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Effect of neoadjuvant chemotherapy on locally advanced upper tract urothelial carcinoma: A systematic review and meta-analysis

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ABSTRACT

Background: The role of neoadjuvant chemotherapy (NAC) for the management of upper tract urothelial carcinoma (UTUC) remains controversial. The aim of present study was to evaluate the contemporary role of NAC for patients with locally advanced UTUC through systematic review and meta-analysis of the literature.

Methods: Systematic literature searches were conducted in PubMed/Medline and Embase for all studies that examined the role of chemotherapy for UTUC. We performed this study according to the Preferred Reported Items for Systematic Reviews and Meta-analysis guidelines. Endpoints were overall survival (OS), cancer-specific survival (CSS), and progression-free survival (PFS).

Results: A total of four trials on 318 patients were included in this study. Each of the included studies was retrospective. Compared to controls, NAC improved OS, CSS, and PFS by 57% (95% confidence interval [CI], 0.25–0.73; $p = 0.002$), 59% (95% CI, 0.27–0.57; $p < 0.00001$), and 45% (95% CI, 0.50–0.60; $p < 0.00001$), respectively. The absolute increases in OS, CSS, and PFS were 11%, 18%, and 13%, respectively, and these increases are equivalent to numbers-needed-to-treat of 9, 5.5, and 7.6, respectively. Pooled odds ratio for the effect of NAC on downstaging was 0.21 (95% CI, 0.09–0.60; $p = 0.004$), which indicates that NAC group had a 4.76-fold higher probability of having pathologic N stage 0 than control group.

Conclusions: NAC treatment before radical nephroureterectomy might provide better survival outcomes in patients with locally advanced UTUC. Prospective randomized studies are needed to confirm the benefits of NAC in locally advanced UTUC patients.

1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) is relatively uncommon, accounting for only approximately 5% of urothelial malignancies. However, recent data have shown that the incidence of UTUC is increasing (Raman and Scherr, 2007; Zigeuner and Pummer, 2008). Radical nephroureterectomy (RNU) with excision of ipsilateral bladder cuff is the preferred therapy that can potentially cure UTUC in patients with normal contralateral kidney (Margulis et al., 2009). Although the standard treatment for UTUC is RNU, the recurrence rate of patients with locally advanced UTUC who underwent RNU is high. Also, there is growing evidence that both neoadjuvant chemotherapy (NAC) and adjuvant chemotherapy (ACH) play an important role in UTUC therapy (Kang et al., 2015; Roupret et al., 2017). UTUC is considered to be a relatively chemosensitive tumor (Yagoda, 1987). According to European Association of Urology (EAU) treatment guidelines, the proposed chemotherapy regimen for UTUC patients is the same as that used for urothelial carcinoma of bladder (UCB) (Oosterlinck et al., 2004). Cisplatin-based NAC is regarded as the treatment standard for both UCB and locally advanced UTUC patients (O'Donnell and Stadler, 2009). Most of the data regarding clinical efficacy of NAC and ACH for UTUC is based on experience from bladder cancer (Raman and Scherr, 2007).

Compared to ACH, NAC might have an extra benefit beyond the general advantage of NAC,as the loss of renal function after RNU may decrease the eligibility for cisplatin-based chemotherapy and might impede the transport of higher doses of chemotherapy (Leow et al., 2014; Tabayoyong et al., 2018; Xylinas et al., 2013). Igawa et al. treated 15 patients with locally advanced UTUC with a cisplatin-based NAC and found pathologic complete response in 13%, pathologic partial response in 40%, and an overall response rate of 53% (Igawa et al., 1995). The researchers reported a positive correlation between pathologic response and patient prognosis. Unfortunately, assessment of the

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ability of NAC to improve the prognosis of locally advanced UTUC patients was not possible due to the low number of patients included in the study. Several retrospective studies also demonstrated the efficacy of NAC in patients with locally advanced or high-grade UTUC (Hosogoe et al., 2018; Kitamura et al., 2012; Matin et al., 2010; Porten et al., 2014; Youssef et al., 2011; Kobayashi et al., 2016; Kubota et al., 2017). The aim of present study was to perform a systematic review and meta-analysis of currently available evidence to evaluate the contemporary role of NAC for patients with locally advanced UTUC.

