Original Study

Neoadjuvant Chemotherapy Prior to Radical Cystectomy for Muscle-Invasive Bladder Cancer With Variant Histology: A Systematic Review and Meta-Analysis of Survival Outcomes and Pathological Features

Do Kyung Kim, Jae Heon Kim, Jun Young Park, Yong Nam Gwon, Ki Min Kim, Won Jae Yang, Seung Whan Doo, Yun Seob Song

Abstract

We conducted systematic review and meta-analysis to evaluate effects of neoadjuvant chemotherapy on survival and histopathological outcomes of variant histology of urothelial carcinoma of bladder. The present study found that bladder cancer patients with variant histology administration of neoadjuvant chemotherapy before surgery had better survival outcomes and higher pathologic down staging rate than those without administration of neoadjuvant chemotherapy before surgery.

Purpose: To conduct systematic review and meta-analysis to evaluate effects of neoadjuvant chemotherapy (NAC) on survival and histopathological outcomes of variant histology (VH) of urothelial carcinoma (UC) of bladder. **Methods:** This systematic review was registered in PROSPERO (CRD42023389115). Literature search was conducted in PubMed/Medline, Embase, and Cochrane Library for studies published up to January 2023. Population, intervention, comparator, outcome, and study design were as follows: bladder cancer patients with VH (population), neoadjuvant chemotherapy (intervention), radical cystectomy only (comparators), oncological survival and pathologic response (outcomes), and retrospective or prospective (study design). **Results:** Finally, a total of 17 studies were included in the present study (quantitative analysis, n = 17; qualitative analysis, n = 12). Pooled HR was 0.49 (95% CI: 0.31-0.76; $P = .002$) for OS. Pooled HR was 0.61 (95% CI: 0.38-0.98; $P = .04$) for CSS. Pooled HR was 0.44 (95% CI: 0.21-0.93; $P = .03$) in PFS. Pooled OR was 6.61 (95% CI: 4.50-9.73; $P < .00001$) in complete pathologic response. Pooled OR was 9.59 (95% CI: 3.56-25.85; $P < .00001$) in any pathologic response. Evidence quality assessments for each 5 comparisons using the GRADE approach were that Certainty was moderate in 1, low in 1, and very low in 3. **Conclusions:** Administration of NAC before surgery in bladder cancer patients with VH might confer better survival outcomes and higher pathologic down staging rate than no administration of NAC before surgery.

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Introduction

Bladder cancer is the most common cancer, accounting for 3% of all new cases and 2.1% of all new deaths worldwide.[1] About 75% of all bladder cancer patients are pure urothelial carcinoma (UC), with the remaining 25% having a variant histology (VH).[2-4] The World Health Organization published guidelines for classification of UC in 2004 and decided to identify distinct VH for increasing its diagnosis using pathology specimens.[5]

VH of the bladder UC is related with an increased risk of disease recurrence, cancer-specific mortality, and overall mortality compared to pure UC[6] Therefore, a better understanding of the histological form of each variant of UC is required to establish prognostic and treatment strategies suitable for individual VH.[7]

Treatment choice of muscle-invasive bladder cancer (MIBC) is neoadjuvant chemotherapy (NAC) with radical cystectomy (RC).[8,9] The advantage of NAC before surgery has been well confirmed for high-grade MIBC in meta-analyses of prospective clinical trials that have reported absolute increase of overall

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survival (OS).[10,11] Moreover, NAC combined with RC can achieve pathologic complete down staging in select patients and pathologic complete down staging after NAC can improve OS and recurrence-free survival in MIBC.[12,13] Nevertheless, evidence regarding preoperative chemotherapy in the treatment of bladder cancer patients with VH is sparse and highly variable. A intergroup randomized trial S8710 performed by the Southwest Oncology Group has shown that NAC is an independent prognostic factor of enhanced OS and cancer-specific survival (CSS) in bladder cancer patients with squamous and glandular differentiation.[14] However, several studies have shown that NAC cannot lead to better OS, CSS, or progression free survival (PFS).[15-17]

Therefore, we evaluated the effects of NAC on survival and pathologic outcomes of bladder cancer patients with VH by summarizing current data through a systematic review and meta-analysis. Based on these considerations, we analyzed survival and histopathological outcomes between patients receiving NAC before RC vs. RC alone to treat histological variants UC.

Materials and Methods

We registered this systematic review in PROSPERO (CRD42023389115).

Literature Search

We searched in PubMed/Medline, Embase, and Cochrane Library for studies published up to January 2023. The present study only included studies written in English. There were no restrictions on the type of design of included studies. To minimize publication bias, conferences and meeting abstracts were excluded even if they met the inclusion criteria. Search terms were: ("bladder cancer" OR "urothelial carcinoma" OR "variant histology"), ("neoadjuvant chemotherapy"), ("cystectomy"), and relevant terms. Search terms are shown in the supplement. Two authors (DKK and JHK) independently reviewed titles and abstracts of identified studies. If there was a disagreement about selections between them, it was discussed with a third reviewer (YSS) to determine whether the paper should be included.

Trial Inclusion Criteria and Exclusion Criteria

The present study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] The population, intervention, comparator, outcome, and study design were as follows: bladder cancer patients with VH (population), NAC (intervention), RC only (comparators), oncological survival and pathologic response (outcomes), and retrospective or prospective (study design). Exclusion criteria were as follows: (1) study in which the intervention was not only chemotherapy, (2) unable to extract outcome data, (3) studies on the effect of VH on outcomes, and (4) studies that did not report survival and pathological outcomes.

Primary end points were OS, CSS, and PFS. Secondary outcomes were complete pathologic down staging (pT0N0) and any pathologic down staging.

Data Extraction

Two authors (DKK and JHK) independently used predefined data sets to extract data. Conflicts between the *2* authors were solved through an agreement with the third author (YSS). The author, year of study, country, design of study, regimens of NAC, type of variant histology, follow period, conflict of interest, and outcomes (numbers of events, hazard ratios [HRs], odds ratios [ORs], 95% confidence intervals [CIs], and *P*-values) were extracted.

