA	NA	NA
Kobayashi *et al.*	2016	2.13	1.01–4.54	2.94	1.49–5.88	3.38	0.87–13.02	5.2	1.49–18.10	NA	0.375
Porten *et al.*	2014	2.38	1.04–1.49	NA	NA	NA	NA	6.75	1.90–24.04	NA	NA
Kitamura *et al.*	2012	3.85	1.29–11.1	NA	NA	NA	NA	NA	NA	0.067	0.467
Youssef *et al.*	2011	NA	NA	NA	NA	NA	NA	5.02	1.49–18.1	NA	NA
Rajput *et al.*	2011	NA	NA	NA	NA	NA	NA	NA	NA	0.15	NA
Matin *et al.*	2010	NA	NA	NA	NA	NA	NA	NA	NA	0.21	0.33
Igawa *et al.*	1995	NA	NA	NA	NA	NA	NA	NA	NA	0.13	0.4

OS, overall survival; CSS, cancer-specific survival; PFS, progression-free survival; DFS, disease-free survival; pCR, pathological complete response; pPR, pathological partial response; NA, not available; HR, hazard ratio; CI, confidence interval.

Table S2 GRADE quality assessments of each pooled outcome

Category	Certainty assessment					Effect relative (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision				
OS	All observational studies	Serious	Not serious	Not serious	Serious	HR 2.18 (1.91–2.49)	9	●○○○ very low	CRITICAL
CSS	All observational studies	Not serious	serious	Not serious	very serious	HR 1.99 (1.50–2.65)	4	●○○○ very low	CRITICAL
PFS	All observational studies	Not serious	Not serious	serious	Very serious	HR 1.98 (1.48–2.66)	4	●○○○ very low	CRITICAL
DFS	All observational studies	Not serious	Serious	Not serious	Very serious	HR 3.76 (2.16–6.56)	4	●○○○ very low	CRITICAL
pCR	9 observational studies; 1 clinical trail	Not serious	Not serious	Not serious	Serious	0.11 (0.07–0.14)	10	●●○○ low	CRITICAL
pPR	All observational studies	Serious	Not serious	Not serious	Serious	0.40 (0.31–0.49)	10	●○○○ very low	CRITICAL

OS, overall survival; CSS, cancer-specific survival; PFS, progression-free survival; DFS, disease-free survival; pCR, pathological complete response; pPR, pathological partial response; HR, hazard ratio; CI, confidence interval.