2. Methods

2.1. Literature search

Systematic literature searches were conducted using PubMed/Medline and Embase in February 2018. All studies examined the role of chemotherapy for UTUC in patients who received NAC before RNU. The following key words were used separately or in combination as search terms: “upper tract,” “urothelial carcinoma,” “urothelial cancer,” “neoadjuvant,” and “chemotherapy.” Two authors independently reviewed the search results. Full articles were retrieved for further qualitative review.

2.2. Trial inclusion and exclusion criteria

We performed this study according to the Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, and the eligibility of study was defined by the Population, Intervention, Comparator, Outcome, and Study design system (PICOS) (Moher et al., 2015). We defined the study population as patients with UTUC and the intervention as NAC. Comparator was defined as UTUC alone. Outcomes were overall survival (OS), cancer-specific survival (CSS), and progression-free survival (PFS). We attempted to include both randomized controlled trials and retrospective trials in our study. Exclusion criteria were the inclusion of bladder urothelial cancer and all UTUC.

2.3. Data extraction

During data extraction from the included studies, two authors independently reviewed full articles and extracted data for each trial. The data were extracted at trial level. Any conflicts in extracted data between the two authors were resolved via consensus. Extracted data included details on study design, inclusion and exclusion criteria, randomization, participant demographic and oncologic characteristics, treatment characteristics (regimen, dosage, planned cycles of NAC, and median follow-up period), outcomes measured (OS, CSS, and PFS), and results (numbers of events, HRs, 95% CIs, and p-values).

2.4. Study quality assessments

Quality evaluation of included clinical trials was performed according to the Newcastle–Ottawa Scale (NOS) (Wells et al., 2012). Three major assessment categories of NOS included selection, comparability, and exposure. A study could be granted up to nine stars, and a final score of six stars or more was considered as high quality.

The Grading of Recommendations, Assessments, Developments, and Evaluation (GRADE) system was used to provide a systematic approach to the evaluation of quality of evidence and strength of recommendations (Guyatt et al., 2008a). Criteria for consideration were assessment of methodology, precision of results, consistency of results, directness, and risk of publication bias. Based on these five criteria, we assessed only direct evidence of pairwise meta-analysis by classifying the quality of evidence as one of four levels (i.e., high, moderate, low, and very low).

2.5. Statistical analysis

Effect measures for the outcomes of OS, CSS, and PFS were hazard ratios (HRs) and 95% confidence intervals (CIs) extracted from published studies. We employed a widely used method to estimate HRs and 95% CIs in studies that had Kaplan-Meier log-rank or Wilcoxon p-values but no published HRs or 95% Cis (Parmar et al., 1998). Selection of the main statistical model for pooled HRs was based on the statistical heterogeneity level of included studies, determined by Cochran Q statistic (p-value for heterogeneity) and I^2 statistic (total percentage of variation resulting from heterogeneity) (Higgins et al., 2003). Significant heterogeneity was defined by Cochran Q p-value of < 0.05 and I^2 value of $> 50\%$ (Higgins et al., 2003). In cases with significant heterogeneity, random-effects models were used to report HRs via the DerSimonian and Laird method (DerSimonian and Kacker, 2007). The main significant advantage of a random-effects model over a fixed-effects model (used in previous meta-analyses) is that it can account for heterogeneity between trials (DerSimonian and Kacker, 2007). Sensitivity analysis was performed by omitting the included studies sequentially, and then evaluating the stability of results. Our plan to use funnel plots to assess small study effects in 10 or more studies was not implemented, as fewer than 10 studies were included in the analysis.

Meta-analysis was performed using Review Manager v.5.1 (Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark, 2008). All p-values were two-sided and, except for the test of discrepancy, p-value < 0.05 was considered to indicate statistically significant result.