Study Quality Assessments and Quality of Evidence

The ROBINS-I tool was applied for Quality assessment.[19] It consisted of *3* assessment phases (preintervention, at-intervention, and postintervention). Preintervention stage included bias due to confounding and bias in selecting participants for the study. At-intervention stage included bias in classification of interventions. Postintervention stage included bias due to deviations from intended interventions, bias due to missing data, bias in measurements of outcomes, and bias in selection of reported result. The quality of each domain had 1 of 5 levels (ie, low, moderate. Serious, critical, and no information). The quality of each domain was integrated to rank the quality of each study in a total of 4 levels (ie, low, moderate, serious, and critical).

We assessed the certainty of evidence using the Grading of Recommendations, Assessments, Developments, and Evaluation (GRADE) approach.[20] Domains of GRADE approach included limitations in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, and publication bias. Based on the GRADE approach, certainty of evidence was rated at 1 of 4 levels (ie, very low, low, moderate, and high).

Statistical Analysis

For outcome measures of survival outcomes (OS, CSS, and PFS), hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted from included studies. Generally used method of measuring HRs and 95% CIs was applied for studies that only presented Kaplan-Meier log-rank or Wilcoxon *P*-values or survival rates.[21] Pathologic down staging was measured as odds ratios (ORs).

Statistical heterogeneity between included studies was evaluated using the Cochran Q statistic (*P*-value for heterogeneity) and the I^2 statistic (total percentage of variation due to heterogeneity).[22] A *P*-value $< .05$ in Cochran Q test and an I^2 value $> 50\%$ means that there is a significant heterogeneity between studies.[22] We used a random-effects model to account for heterogeneity between trials according to the DerSimonian and Laird method.[23] Sensitivity analysis was evaluated by sequentially ommiting outcomes of included studies and evaluating changes of results. A funnel plot was used to assess publication bias. A symmetric funnel diagram implied no publication bias.

Review Manager v.5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2008) was used for analysis. All *P*-values were *2*-sided and a *P*-value $< .05$ indicated statistical significance.

Results

Systematic Review Process

The systematic review process of the present study was represented in a PRISMA flow diagram (Figure 1). The initial search found a total of 659 studies, of which 157 duplicates were excluded. Titles and abstracts of the remaining 502 articles were reviewed

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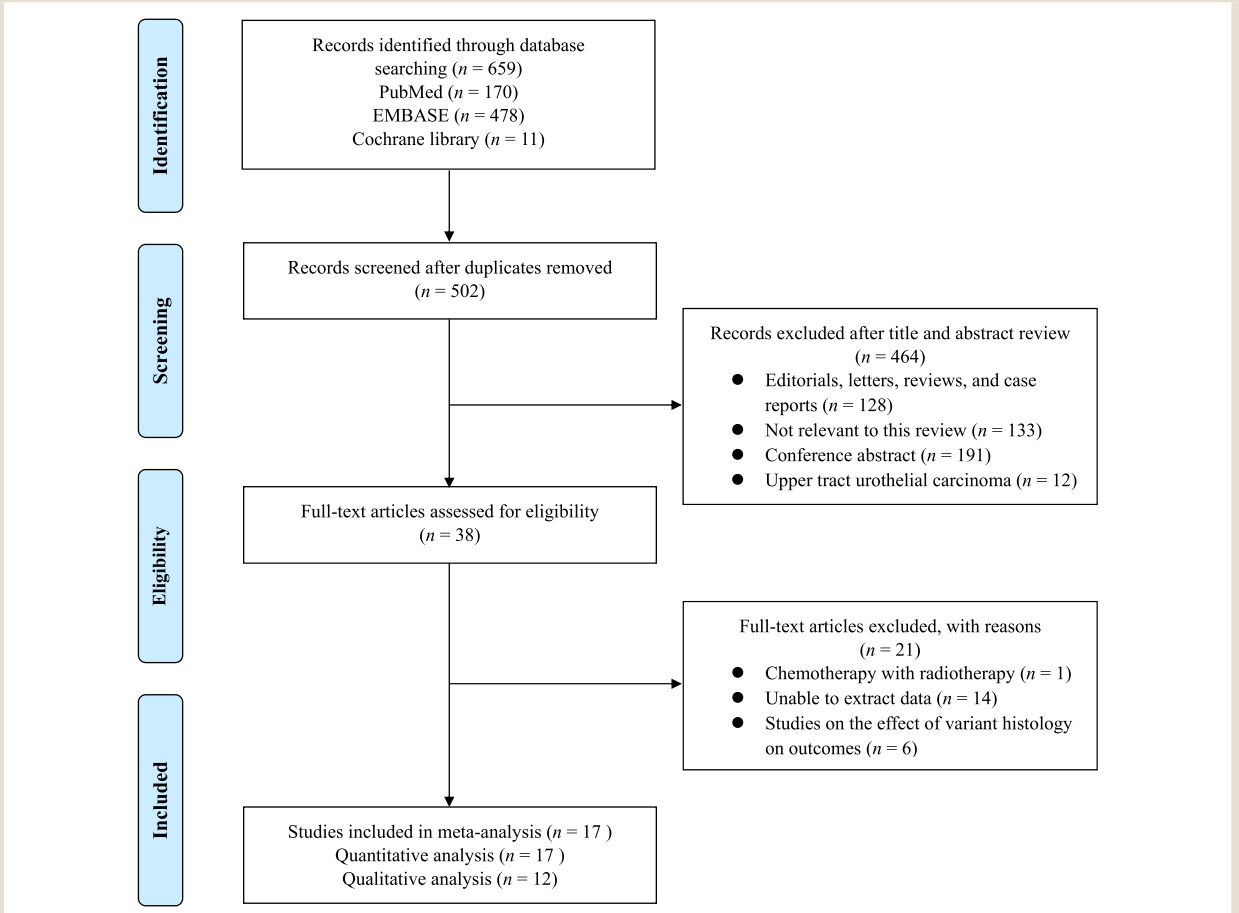
Figure 1 Flowchart of preferred reporting items for systematic reviews and meta-analysis (PRISMA).



