

# Impact of neoadjuvant chemotherapy on survival prognosis and pathological downstaging in patients presenting with high-risk upper tract urothelial carcinoma

## A protocol for systematic review and meta analysis

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### Abstract

**Purpose:** Controversy remains with using neoadjuvant chemotherapy (NAC) in patients with upper tract urothelial carcinoma (UTUC). Thus, we conducted a systematic review and meta-analysis of the peer-reviewed literature to assess the role of NAC in high-risk UTUC patients.

**Methods:** PubMed, EMBASE, and the Cochrane Library were the main sources of relevant studies. The search terms included: “Upper urothelial carcinoma”; “UTUC”; “Urinary tract cancer”; and “Transitional cell carcinoma” combined with “Neoadjuvant chemotherapy” and “adjuvant chemotherapy”. We studied the relationship of UTUC and NAC. Overall survival, recurrent-free survival, cancer-specific survival and pathological response rate in patients treated with/without NAC before radical surgery were evaluated.

**Results:** Five trials were selected, and included 532 participants. Each of the included studies was retrospective. The combined analysis showed that when compared to controls, the pooled hazard ratios of overall survival, recurrence-free survival and cancer-specific survival were 0.47 (95% confidence interval [CI], 0.34–0.64;  $P < .00001$ ); 0.50 (95% CI, 0.37–0.66;  $P < .00001$ ); and 0.37 (95% CI, 0.25–0.54;  $P < .00001$ ), respectively. It indicates the beneficial effects of NAC for the prognosis of survival in UTUC. Additionally, NAC was significantly associated with T-stage down-grading (T3/4 to  $\leq$ T2; OR=7.58 [4.66, 12.33];  $P < .0001$ ) and pathological lymph node status (N+ to N0; OR=6.24 [2.57, 15.15];  $P < .00001$ ).

**Conclusions:** NAC treatment before radical nephron-ureterectomy significantly improves survival prognosis in patients with high-risk upper tract urothelial carcinoma. However, considerable prospective and randomized studies are needed to confirm this perspective.

**Abbreviations:** CI = confidence interval, CR = complete response, CSS = cancer-specific survival, HR = hazard ratio, NAC = neoadjuvant chemotherapy, NOS = Newcastle–Ottawa scale, OR = odds ratio, OS = overall survival, RFS = recurrence-free survival, RNU = radical nephroureterectomy, UCB = urothelial carcinoma of bladder, UTUC = upper tract urothelial carcinoma.

**Keywords:** meta-analysis, neoadjuvant chemotherapy, nephroureterectomy, upper tract urothelial carcinoma

### 1. Introduction

Upper tract urothelial carcinoma (UTUC) refers to any particular type of malignancy that arise from the urothelial lining of the urinary tract, from the calyceal system to the distal ureter. UTUC

is a relatively uncommon entity, accounting for 5% to 10% of all urothelial tumors.<sup>[1,2]</sup> Several studies have suggested that patient prognosis after radical surgery for high-risk UTUC has not improved over the 18-year period that this condition has been

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assessed.<sup>[3]</sup> Adjuvant chemotherapy has been regarded as an acceptable therapeutic choice; however, deterioration of renal function after radical nephroureterectomy (RNU) can lead to a decreased eligibility to be considered for systemic chemotherapy.<sup>[4,5]</sup> The evidence strongly suggests an urgent need to alter treatment options. A multimodal means of managing high-risk UTUC by incorporating neoadjuvant chemotherapy (NAC) and RNU with excision of the ipsilateral bladder cuff might improve patient outcomes.<sup>[6]</sup> Several studies on bladder cancer have indicated that NAC has significantly improved outcomes in invasive bladder cancer,<sup>[7]</sup> although the benefit of NAC in high-risk UTUC remains controversial and somewhat disputed. Although some retrospective studies have assessed the potential benefit of NAC for UTUC,<sup>[6,8–11]</sup> there are few prospective cohort studies that have actually evaluated the benefit.<sup>[4,12]</sup> Chemotherapy regimens for patients with UTUC are similar to those of urothelial carcinoma of bladder (UCB) based on the European Association of Urology (EAU) guidelines. In addition, cisplatin-based NAC is considered to be the most reasonable standard of therapy in patients with UCB or locally advanced UTUC.<sup>[13]</sup> Matin et al<sup>[14]</sup> reported their experience with 43 patients that presented with high-risk UTUC and received a cisplatin-based NAC. These patients demonstrated a 53.5% overall response rate and a 14% pathologic complete response (CR) rate. A recent retrospective study included 61 patients with high-grade UTUC. Of these 25 patients who received NAC, 80% had any reduction in tumor size observed by imaging. In postoperative pathology, only 20% of patients in the NAC group have  $\geq$ pT2 disease, compared with 64% of patients undergoing only RNU surgery.<sup>[15]</sup> However, owing to the limited number of subjects that were included in these studies, it was impossible to appraise the benefits of NAC in patients considered for this mode of therapy. In the current work, we conducted a meta-analysis to assess the role of NAC in patients presenting with high-risk UTUC.