3. Results

3.1. Search results

PRISMA flow diagram summarizing the data is shown Fig. 1. We identified a total of 720 studies, of which 695 remained after removing duplicates. Two authors (DKK and YSH) reviewed the 695 relevant articles based on titles and abstracts, and excluded 684 based on inclusion criteria described in the Methods section. Next, the authors analyzed full-text of the remaining 11 articles to ensure they satisfied the inclusion criteria. This process ultimately resulted in a total of four studies that investigated the role of NAC for locally advanced UTUC being included in the current meta-analysis. A total of 189 patients received NAC before undergoing RNU, and 379 patients underwent RNU alone. Detailed information of each included study, all of which were retrospective and conducted in Japan, is presented in Table 1 (Hosogoe et al., 2018; Kitamura et al., 2012; Kobayashi et al., 2016; Kubota et al., 2017). Three of the studies were single-institution studies (Hosogoe et al., 2018; Kitamura et al., 2012; Kobayashi et al., 2016), and one was a multi-institution study (Kubota et al., 2017). The study by (Hosogoe et al., 2018) was included in the multi-institution study by (Kubota et al., 2017).

3.2. Meta-analyses for neoadjuvant chemotherapy

3.2.1. Overall survival

Three studies reported OS results for meta-analysis (Kitamura et al., 2012; Kobayashi et al., 2016; Kubota et al., 2017). Pooled HR across these three studies was 0.46 (95% CI, 0.27–0.79; $p = 0.005$), which represents a 51% benefit in OS among patients treated with NAC plus RNU compared to those who received RNU alone (Fig. 2A). There was no heterogeneity between studies based on Cochran Q statistics ($p = 0.16$) and $I^2 = 45\%$. Absolute increase in OS for all trials was 11% (i.e., equivalent to a numbers-needed-to-treat value of 9).

3.2.2. Cancer-specific survival

Two studies reported CSS (Kobayashi et al., 2016; Kubota et al., 2017). Pooled HR across these studies was 0.41 (95% CI, 0.26–0.65;