according to the established inclusion and exclusion criteria. We evaluated full texts of the 21 studies to determine their eligibility for inclusion in the present study. Finally, a total of 17 studies were included in the present study (quantitative analysis, n = 17; qualitative analysis, n = 12) for assessing effects of NAC for VH of bladder cancer on survival outcomes and pathologic responses. The list of included 17 studies was shown in the supplement. This systematic review included a total of 8953 participants. Detailed characteristics of included studies are presented in Table 1 . Among the 17 studies, 6 were conducted using the same National Cancer Database (NCDB).[12, 24-28] Among these 6 studies conducted with the NCDB, only *1* study was included in the qualitative analysis through agreement among authors considering the duration of the study and the number of patients.[24]

Survival Outcomes

Overall Survival. A total of 9 studies were included in the analysis for OS. Pooled HR was 0.49 (95% CI: 0.31-0.76; $P = .002$) for OS (Figure 2A). There was heterogeneity between studies (Cochran Q statistics $P < .00001$ and $I^2 = 84\%$). In the subgroup analysis with micropapillary variant UC only, pooled HR was 0.90 (95% CI: 0.66-1.22; $P = .002$) for OS (Figure 2A). In the subgroup analysis with small cell UC only, pooled HR was 0.45 (95% CI: 0.29-0.71; $P = .002$) for OS (Figure 2A).

Cancer Specific Survival. A total of 5 studies were included in this analysis. Pooled HR was 0.61 (95% CI: 0.38-0.98; $P = .04$) for CSS (Figure 2B). There was no heterogeneity between studies (Cochran Q statistics $P = .04$ and $I^2 = 44\%$).

Progression Free Survival. A total of 4 studies were included in this analysis. Pooled HR was 0.44 (95% CI: 0.21-0.93; $P = .03$) in PFS (Figure 2C). There was heterogeneity between studies (Cochran Q statistics $P = .0004$ and $I^2 = 84\%$).

Pathologic Down Staging

Complete Pathologic Down Staging. A total of 8 studies were included in this analysis. Pooled OR was 6.54 (95% CI: 4.65-9.20; $P < .00001$) in complete pathologic response (Figure 3A). There was no heterogeneity between studies (Cochran Q statistics $P = .68$ and $I^2 = 0\%$). In the subgroup analysis with micropapillary variant UC only, pooled OR was 5.66 (95% CI: 2.80-11.45;

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Table 1 Characteristics of Studies Included in the Meta-Analysis

Study	Country	Design of study	Source of data (year)	Regimen of CTx	Type of variant histology	Period of F/U (month)	No. of NAC with Surgery	No. of Surgery only	Conflict of interest
Buisan et al. 2017	Sapin	Retrospective	Hospital Germans Trials Pujol (2008 – 2016)	NA	Squamous cell carcinoma	29 (2 – 99)	19	31	None
Chakiryan et al. 2021	United States	Retrospective	NCDB (2004 – 2017)	NA	Adenocarcinoma Micropapillary variant UC Neuroendocrine carcinoma Sarcomatoid variant UC Squamous cell carcinoma	NA	712	2727	Financial interest and/or other relationship with AstraZeneca, Bayer, Seagen, Clovis Oncology, Dendreon, Merck and Sanofi. Financial interest and/or other relationship with Seattle Genetics, Gilead and EMD Soreno. Financial interest and/or other relationship with Merck, Department of Defense and University of South Florida Office of Continuing Medical Education, and NCCN speaker and panel member, GU ASCO speaker, AUA Urology Care Scholar Award recipient, expert witness and recipient of Kidney Cancer Association Young Investigator Award.
Diamantopoulos et al. 2021	United States	Retrospective	SEER (2004 – 2015)	Cisplatin-based and other regimens	Micropapillary variant UC	NA	27	19	None
Doston et al. 2019	United States	Retrospective	NCDB (2004 – 2015)	NA	Squamous cell carcinoma	NA	48	623	None
Fernandez et al. 2017	United States	Retrospective	MD Anderson Cancer Center (1989 – 2012)	NA	Micropapillary variant UC	NA	29	74	None
Hajiran et al. 2021	United States	Retrospective	Moffitt Cancer Center (2007 – 2017)	Cisplatin-based and other regimens	Micropapillary variant UC Nested variant UC Neuroendocrine carcinoma Plasmacytoid variant UC Sarcomatoid variant UC Squamous differentiation Glandular differentiation	NA	78	95	NA
Kaimakliotis et al. 2016	United States	Retrospective	Indiana University School of Medicine (1990 – 2013)	MVAC GC	Clear cell and rhabdoid Lymphoepithelioma-like Micropapillary variant UC Nested variant UC Plasmacytoid variant UC Sarcomatoid variant UC Squamous differentiation Glandular differentiation Other	77 (35 – 153)	31	151	None

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Design of study	Source of data (year)	Regimen of CTx	Type of variant histology	Period of F/U (month)	No. of NAC with Surgery	No. of Surgery only	Conflict of interest
Lynch et al. 2013	United States	Retrospective	MD Anderson Cancer Center (1985 – 2010)	IA/EP EP MVAC TMP CGI EAP IA GCtx GTA	Small Cell UC	NA	48	47	None
Matulay et al. 2019	United States	Retrospective	NCDB (2004 – 2015)	NA	Squamous cell carcinoma	NA	75	938	None
Meeks et al. 2013	United States	Prospective	Memorial Sloan-Kettering Cancer Center (1997 – 2010)	NA	Micropapillary variant UC	NA	29	15	None
Pereira et al. 2022	Portugal	Retrospective	Portuguese Institute of Oncology (2013 – 2019)	NA	Micropapillary variant UC Plasmacytoid variant UC Sarcomatoid variant UC Nested variant UC Microcystic variant UC Squamous differentiation Glandular differentiation Other	NA	20	58	NA
Rahman et al. 2022	United States	Retrospective	NCDB (2004 – 2017)	NA	Micropapillary variant UC	NA	189	553	None
Scosyrev et al. 2011	United States	RCT	SWOG 8710	MVAC	squamous differentiation adenonocarcinoma Small Cell Urothelial Cancer signet ring	NA	32	27	NA
Speir et al. 2021	United States	Retrospective	Indiana University School of Medicine (2008 – 2018)	NA	Squamous differentiation	NA	20	51	None