## 2. Materials and methods

The PRISMA guidelines were used in the design of this study, which was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

### 2.1. Literature search strategy

PubMed, EMBASE, and the Cochrane Library were the main sources of relevant primary peer-reviewed studies for his study. Two independent reviewers searched records from January 1998 through January 2019. All studies evaluated the role of NAC in the setting of UTUC. Literature searches were limited to the English language. Nevertheless, we referred to the reference citations of the papers to identify additional eligible articles.

## 3. Study selection

The criteria of the study included the following:

- (1) The study evaluated the role of NAC for UTUC;
- (2) All patients were diagnosed with primary high-risk UTUC;
- (3) All patients were not treated with chemotherapy after surgery;
- (4) Outcomes were OS, cancer-specific survival (CSS), recurrence-free survival (RFS) and the pathological response rate.

Both prospective cohort studies and retrospective trials were included in our study. Data from summaries, reviews, editorials, animal studies, case reports, and letters were excluded. Lower urothelial carcinoma and those studies with participants that contained incomplete data were also excluded.

### 3.1. Data extraction and quality assessment

The statistics below were collected from individual studies by 2 reviewers independently: details on study design, age of patients, the number of test and control groups, and treatment regimen, median follow-up period, T stage, and outcomes measured (ie, pathological response rate, OS, CSS, and RFS) were interrogated. According to the suggestions put forward by the Cochrane Non-Randomized Studies Methods Working Group, the Newcastle–Ottawa Scale (NOS) was applied to quality assess the included studies in this meta-analysis. This scale allocates up to nine stars according to an assessment of selection, comparability, and exposure. Studies that received six or more stars were considered to be high quality.

### 3.2. Statistical analysis

Meta-analyses were performed in Review Manager v.5.3 software (RevMan, The Cochrane Collaboration). The hazard ratio (HR, for OS; RFS and CSS) or the odds ratio (OR, for T-stage down-grading and the incidence of declining lymph node-positive disease) with its corresponding 95% confidence interval (CI) were used to assess the pooled influence. The  $I^2$  statistic and Cochran  $Q$  statistic was used to assess the heterogeneity across the included studies.  $I^2 > 50\%$  or the  $Q$  statistic  $< .05$  was considered to be significantly heterogeneous. If the heterogeneity was obvious, we would use a randomized effects model; otherwise, a fixed effects model was used. Sensitivity analyses were conducted to evaluate the influence of individual studies on the overall estimates by omitting 1 study at each turn. According to the Cochrane manual, we did not use funnel plots to assess publication bias because fewer than 10 studies were included in the current study.

## 4. Search results

The literature screening flow chart is shown in Figure 1. Overall, 1084 studies were identified from the databases and relevant references, of which 902 were reserved after removing duplicates. Two reviewers assessed the selected 902 relevant articles on the basis of titles and abstracts, and 872 were excluded from this analysis. Next, after evaluating the full-text articles, 5 were identified as eligible for this meta-analysis, including a total of 532 participants. There were 222 patients who received NAC before surgery, and 310 patients experienced RNU alone. The detailed information of each included study is presented in Tables 1 and 2. According to the NOS criteria, the overall quality of the included study was at low risk of bias in the NOS scores  $\geq 6$ . The results are presented in Table 3.