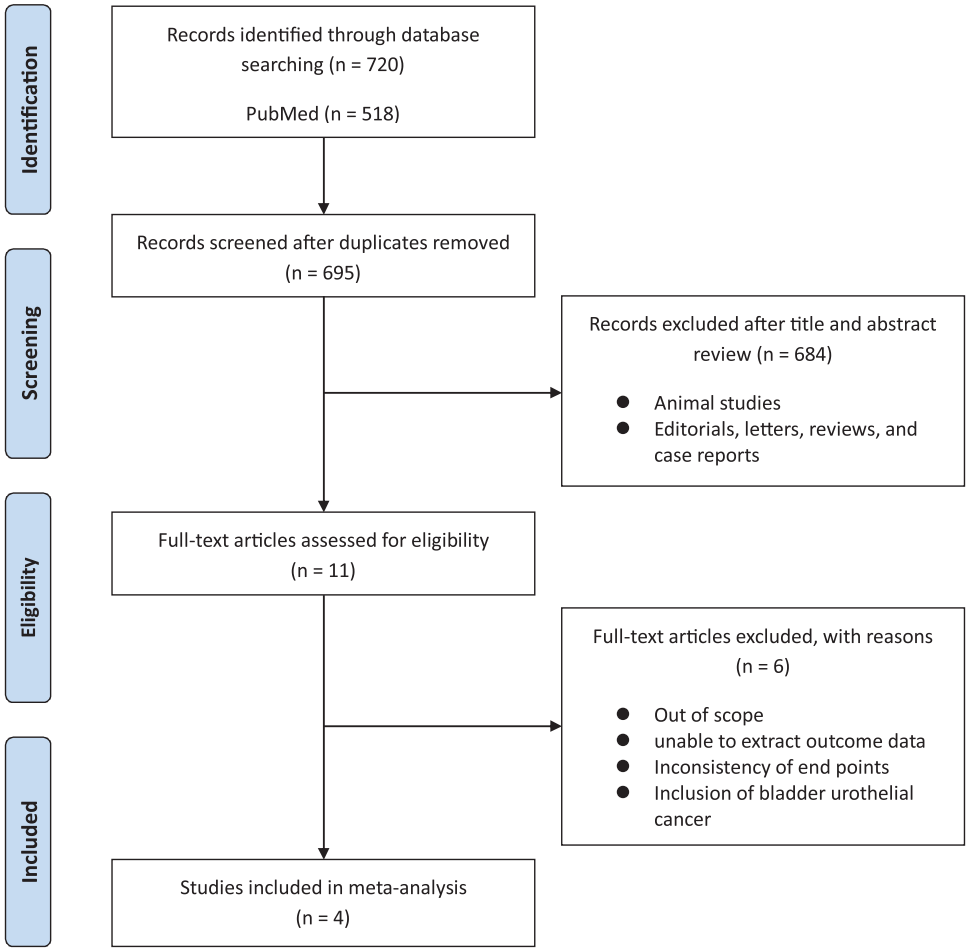

Fig. 1. Flowchart of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

p = 0.0001), representing a 59% benefit in CSS of patients treated with NAC plus RNU compared with RNU alone (Fig. 2B). Analysis displayed no heterogeneity between studies based on Cochran Q statistics (p = 0.46) and I^2 = 0%. Absolute increase in CSS for all trials was 18% (i.e., equivalent to a numbers-needed-to-treat of 5.5).

3.2.3. *Progression-free survival*

Two studies were included in PFS subgroup (Kobayashi et al., 2016; Kubota et al., 2017). In one study, intravesical and visceral PFS were separated and reported respectively (Kubota et al., 2017). Pooled HR across these studies was 0.53 (95% CI, 0.39–0.73; p < 0.0001), representing a 47% benefit in PFS (Fig. 2C). There was no heterogeneity between studies based on Cochran Q statistics (p = 0.92) and I^2 = 0%. Absolute increase in PFS for all trials was 13% (i.e., equivalent to a numbers-needed-to-treat value of 7.6).

3.2.4. *Effect of NAC on downstaging from clinical to pathological diagnosis*

Three studies reported the effect of NAC on downstaging (Hosogoe et al., 2018; Kitamura et al., 2012; Kobayashi et al., 2016). Pooled odds ratio (OR) across these studies was 0.21 (95% CI, 0.09–0.60; p = 0.004) (Fig. 2D). NAC group had a 4.76-fold higher probability of having pathologic N stage 0 than control group.

3.3. *Quality assessment, sensitivity, and publication bias*

Results of quality assessment for the included studies using NOS are shown in Table 2. Each of the included studies received 6 points.

Sensitivity analysis was conducted to evaluate the influence of individual studies on the overall meta-analysis results by omitting one study at a time. Omission of any study made no significant difference, demonstrating that our results are statistically reliable.

Results of GRADE quality assessment of direct evidence of each comparison are shown in Table 3. Certainty was low in each of the four comparisons.

4. Discussion

Although UTUC is morphologically similar to UCB, it can be distinguished from UCB based on phenotypic and genotypic differences. Greater than 60% of UTUC patients present with invasion at diagnosis compared with 15% to 25% for UCB (Leow et al., 2016). Invasive UTUC has a poor prognosis; 5-year survival rates for patients with stage T2 disease is 73% and that for patients with stage T3 disease is 40%. Moreover, the median survival for patients with T4 disease is approximately 6 months (Audenet et al., 2013). Although RNU is still the standard of care for high-grade UTUC, perioperative chemotherapy has been proposed for high systemic recurrence rate. Similar to NAC treatment for UCB, NAC for invasive UTUC is believed to have the potential to downstage tumors and eradicate occult micrometastatic disease (Tabayoyong et al., 2018). Currently available treatment guidelines suggest that NAC may be considered for select patients with UTUC, particularly for those with higher stage and/or grade tumors, because renal function will decline after RNU and may preclude adjuvant therapy (Roupret et al., 2017; Spiess et al., 2017). However, these guidelines for NAC in the treatment of UTUC were derived from the overwhelming level 1 evidence for this approach for UCB (C. V, 2005).

Prospective data on the use of NAC in patients with UTUC are very

Table 1
Characteristics of the studies included in meta-analysis.