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Design of study	Source of data (year)	Regimen of CTx	Type of variant histology	Period of F/U (month)	No. of NAC with Surgery	No. of Surgery only	Conflict of interest
Sui et al. 2016	United States	Retrospective	NCDB (2004 – 2014)	NA	Micropapillary variant UC	NA	31	63	None
Teo et al. 2020	United States	Retrospective	Memorial Sloan-Kettering Cancer Center (1990 – 2015)	NA	Small Cell Urothelial Cancer	52	71	37	This study was funded in part by the National Institutes of Health/National Cancer Institute to Memorial Sloan Kettering Cancer Center (P30 CA008748), R01 CA233899, P01CA221757, SPORE in Bladder Cancer P50CA221745 and Cycle for Survival. B.J. Guercio is supported by the National Institutes of Health/National Cancer Institute via T32-CA009207, an Oncocyte Conquer Cancer Foundation Young Investigator Award, and a Bladder Cancer Advocacy Network Young Investigator Award. E. Pietzak is supported by the NIH/NCI K12 Paul Calabresi Career Development Award for Clinical Oncology [K12 CA184746]. B. Weigelt is funded in part by the Breast Cancer Research Foundation and Cycle for Survival grants.
Vetterlein et al. 2017	United States	Retrospective	NCDB (1998 – 2012)	NA	Micropapillary variant UC Sarcomatoid variant UC squamous differentiation adenocarcinoma Neuroendocrine carcinoma Other	NA	336	1649	None

CGI = cisplatin, gemcitabine, ifosfamide; EAP = etoposide, doxorubicin, cisplatin; ECarbo = etoposide, carboplatin; EP = etoposide, cisplatin; GC = gemcitabine and cisplatin; GCtx = gemcitabine, cyclophosphamide; GTA = gemcitabine, doxorubicin, paclitaxel; IA = ifosfamide, doxorubicin; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; NA = Not available; NCDB = National Cancer Database; SWOG = Southwest Oncology Group; TMP = paclitaxel, methotrexate, cisplatin; UC = Urothelial carcinoma; VACtx = vincristine, doxorubicin, cyclophosphamide; 5-FUCarbo = 5-fluorouracil, carboplatin

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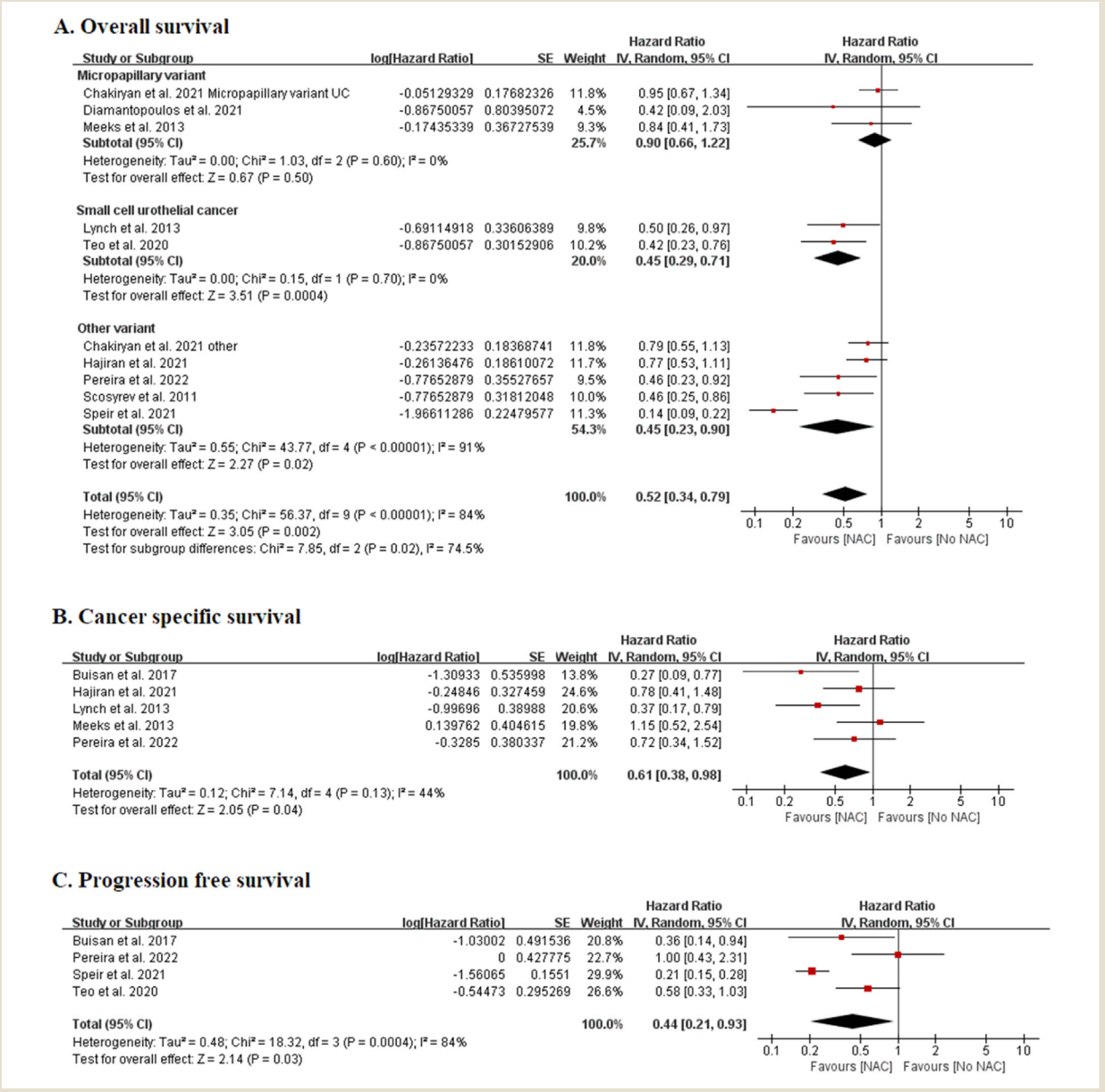
Figure 2 Forest plots of survival outcomes. (A) Overall survival (unadjusted), (B) Cancer-specific survival (unadjusted), (C) Overall survival (adjusted), and (D) Cancer-specific survival (adjusted).