## 5. Main findings

### 5.1. Survival index

**5.1.1. OS.** Five studies were included in the OS subgroup.<sup>[8–11,16]</sup> Statistical analysis showed that the pooled HR was 0.47 (95% CI: 0.34–0.64;  $P < .00001$ ), which indicated that NAC plus RNU was associated with a significant OS improvement as compared

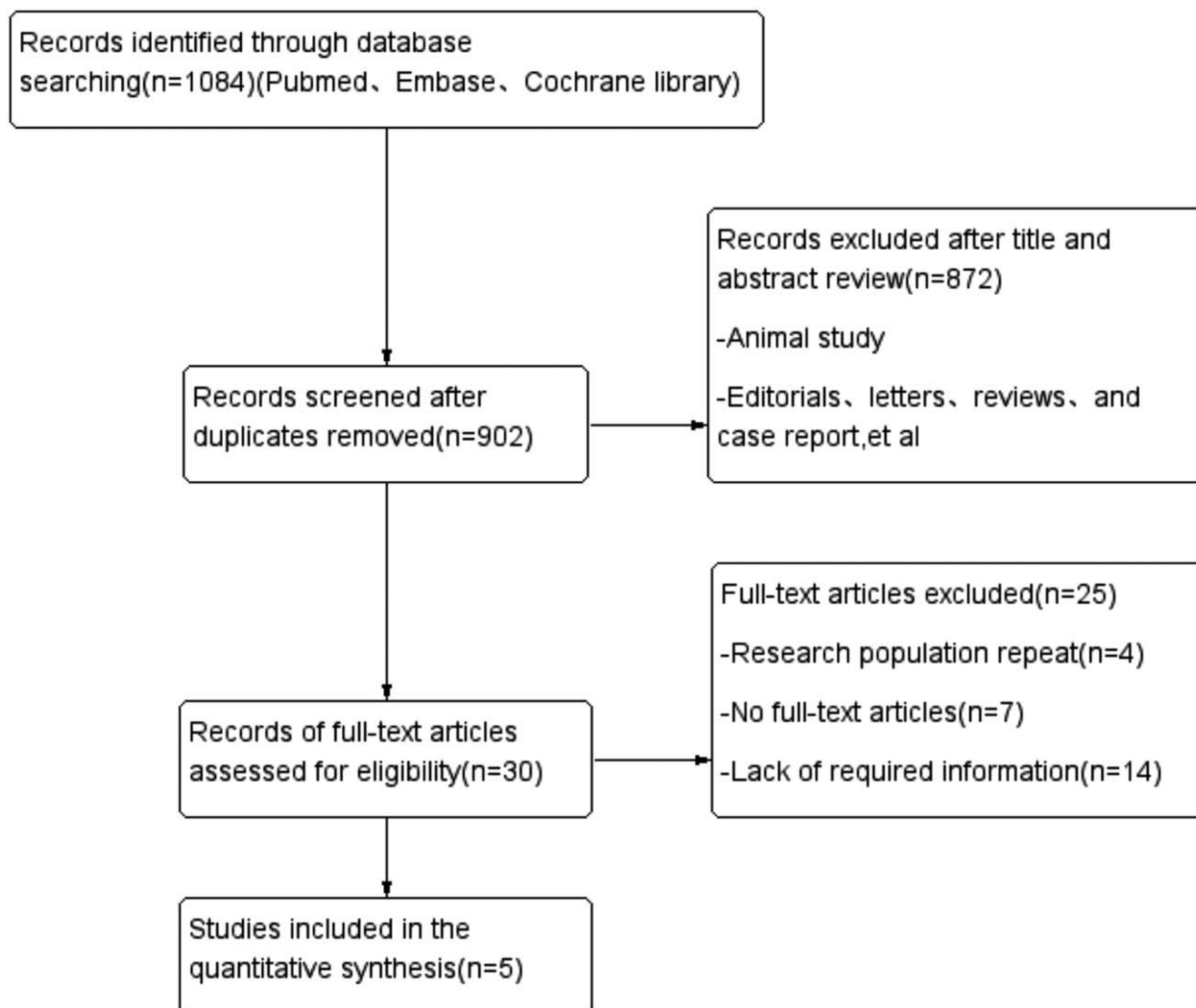


Figure 1. Flow chart of the study selection process in this meta-analysis.

with those that underwent RNU alone (Fig. 2). There was no statistically significant heterogeneity among any of the studies according to the Cochran  $Q$  statistical analysis ( $P = .41$ ) and  $I^2 = 0\%$ .