Author	Year	Country	Type	NAC regimen	Number	Stage	Intervention	Overall survival		Cancer-specific survival		Recurrence-free survival		Follow-up (months)
								HR	95%CI	HR	95%CI	HR	95%CI	Median (range)
Hosogoe et al. (2017)	2017	Japan	Retrospective single center	GC GCarbo	NAC: 51 Control: 51	cT3-4 or cN +	RNU vs. NAC + RNU	0.39	0.17-0.91	0.34	0.13-0.90	0.32	0.15-0.69	
Kitamura et al. (2012)	2012	Japan	Retrospective single center	NA	NAC: 15 Control: 14	cTany and cN +	RNU vs. NAC + RNU	0.26	0.09-0.77					81 (19-201)
Kobayashi et al. (2016)	2016	Japan	Retrospective single center	MEP MVAC GC	NAC: 24 Control: 31	cTany and cN +	RNU vs. NAC + RNU	0.38	0.20-0.73					33 (8-168)
Kubota et al. (2017)	2017	Japan	Retrospective multicenter	GC GCarbo	NAC: 101 Control: 133	cT3-4 or cN +	RNU vs. NAC + RNU	0.69	0.41-1.15	0.48	0.26-0.87	0.55	0.50-0.61	27

GC: gemcitabine and cisplatin, GCarbo: gemcitabine and carboplatin, HR: hazard ratio, CI: confidence interval, MEP: methotrexate, etoposide, and cisplatin, MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin, NA: not available, NAC: neoadjuvant chemotherapy, RNU: radical nephroureterectomy.

limited. A phase 2 clinical trial at MD Anderson Cancer Center investigated neoadjuvant cisplatin-based sequential triplets before surgery in patients with locally advanced urothelial cancer (Siefker-Radtke et al., 2013). Only five of 65 patients were high-grade upper tract cancer of the ureter or renal pelvis. After NAC and RNU, pathologic downstaging to ≤ pT1N0 disease was seen in three (60%) of these five patients, proving the efficacy of NAC for UTUC. However, the limited number of patients in this report prohibits the conclusion of clinical benefit of NAC for UTUC. Martin et al. investigated the incidence of pathologic downstaging and complete remission (CR) in patients with high-grade UTUC who received NAC followed by surgery (Matin et al., 2010). They reported that NAC is associated with a 14% CR rate. Moreover, (Margulis et al. (2009)) reported that five of 41 patients with UTUC, who received NAC followed by surgery, had no pathologic evidence of malignancy. In the present study, three studies reported downstaging from clinical to pathological diagnosis (Hosogoe et al., 2018; Kitamura et al., 2012; Kobayashi et al., 2016), and NAC group had a 4.76-fold higher probability of having pathologic N stage 0 than control group.

Several retrospective studies and meta-analyses suggested the efficacy of NAC in patients with locally advanced or high-grade UTUC (Margulis et al., 2009; Leow et al., 2014; Igawa et al., 1995; Matin et al., 2010; Porten et al., 2014; Youssef et al., 2011; Yang et al., 2017). In patients with node-positive UTUC, only a few retrospective studies reported the impact of preoperative chemotherapy on oncological outcomes (Igawa et al., 1995; Matin et al., 2010; Porten et al., 2014; Youssef et al., 2011). (Leow et al. (2014)) conducted a systematic review and meta-analysis of currently available evidence to evaluate the contemporary role of chemotherapy for patients with UTUC. There was a CSS benefit of 48% reduction in risk across two retrospective studies investigating NAC (Porten et al., 2014; Youssef et al., 2011). (Gregg et al. (2018)) investigated whether perioperative chemotherapy (ACH and NAC) improved OS for UTUC in patients undergoing potentially curative surgery. They also included only two retrospective studies investigating NAC, and reported an OS benefit of a 64% reduction in risk. (Yang et al. (2017)) used network meta-analysis to investigate the prognosis of UTUC patients who received different treatment strategies after RNU. They reported that NAC shows a significant improvement in CSS relative to the control, and suggested that NAC might be more favorable than ACH in terms of CSS. In our present study, we reported that NAC improved the survival outcomes of patients with locally advanced UTUC. The present meta-analysis also showed that NAC increased OS, CSS, and PFS of these patients by 57%, 59%, and 45%, respectively.

Previous meta-analyses were performed with very small numbers of studies (Leow et al., 2014; Yang et al., 2017; Gregg et al., 2018). (Yang et al. (2017)) reported a network analysis of the effect of different treatments, including both ACH and NAC, in UTUC patients. However, only two studies on NAC were included (one for OS analysis and the other for CSS analysis). Meanwhile, meta-analyses by (Leow et al., 2014) and (Gregg et al. (2018)) had the same drawback; that is, only two retrospective studies were included in their analyses. In addition, the included studies were heterogeneous in terms of patient characteristics; one study included high-risk UTUC patients (Porten et al., 2014), while another study targeted node-positive UTUC patients only (Youssef et al., 2011). The explanation for this patient heterogeneity involved the fact that the definition for high-risk UTUC was not based on TNM staging system (based on primary tumor size, number of nearby lymph nodes with tumors, and whether the tumor metastasized), but on tumor grade, tumor burden, and architecture (Porten et al., 2014). Therefore, evidence for the effectiveness of NAC provided by these studies could be insufficient.