$P < .0001$) for complete pathologic response (Figure 3A). In the subgroup analysis with squamous cell carcinoma only, pooled OR was 5.85 (95% CI: 2.05-16.64; $P = .0009$) for complete pathologic response (Figure 3A).

Any Pathologic Down Staging. A total of 4 studies were included in this analysis. Pooled OR was 9.59 (95% CI: 3.56-25.85; $P < .00001$) in any pathologic response (Figure 3B). There was heterogeneity between studies (Cochran Q statistics $P < .0001$ and $I^2 = 88\%$).

Quality Assessment and Qualitative Risk of Bias

Quality assessment results of included studies using ROBINS-I are shown in Figure 4. Of the total of 17 studies, 6 were serious and the remaining 11 studies were moderate.

Evidence quality assessments for each 5 comparison using the GRADE approach are shown in Table 2. Certainty was moderate in 1, low in 1, and very low in *3* among 7 comparisons.

The sensitivity analysis did not reveal significant differences, meaning that the results are statistically reliable.

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Table 2 Grading of Recommendations, Assessments, Developments, and Evaluation (GRADE) Quality Assessment of Direct Evidence of Each Comparison

Certainty Assessment							Effect	Certainty	Importance
Number of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Relative (95% CI)		
Overall survival									
9	observational studies	serious	serious[a]	not serious	not serious	strong association	**HR 0.49** (0.31 to .76)	⊕⊕◯◯ Low	CRITICAL
Cancer-specific survival									
5	observational studies	serious	not serious	not serious	not serious	none	**HR 0.61** (0.38 to 0.98)	⊕◯◯◯ Very low	CRITICAL
Progression-free survival									
4	observational studies	serious	serious[a]	not serious	not serious	strong association	**HR 0.44** (0.21 to 0.93)	⊕⊕◯◯ Low	CRITICAL
Complete pathologic response									
7	observational studies	serious	not serious	not serious	not serious	very strong association	**OR 6.61** (4.50 to 9.73)	⊕⊕⊕◯ Moderate	CRITICAL
Any pathologic response									
4	observational studies	serious	serious[b]	not serious	not serious	very strong association	**OR 9.59** (3.56 to 25.85)	⊕⊕◯◯ Low	CRITICAL

[a] $I^2 = 84\%$;
[b] $I^2 = 88\%$

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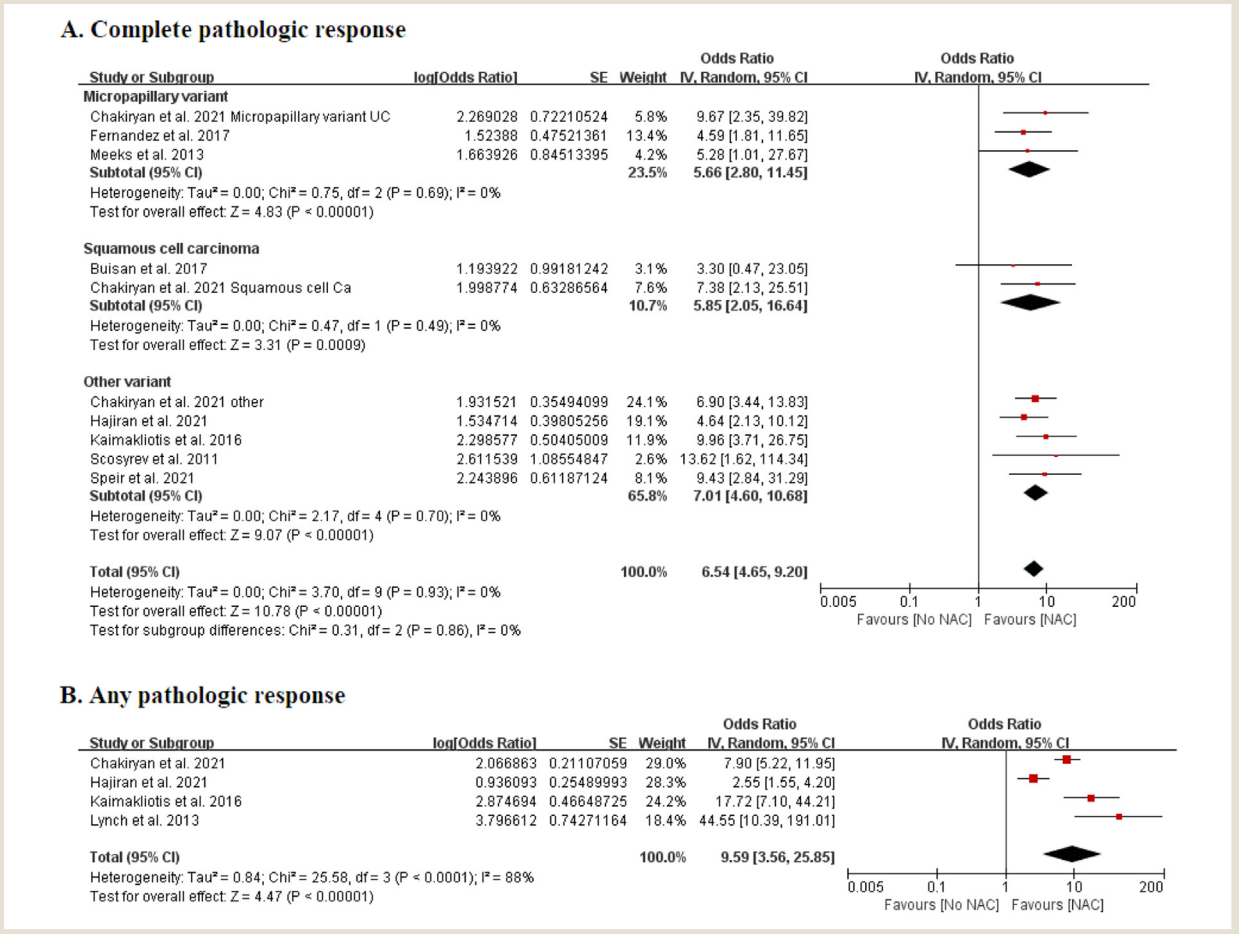
Figure 3 Forest plots of clinicopathological outcomes. (A) lymph node positive, (B) pathologic T stage 3 and 4, and (C) ureteral margin positive.