## 5.2. RFS

RFS results were reported in 3 studies.<sup>[9–11]</sup> In 1 study, however, intravesical and visceral RFS were done separately and respectively.<sup>[11]</sup> The meta-analysis revealed that pooled HR was 0.50 (95% CI: 0.37–0.66;  $P < .00001$ ), which indicated that NAC plus RNU was also associated with a significant RFS improvement as compared those that received RNU alone (Fig. 3). Analysis showed no statistically significant heterogeneity among studies according to Cochran  $Q$  statistics ( $P = .64$ ) and  $I^2 = 0\%$ .

## 5.3. CSS

CSS were provided in 4 studies.<sup>[8–11]</sup> The pooled HR was 0.37 (95% CI: 0.25–0.54;  $P < .00001$ ), which indicated that NAC plus RNU was also associated with significant CSS improvement as compared with those that underwent RNU alone (Fig. 4). There

was no statistically significant heterogeneity among studies on the basis of Cochran  $Q$  statistics ( $P = .56$ ) and  $I^2 = 0\%$ .

## 5.4. Pathological downgrading

**5.4.1. T stage.** The possible association between NAC and T stage down-grading was investigated in 4 studies,<sup>[9–11,16]</sup> which collectively showed no statistically significant heterogeneity among studies on the basis of Cochran  $Q$  statistics ( $P = .94$ ) and  $I^2 = 0\%$ . The pooled OR of having T stage down-grading was 7.58 (95% CI: 4.66–12.33;  $P < .00001$ ; Fig. 5). These results inform us that the NAC group had a 6.58-fold higher possibility of having T stage down-grading (T3/4 to  $\leq$ T2) as compared the control group.

## 5.5. Pathologic lymph node status

The role of NAC before RNU on the rate of lymph node-positive disease was reported in 4 studies.<sup>[9–11,16]</sup> There was no statistically significant heterogeneity in these studies ( $P = 0.63$ ,  $I^2 = 0\%$ ). The pooled OR of the declined incidence of lymph node-positive disease was 6.24 (95% CI: 2.57–15.15;  $P < .0001$ ; Fig. 6). The results illustrate that the NAC group had a 5.24-fold

**Table 1**  
Characteristics of neoadjuvant chemotherapy and included studies.

First author	Kubota (11)	Hosogoe (10)	Kobayashi (9)	Porten (8)	Kitamura (16)
Year	2017	2018	2016	2014	2012
Country	Japan	Japan	Japan	USA	Japan
Design	Case-control	Case-control	Case-control	Case-control	Case-control
NAC regimen	GC/GCARBO	GC/GCARBO	GC/MVAC	GC/MVAC	GC/MVAC
NAC+RNU/RNU	101/133	51/51	24/31	31/81	15/14
Stage	cT3-4 or cN+	cT3-4 or cN+	cT3-4 or cN+	cT3-4 or cN+	cT3-4 or cN+
OS (HR 95%CI)	0.69 (0.41–1.15)	0.39 (0.17–0.91)	0.38 (0.20–0.73)	0.42 (0.19–0.94)	0.26 (0.09–0.77)
RFS (HR 95%CI)	0.55 (0.50–0.61)	0.32 (0.15–0.69)	-	-	-
CSS (HR 95%CI)	0.48 (0.26–0.87)	0.34 (0.13–0.90)	-	0.19 (0.06–0.61)	-

GC=gemcitabine and cisplatin, GCARBO=gemcitabine and carboplatin Control, GTA=gemcitabine, paclitaxel, and doxorubicin, MVAC= methotrexate, vinblastine, doxorubicin, and cisplatin, NAC= neoadjuvant chemotherapy, RNU=radical nephroureterectomy.