Our analysis of OS, CSS, PFS, and the chance of downstaging in pathologic diagnosis in four published studies showed that the absolute increase in OS for use of NAC in patients with locally advanced UTUC is 11% (i.e., numbers-needed-to-treat of 9). (Lucca et al. (2015)) reported

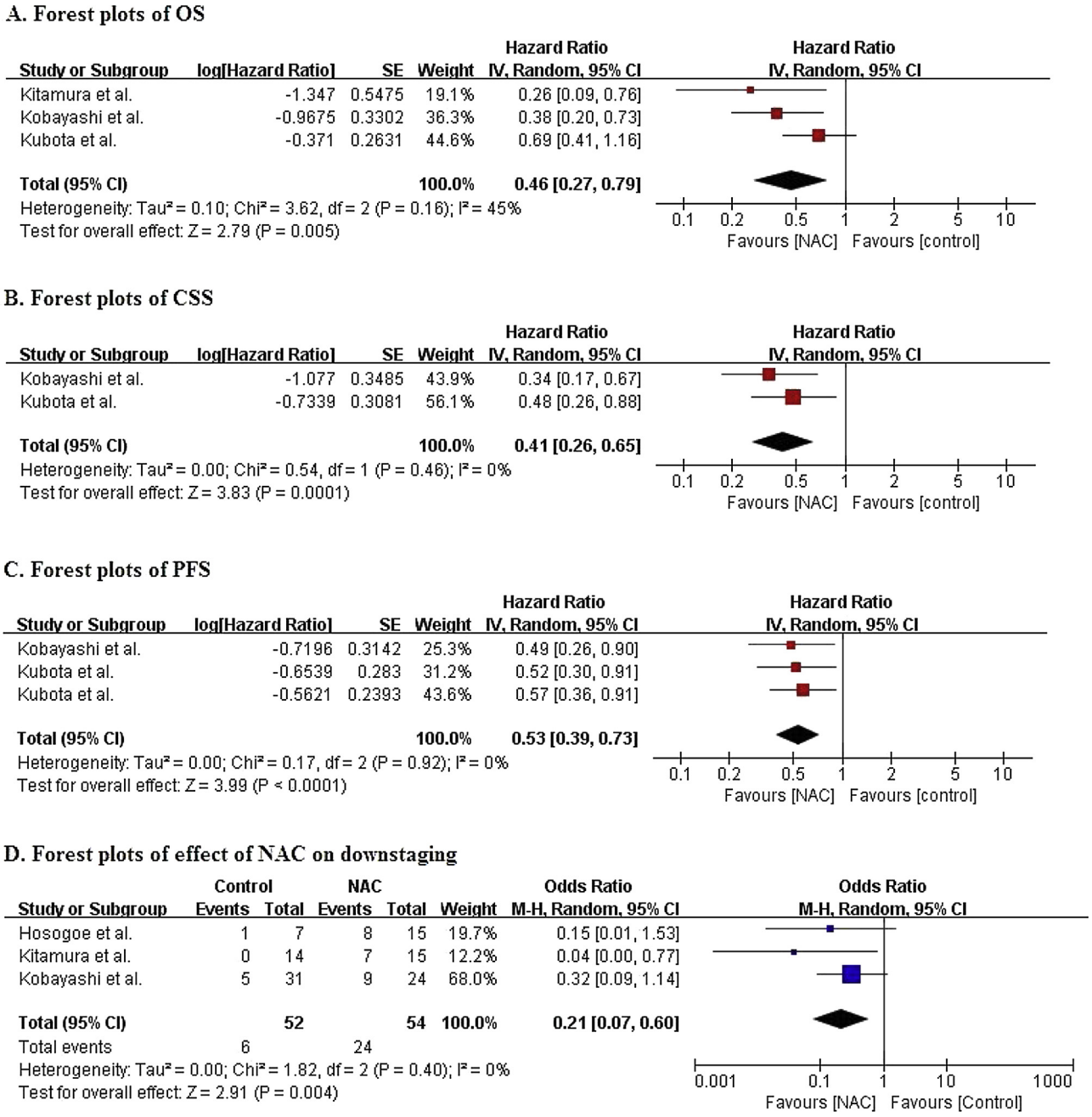

Fig. 2. Forest plots on downstaging of (A) overall survival, (B) cancer-specific survival, (C) progression-free survival, and (D) effect of NAC on downstaging.

that the maximal absolute reduction in mortality for ACH use in lymph node-positive UTUC is 9% (i.e., numbers-needed-to-treat of 11). Although there are no level 1 data comparing NAC plus RNU with ACH plus surgery, the number-needed-to treat to assess the impact of NAC on survival outcomes may be lower than that for ACH (9 versus 11). In addition, we made an effort to qualify the confidence of our work by using GRADE for the certainty of evidence in accordance with the recent format of meta-analysis (Guyatt et al., 2008b). Given the approaches we used, our study adds further evidence for the effectiveness of NAC on UTUC. This study will also be of great help to clinicians who are concerned about the use of NAC in the treatment of locally advanced UTUC patients.

Nonetheless, our study had several limitations. Since we did not analyze individual patient data, similar covariates existing at individual

Table 2
Results of quality assessment by Newcastle–Ottawa Scale.

Study	Selection 1	Selection 2	Selection 3	Selection 4	Comparability A	Comparability B	Exposure 1	Exposure 2	Exposure 3	Scores
Hosogoe et al. (2017)	*	*	–	–	*	*	*	*	–	6
Kitamura et al. (2012)	*	*	–	–	*	*	*	*	–	6
Kobayashi et al. (2016)	*	*	–	–	*	*	*	*	–	6
Kubota et al. (2017)	*	*	–	–	*	*	*	*	–	6

Table 3
Grading of Recommendations, Assessments, Developments, and Evaluation (GRADE) quality assessment of direct evidence for each comparison.

Certainty assessment							Number of patients		Effect	Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NAC	Placebo	Relative (95% CI)		
Overall survival											