Publication bias for survival outcomes (OS, CSS, and PFS) and pathology outcomes were not significant. Funnel plots for publication bias for all results showed some degree of symmetry (Figure 5).

Discussion

With advances in molecular medicine, a variety of possible biomarkers to forecast response to cisplatin-based chemotherapy have been researched. The use of NAC might be guided by tumor molecular characteristics in the future.[29] Although various VH of UC are considered precious biomarkers for decision-making of clinicians, their prognostic value has not been fully elucidated yet.[30] In addition, a tailored treatment approach according to each type of VH has not been established yet.[31] The present study demonstrated that bladder UC patients with VH could benefit from NAC for survival outcomes (OS, CSS, PFS). Moreover, NAC with surgery showed a pathologic complete and any down-staging rate over surgery-only treatment in bladder UC patients with VH. We evaluated the certainty of evidences of our results using the GRADE approach. The certainty of the evidence for pathologic complete response had a moderate level. Certainties of the evidence for OS, PFS, and any pathologic down staging had a low level. The certainty of evidence for CSS had a very low level.

As knowledge with UC has increased, the spectrum of microscopic morphology of UC has broadened to include several distinct VH.[32] Recognizing VH in urothelial tumors is important for the following reasons: (1) some types might have different clinical outcomes, (2) Some might require a different treatment approach than UC, and (3) recognition of unusual histologic patterns might be important to avoid diagnostic errors.[33,34] Nevertheless, RCTs focusing on the rarity and aggressiveness of the VH subtype of bladder UC have not been reported. Thus, there is very little evidence for an ideal treatment modality for VH with varying prognosis.[35]

The most common type of VH is UC with variable differentiation (eg, squamous and glandular differentiation).[36] Although these types of VH are usually diagnosed at a stage of more advancement than pure UC, there is no consensus on survival outcomes.[37] The prognosis of squamous or glandular differentiation is difficult to predict, but some studies have reported poor results.[38,39] The literature on the treatment effect of NAC for squamous and

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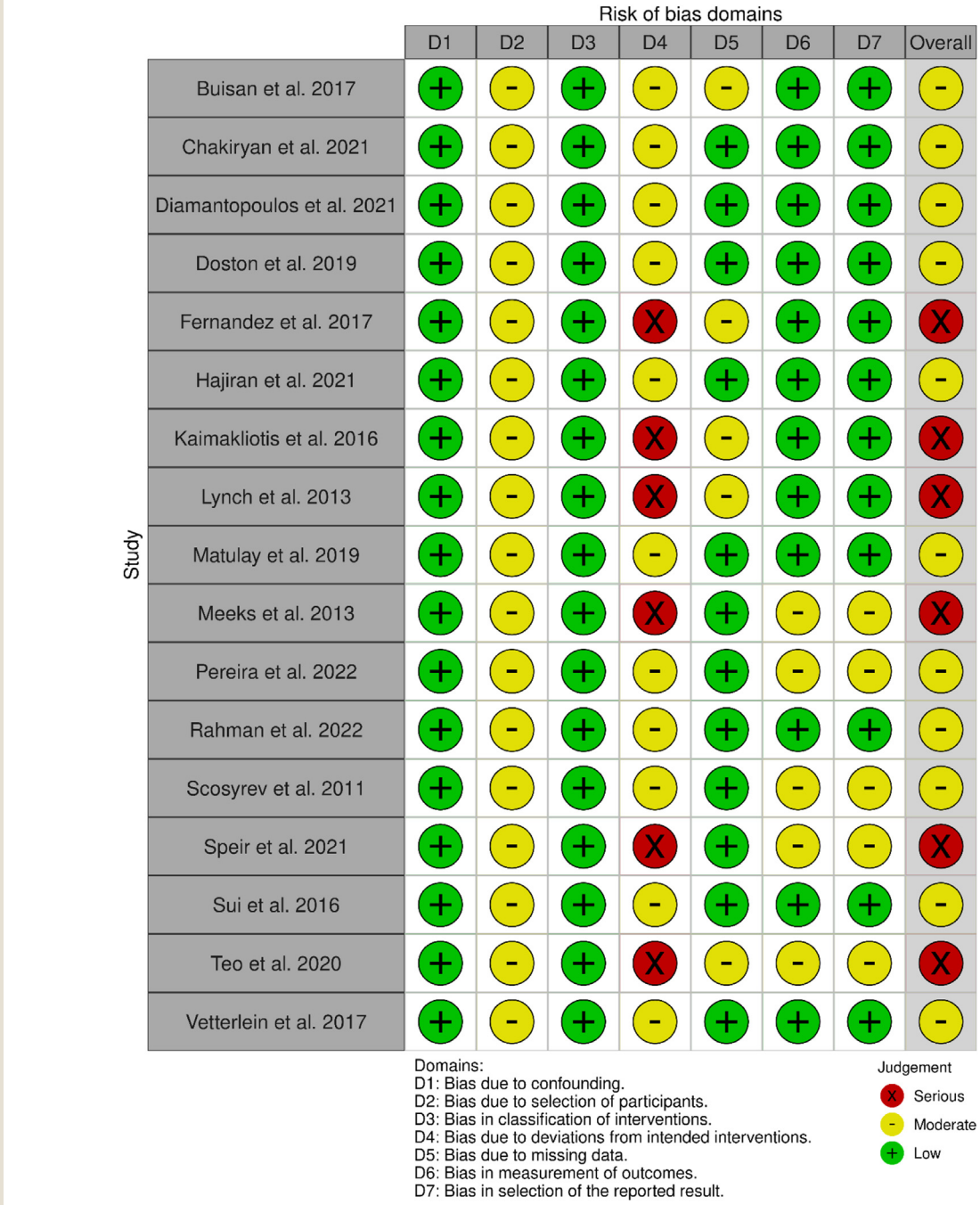
Figure 4 Funnel plot of survival outcomes. CSS = cancer-specific survival; OS = overall survival.