**Table 2**  
Characteristics of neoadjuvant chemotherapy and parameters of UTUC.

First author	NAC cases (n)	Age (yr)	cN+	pN+	cT3-4	pT3-4	Median follow-up time (mo)
Kubota (11)	101	70 ± 9.5	19	11	100	36	26
Hosogoe (10)	51	70 ± 9.6	15	7	49	17	24
Kobayashi (9)	31	67 ± 15	24	14	22	18	33
Porten (8)	15	70 (32–85)	–	–	–	–	–
Kitamura (16)	24	65	15	4	11	7	–

**Table 3**  
Quality assessment of studies included in meta-analysis.

First author	Selection	Selection	Selection	Selection	Comparability	Exposure	Exposure	Exposure	Scores
Kubota (11)	*	*			**	*	*		6
Hosogoe (10)	*	*			**	*	*		6
Kobayashi (9)	*	*			**	*	*		6
Porten (8)	*	*			**	*	*		6
Kitamura (16)	*	*			**	*	*		6

higher possibility of having a declining incidence of lymph node-positive disease as compared the control group.

**5.6. Sensitivity analyses**

We performed sensitivity analyses by omitting 1 study at a time, generating pooled estimates and comparing the pooled with the original estimates. These findings demonstrated that our results were trustworthy.

**6. Discussion**

RNU with bladder cuff excision is considered a standard treatment for high-risk UTUC, regardless of the location of the tumor. However, Margulis et al<sup>[17]</sup> found that patients undergoing RNU surgery alone could not bring an oncological benefit to those patients with high-risk UTUC. Increasing evidence shows that UTUC is a distinct disease entity from UCB on the basis of both phenotypic and genotypic (genetic and epigenetic) differences. In addition, more than 60% of UTUCs,

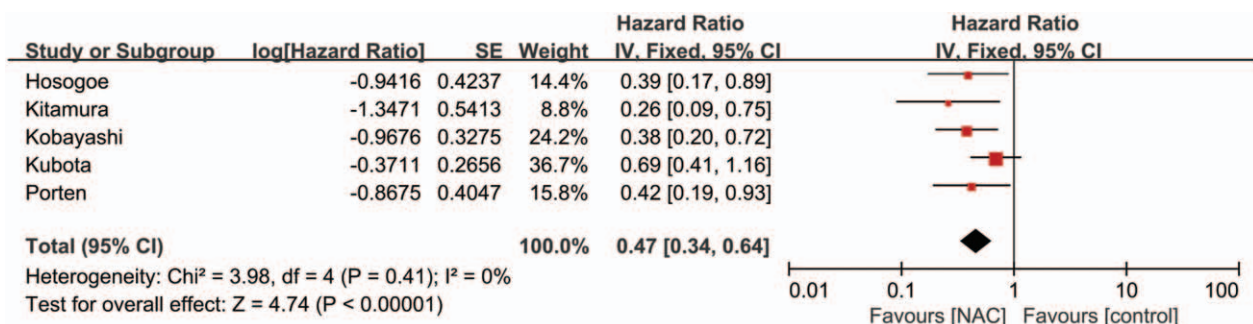


Figure 2. Forest plots of 5-yr overall survival rates.

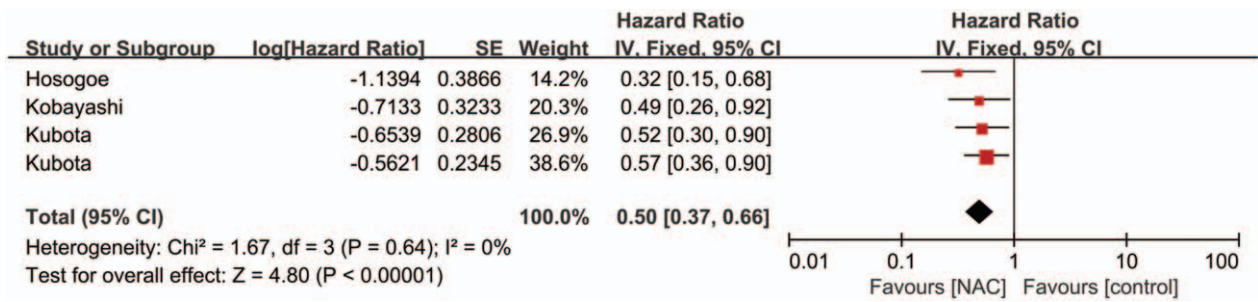


Figure 3. Forest plots of 5-yr recurrence-free survival rates.