3	Observational studies	Not serious	Not serious	Not serious	Serious[a]	Strong association	140	178	**HR 0.46** (0.27 to 0.79)	●●◯◯ LOW	CRITICAL
Cancer-specific survival											
2	Observational studies	Not serious	Not serious	Not serious	Serious[a]	Strong association	125	164	**HR 0.41** (0.26 to 0.65)	●●◯◯ LOW	CRITICAL
Progression-free survival											
2	Observational studies	Not serious	Not serious	Not serious	Serious[a]	Strong association	125	164	**HR 0.53** (0.39 to 0.73)	●●◯◯ LOW	CRITICAL
Downstaging											
3	Observational studies	Not serious	Not serious	Not serious	Serious[a]	Strong association	90	96	**OR 0.21** (0.07 to 0.60)	●●◯◯ LOW	CRITICAL

NAC, neoadjuvant chemotherapy; HR, hazard ratio; OR, odd ratio.
[a] Total number of participants was less than 400.

patient level were not considered, which could affect the end result. In addition, the definition of survival endpoint was not exactly defined across studies. The number of included studies in the present analysis was small. Since the included studies in our analysis were all retrospective studies, there is a possibility of some selection bias affecting our results. Another limitation which could have influenced survival to a large extent is that RNU and lymph node dissection were performed by various surgeons across different institutions. There is still a lot of controversy regarding the use of NAC for UTUC, due to factors such as the potential risk of over-treatment and increasing the perioperative morbidity (Leow et al., 2014). To overcome these limitations and find more evidence to support NAC use, a larger, collaborative, international, well-designed randomized control trial should be performed to determine the true value of preoperative chemotherapy.

5. Conclusions

Our results suggest that NAC can increase pathologic CR rate after RNU in locally advanced UTUC patients. NAC may also provide better survival outcomes in patients with locally advanced UTUC after RNU. Prospective randomized studies will be needed to confirm the benefits of NAC in locally advanced UTUC patients.

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