glandular differentiation is also inconsistent, with some studies reporting lower disease stages after NAC with surgery while others showing a poor response.[14,40,41]

Micropapillary carcinoma incidence is .7% in UC. [42] This VH has a micropapillary structure, which is suggestive of the papillary profile found in ovarian papillary serous tumors.[43] Micropapillary carcinoma is an aggressive VH commonly seen in advanced stages with frequent lymph node metastasis and high metastatic risk.[44] Abufaraj et al.[45] have conducted meta-analysis to assess the effect of NAC for patients with bladder cancer harboring micropapillary

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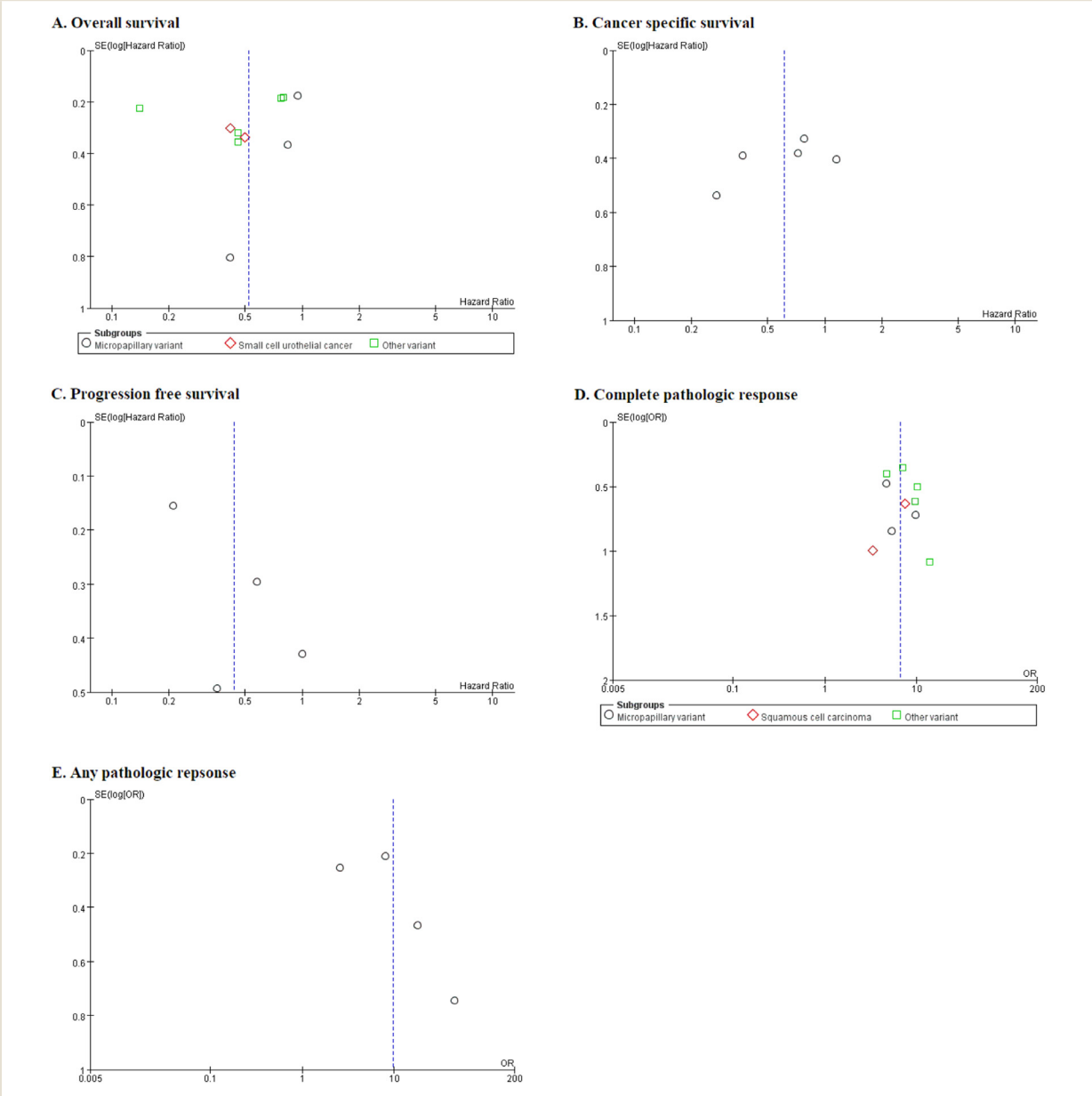
Figure 5 Funnel plot of clinicopathological outcomes.



carcinoma component. They reported that NAC was not significantly associated with improved survival outcomes, although it was associated with pathological downstaging.