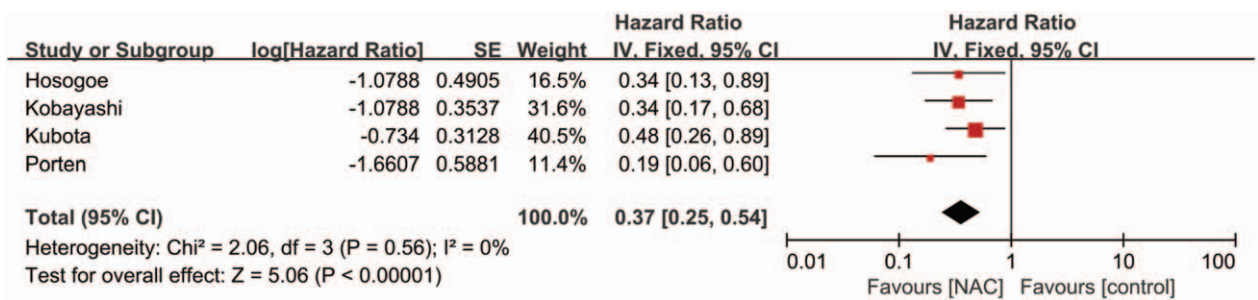


Figure 4. Forest plots of 5-yr cancer-specific survival rates.

and only 15% to 25% of UCB present with invasion at the time of diagnosis.<sup>[18]</sup> There is usually a poor prognosis if UTUCs have invaded the muscle wall. The 5 year specific survival rate is < 50% for pT2/pT3 and < 10% for pT4.<sup>[19,20]</sup> Some scholars have proposed perioperative chemotherapy due to the high recurrence

rate of UTUC. Similar to UCB, several platinum-based chemotherapeutic regimens have been put forward for UTUC. Some studies report that many patients are unable to receive chemotherapy after RNU due to decreased renal function<sup>[21]</sup>; however, NAC capitalizes on the patient's maximal renal reserve

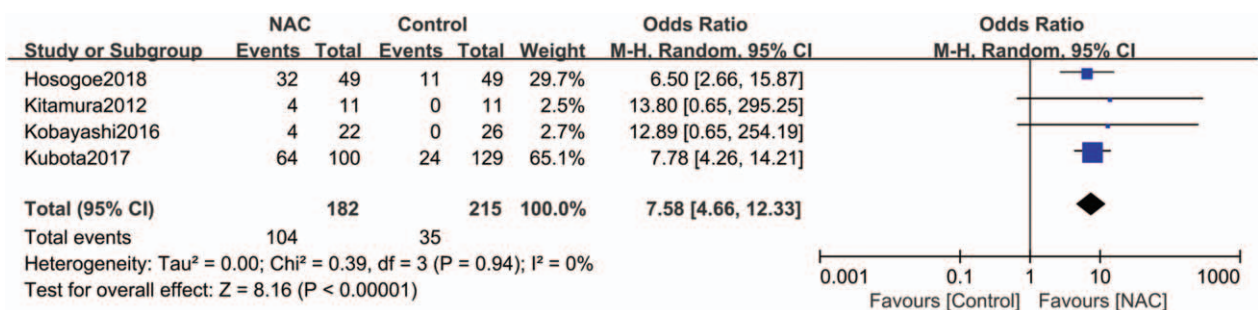


Figure 5. Forest plots of NAC effects on T-stage down-grading (T3/4 to ≤T2).

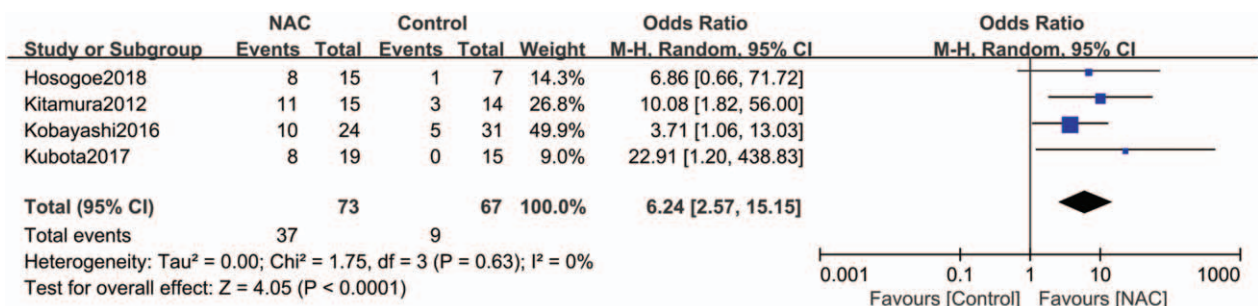


Figure 6. Forest plots of NAC effects on the pathologic lymph node status (N+ to N0).