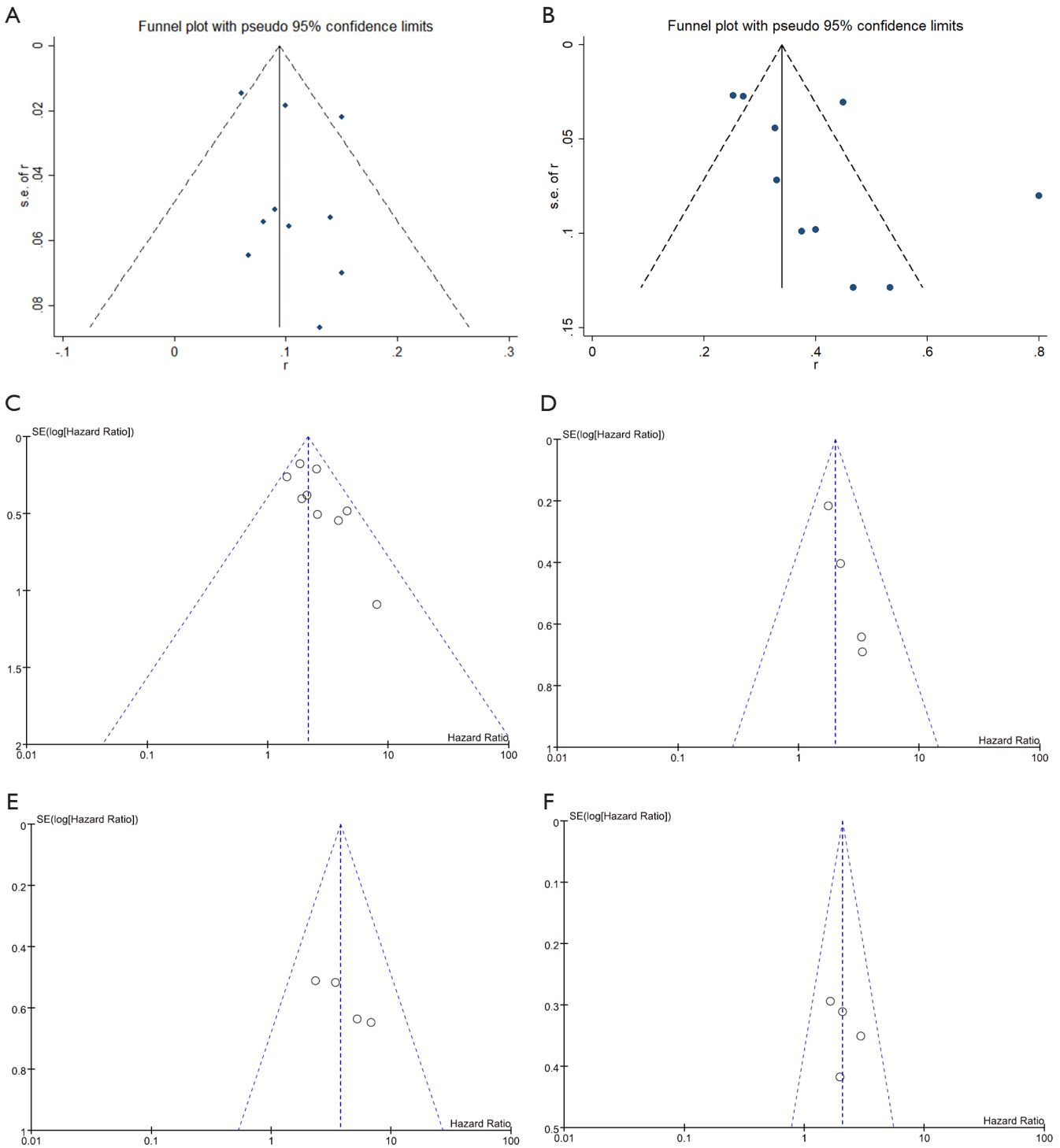

Figure S1 Funnel pots of each pooled survival outcomes and efficiency rates of NAC: (A) pathological complete response (pCR); (B) pathological partial response (pPR); (C) overall survival (OS); (D) progression-free survival (PFS). (E) disease-free survival (DFS); (F) cancer-specific survival (CSS). NAC, neoadjuvant chemotherapy.

Table S3 Research status of clinical trials about NAC in UTUC

NCT number	Title	Status	conditions	Interventions	Outcome measures	Population	Dates and results posted
NCT02876861	Neoadjuvant chemotherapy versus surgery alone in patients with high-grade UTUC	Recruiting	High-grade UTUC	•Procedure: radical nephroureterectomy •Procedure: distal ureterectomy •Drug: neoadjuvant chemotherapy	DFS, ORR, OS, chemotherapy related adverse events	Enrollment: 50; age: 18–80 years old	Study start: February 2014; last update posted: July 8, 2019; no results posted
NCT01261728	Gemcitabine and cisplatin as neoadjuvant chemotherapy in patients with high-grade UTUC	Active, not recruiting	Urothelial carcinoma	Drug: gemcitabine and cisplatin	pPR rate, DFS, OS, drug safety and tolerability	Enrollment: 57; age: ≥18 years and older	Study start: December 14, 2010; Last update posted: October 17, 2019; no results posted
NCT01663285	Clinical trial of neoadjuvant chemotherapy (NAC) in UTUC	Terminated	Urothelial cancer, bladder cancer	Drug: neoadjuvant cisplatin and gemcitabine	PFS, pCR rate, pPR rate, chemotherapy related adverse events	Enrollment: 1; age: ≥18 years and older	Study start: September 2012; last update posted: December 3, 2015; no results posted
NCT02969083	Feasibility of neoadjuvant versus adjuvant chemotherapy in UTUC	Recruiting	Upper tract urothelial carcinoma	•Procedure: RNU •Drug: gemcitabine/cisplatin •Drug: M-VAC protocol	DFS, CSS, OS	Enrollment: 200; age: ≥18 years and older	Study start: May 28, 2018; last update posted: July 22, 2019; no results posted
NCT00696007	Neoadjuvant chemotherapy plus nephroureterectomy for locally advanced UTUC	Withdrawn	Transitional cell carcinoma	•Drug: gemcitabine and cisplatin •Other: retrospective comparison	OS	Enrollment: 0; age: ≥18 years and older	Study start: April, 2008; last update posted: February 17, 2012; no results posted
NCT02412670	Chemotherapy before surgery in treating patients with high grade UTUC	Active, not recruiting	Localized or recurrent upper tract urothelial carcinoma	•Drug: methotrexate, vinblastine, doxorubicin hydrochloride, cisplatin, carboplatin *et al.* •Procedure: therapeutic conventional surgery •Other: laboratory biomarker analysis	pCR rate, RFS, CSS, changes in renal function post chemotherapy and post-surgery, Incidence of toxicities *et al.*	Enrollment: 36; age: ≥18 years and older	Study start: April, 2015; last update posted: July 29, 2019; 1 published article
NCT04099589	Neoadjuvant treatment of upper urinary and muscular invasive bladder urothelial carcinoma	Recruiting	•Upper tract urinary carcinoma •Muscle invasive bladder cancer	•Drug: toripalimab	pCR rate	Enrollment: 60; age: 18–70 years and older	Study start: October 28, 2018; last update posted: July 22, 2019; no results posted

PFS, progression-free survival; DFS, disease-free survival; pCR, pathological complete response; pPR, pathological partial response; UTUC, upper tract urothelial carcinoma; OS, overall survival; CSS, cancer-specific survival.