Plasmacytoid UC is represented by discohesive cells with eccentric nuclei and abundant cytoplasm.[30] The morphology of plasmacytoid UC has almost identical to gastric signet ring cancer and lobular breast cancer.[46] Plasmacytoid UC is characterized by an ambiguous plane between the tumor and normal tissue, which is associated with failure of complete tumor resection and high rates of positive surgical margins.[47] Kim et al.[30] have reported that plasmacytoid UC is significantly realted with unfavorable clinicopathological outcomes and worse OS compared to pure UC of bladder. There are no confirmed guidelines to determine whether NAC should be performed prior to surgery for MIBC patients with plasmacytoid UC.[30]

Sarcomatoid, giant cell, and microcystic VH are associated with advanced stage at diagnosis. They have a poor prognosis.[36] Nested UC is characterized by a high rate of locally advanced disease and possibility of metastasis, although its survival outcomes appear to be similar to pure UC when controlled for tumor stage.[48] Clear cell tumors are very rare. Available data suggest that this VH might be releated with rapid disease progression and metastasis, which may

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require aggressive treatment with early RC.[49] Lymphoepithelioma-like carcinoma is similar to nasopharyngeal carcinoma. It responds well to platinum-based chemotherapy in its pure form.[36]

The treatment of choice for bladder cancer that invades the muscularis propria (≥ stage cT2) is RC, which can enhance survival.[50] Survival rates are further improved if NAC, usually gemcitabine and cisplatin, or MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) is administered before RC.[13] However, survival improvement is primarily observed in patients whose tumors histologically can respond to chemotherapy with complete pathologic down staging (ie, complete absence of cancer on the histologic specimen).[13] Although several studies have shown that NAC has a poorer response in patients with VH,[51,52] studies on whether NAC is effective for VH are sparse with different conclusions. In this respect, the present study added evidence for the effect of NAC in VH. We found that in patients with VH, those who used NAC before RC had significantly higher OS (HR: 0.49, 95% CI: 0.31-0.76; $P = .002$), CSS (HR: 0.61, 95% CI: 0.38-0.98; $P = .04$), and PFS (HR: 0.44, 95% CI: 0.21-0.93; $P = .03$) than those who only received RC. Moreover, patients using NAC before RC had significantly higher pathologic complete rate (OR: 9.59, 95% CI: 3.56-25.85; $P < .00001$) and pathologic complete rate (OR: 6.61, 95% CI; 4.50-9.73; $P < .00001$) than those using only RC. However, because NAC is performed before surgery despite benefits for survival outcomes and pathologic response, there is a possibility of overtreatment due to inaccurate staging information from preoperative imaging studies.[53] Therefore, clinicians should carefully select patients who need NAC among VH patients and perform NAC carefully in VH patients.

There is a meta-analysis on effect of NAC for VH.[54] The difference between that study and the present study was that we analyzed pathologic response (complete and any response) in addition to survival outcome (OS, CSS, PFS). The present study found that NAC for VH was effective in all outcomes compared to only surgery treatment. Pathologic response is important because it is related to survival rate of bladder cancer patients. Petrelli et al.[13] have suggested that bladder cancer patients with complete pathologic down staging (pT0N0M0 stage) after NAC have better OS and PFS than patients without complete pathologic down staging. Our results demonstrated that the complete pathologic down staging rate was high in the group that received NAC for VH. Moreover, the level of evidence for complete pathologic down staging by GRADE approach was moderate. Nevertheless, our study could not avoid several limitations. All studies included in the present research are retrospective study that have inherent flaws such as selection bias. The lack of studies on 1 type of VH might introduce bias as results for different types of VH were pooled and analyzed. Due to variability in the type of VH included in studies of VH, bias might have occurred because different types of VH were pooled and analyzed.

Conclusion

We found that bladder cancer patients with VH administration of NAC before RC had better survival outcomes and higher pathologic down staging rate than those without administration of NAC before RC. Therefore, the present study might help physicians discuss management options for bladder cancer patients with VH during the decision-making process. Nevertheless, due to the rather low level of evidence caused by the rarity of the disease, well-designed studies are needed to elucidate the value of the comprehensive treatment strategy in bladder cancer patients with VH.

Clinical Practice Points

- An adequate understanding of the variant histological forms of bladder cancer is important for the best prediction of prognosis and the provision of optimal management strategies. However, the behavior of variant histology of urothelial carcinoma of the bladder and its management strategy is not yet established because there are insufficiency and inconsistency in the data. Therefore, we evaluated the effects of neoadjuvant chemotherapy on survival and pathologic outcomes of bladder cancer patients with variant histology by summarizing current data through a systematic review and meta-analysis.
- The key findings of our meta-analysis are summarized as follows:
  1) bladder urothelial carcinoma patients with variant histology could benefit from neoadjuvant chemotherapy for survival outcomes (overall survival, cancer-specific survival, and progression free survival)
  2) neoadjuvant chemotherapy with surgery showed a pathologic complete and any down-staging rate over surgery-only treatment in bladder urothelial carcinoma patients with variant histology.
- To the best of our knowledge, this is the first meta-analysis to analyse effects of neoadjuvant chemotherapy on the clinicopathological features and survival outcomes of bladder cancer patients with variant histology as compared to surgery-only treatment. This study may help the clinicians discuss the prognosis and choice of management with bladder cancer patients with variant histology.

Disclosure

The authors report no conflicts of interest in relation to this work.

CRediT authorship contribution statement

Do Kyung Kim: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Jae Heon Kim:** Validation. **Jun Young Park:** Methodology. **Yong Nam Gwon:** Investigation. **Ki Min Kim:** Resources. **Won Jae Yang:** Resources. **Seung Whan Doo:** Formal analysis. **Yun Seob Song:** Conceptualization, Validation, Data curation, Writing – original draft, Writing – review & editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2023.07.005.

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