to deliver optimal doses of chemotherapy. Unfortunately, these guidelines were intended to align with UTUC treatment with NAC, and primarily based on UCB treatment guidelines.<sup>[22]</sup> Some retrospective studies have explored the role of NAC in patients with high-risk UTUC. Igawa et al reported a 13% pathological CR rate and a 40% partial response rate when using cisplatin-based NAC in locally advanced UTUC.<sup>[23]</sup> Matin et al found that when using NAC before radical surgery, this resulted in an obvious rate of downstaging and a 14% pathological CR rate.<sup>[14]</sup> After comprehensively searching for the relationship between NAC and survival prognosis in UTUC patients, 2 meta-analyses showed significant improvements in OS and CSS in the NAC group as compared to controls.<sup>[24,25]</sup> A recent study from China has also confirmed the survival benefits of NAC in high-grade UTUC patients. Patients who received NAC before surgery had significantly improved overall and disease-free survival.<sup>[26]</sup> In addition, 2 prospective studies were identified that reported using NAC in UTUC patients. Both studies were phase 2 clinical trials that were conducted at the MD Anderson Cancer Center, Texas, USA. A study consisted of 65 subjects, among which only 5 were high-grade UTUC. These 5 patients received NAC before radical surgery, and 3 of these patients (60%) showed a pathologic down-staging to  $\leq$  pT1N0 disease, which demonstrated that NAC was effective in UTUC patients.<sup>[12]</sup> Another study reported that NAC led to a pathologic down-staging in twelve (75%) of sixteen patients with upper tract cancer.<sup>[27]</sup> However, due to an insufficient number of subjects in these studies, the conclusion with regard to the clinical benefits of NAC for UTUC were unconvincing.

The present study was based on a retrospective case-control study and explored the effect of NAC on the risk of OS, RFS, CSS and pathological down-grading when treating UTUC. The pooled HR for 5 year OS, RFS, and CSS were 0.47 (95% CI, 0.34–0.64), 0.50 (95% CI, 0.37–0.66), and 0.37 (95% CI, 0.25–0.54), respectively. These findings from the meta-analysis indicated that when compared with control subjects, NAC was significantly beneficial on OS, RFS, and CSS. With regard to the pathological changes, the data showed that the NAC group had a 6.58-fold higher probability of having T stage down-grading (T3/4 to  $\leq$ T2) and had a 5.24-fold higher probability of demonstrating a declining incidence of lymph node-positive disease as compared to the control group. These findings have significant reference value on treating high-risk UTUC.

### 6.1. Limitations

The main limitation of this systematic review was the lack of included RCTs for evaluation, and a possibility of some selection bias that might have affected our results. Further, the number of samples included in this study was small, and the availability of adequate data is challenging when considering the acquisition of meaningful results. The difference in the skills and technical knowledge of practicing surgeons might also markedly impact the outcomes. Although some studies had confirmed the survival benefit of NAC, it remains controversial when considering the use of NAC before RNU. Therefore, it is imperative to carry out large-scale, well-designed randomized controlled trials in this context.

### 7. Conclusions

NAC treatment before RNU can significantly improve survival prognosis and increase the pathological down-grading rate in

patients with high-risk UTUC. However, we still need many other prospective randomized studies to permit a confirmation of this perspective.

### Author contributions

Study conception: J.C, K.L. Study design: J.C, K.L, and L.G. Acquisition of data: K.L, G.M.H, and B.Y.M. Analysis and Interpretation of data: K.L, J.C, L.G, G.M.H, J.M. Z, and W.J.X. Drafting of the Manuscript: K.L, J.C, and W.J.X. All authors have contributed to the critical revision and approval of the final manuscript.

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