

Pathological T0 Following Cisplatin-Based Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Network Meta-analysis

Hyung Suk Kim, Chang Wook Jeong, Cheol Kwak, Hyeon Hoe Kim, and Ja Hyeon Ku

Abstract

Purpose: To systematically assess and compare the relationship between various neoadjuvant chemotherapy regimens and pCR in patients with muscle-invasive bladder cancer.

Experimental design: We performed a literature search of PubMed, Embase, and the Cochrane Library for all articles published before March 2015 and according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. There were 17 articles that met the study eligibility criteria and were selected for the final analysis. A direct pair-wise meta-analysis was performed for studies that compared the same regimen. Finally, a Bayesian network meta-analysis was used to indirectly compare the regimens.

Results: In a pair-wise meta-analysis, the methotrexate/vinblastine/Adriamycin/cisplatin [MVAC; OR, 4.36; 95% confidence interval (CI), 2.71–7.02] and gemcitabine/cisplatin (GC) regi-

mens (OR, 4.92; 95% CI, 2.93–8.24) were significantly associated with a better pCR than RC alone. In a network meta-analysis, there was no significant difference in terms of pCR achievement between the GC and MVAC regimens (OR, 1.14; 95% CI; 0.85–1.70). However, in a subgroup network meta-analysis that only included prospective randomized trials, the MVAC regimen was significantly correlated with a higher rate of pCR (OR, 5.75; 95% CI, 1.96–24.18).

Conclusions: The results of this meta-analysis suggest that a GC regimen was associated with a pCR rate that was similar to that of a MVAC regimen based on retrospective data, but only the MVAC regimen was proven to achieve pCR in prospective randomized trials. Additional prospective randomized trials comparing both regimens will be necessary to establish the optimal neoadjuvant chemotherapy regimen. *Clin Cancer Res*; 22(5); 1086–94. ©2015 AACR.

Introduction

Radical cystectomy (RC) with bilateral pelvic lymphadenectomy is the recommended treatment for patients with muscle-invasive bladder cancer (MIBC). This is a curative procedure for many patients; however, some patients may experience disease recurrence (1–3). Bladder cancers usually recur distantly rather than locoregionally. In patients with pT2 and pT3/pT4 tumors, local recurrence has been observed in 3% to 4% and 11% to 16% of patients, respectively, whereas distant failure has occurred in 10% to 27% and 19% to 35% of patients, respectively (1, 4). The latter findings make a strong argument for the administration of perioperative chemotherapy, as a failure to cure is usually due to the presence of occult metastatic disease at sites that are beyond the margins of local therapy. In addition, these findings indicate that radical surgery alone may be inadequate for the majority of patients with locally advanced bladder cancer. Thus, some form of effective systemic treatment is required to improve patient survival. A meta-analysis that included 11 randomized studies sug-

gested that neoadjuvant chemotherapy (NACH) followed by RC was associated with a 5% improvement in overall survival (OS) and a 9% improvement in disease-free survival (5). Therefore, NACH is recommended for nearly all patients with MIBC.

Despite this recommendation, only 15% to 20% of patients with MIBC have received NACH, though the prevalence has increased over time (6). Importantly, the optimal regimen of NACH is controversial because few studies have compared the efficacy of the different NACH regimens. The European Society of Medical Oncology does not recommend one particular NACH regimen (7). The National Comprehensive Cancer Network (NCCN) recommends the use of gemcitabine/cisplatin (GC) NACH based on the data from several comparative trials, as well as the methotrexate/vinblastine/Adriamycin/cisplatin (MVAC) regimen as the preferred neoadjuvant regimens (8). However, this trial was performed in patients with advanced and metastatic bladder cancer, and therefore the results may not be applicable to patients in a neoadjuvant setting.

Patients that do not respond to NACH may experience reduced quality of life and substantial delays in definitive treatment. Tumor downstaging might be a valuable measurement for individualizing MIBC treatment until adequate molecular markers to detect chemosensitive tumors are identified. Previous studies have demonstrated that NACH increased the rate of downstaging, leading to an improved prognosis (9–11). In contrast, a lack of response to NACH was associated with a significantly higher rate of local and distant recurrence, and with lower OS (12). Therefore, several investigators have suggested that tumor downstaging might be used as a surrogate endpoint for OS (13). In particular, downstaging to pT0 (pCR, pT0N0M0; pCR) is currently the best

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

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Translational Relevance

Although radical cystectomy (RC) with bilateral pelvic lymphadenectomy may be curable treatment option for some patients with muscle-invasive bladder cancer (MIBC), a substantial portion of patients experienced disease recurrence after surgery. Therefore, the administration of neoadjuvant chemotherapy (NACH) before surgery is currently recommended in almost all patients with MIBC for the improvement of patient's survival. On the basis of previously published articles, tumor downstaging to pathologic complete response (pCR) after NACH is considered to be a surrogate predictor of favorable outcomes after RC for MIBC. However, the optimal NACH regimen to achieve pCR has not yet been definitively established. In this study, we analyzed initial and updated publications along with subsequent meta-analyses with respect to NACH for patients with MIBC. In addition, we sought to assess and compare the pCR rates of various NACH regimens in patients with muscle-invasive urothelial carcinoma of the bladder on the basis of the meta-analysis.

predictor of favorable outcomes (14, 15). The results of the SWOG 8710 trial demonstrated that patients who achieved pCR status after RC had an 80% probability of survival at 5 years (14). Patients with pCR in the four main prospective NACH trials experienced similar survival times, which exceeded those of the groups that did not achieve pCR (15). A recent meta-analysis also demonstrated that patients who achieved pCR after NACH had better overall and recurrence-free survival times than those who did not achieve pCR (16).

In this study, we analyzed initial and updated publications along with subsequent meta-analyses with respect to NACH for patients with MIBC. In addition, we sought to assess and compare the pCR rates of various NACH regimens in patients with muscle-

invasive urothelial carcinoma of the bladder on the basis of the meta-analysis.

Materials and Methods

The meta-analysis was performed in agreement with the recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA; ref. 17).

Search strategy

A comprehensive literature search was conducted of studies published before March 30, 2015, using PubMed, Embase, and the Cochrane Library. The search was restricted to articles for which the full-text publications were available in English. The following key words were used: (urothelial cancer OR urinary bladder OR bladder cancer OR bladder carcinoma) and (NACH OR induction chemotherapy OR pre-operative chemotherapy) and (RC). The reference lists from eligible studies and meta-analyses were also reviewed. Two independent evaluators (H.S. Kim and C.W. Jeong) selected the articles and any discrepancies were resolved.

Eligible criteria

We defined study eligibility according to predefined selection criteria (17).

Population: Patients with muscle-invasive urothelial carcinoma of the bladder.

Interventions: Cisplatin-based combination NACH followed by RC.

Comparators: RC only.

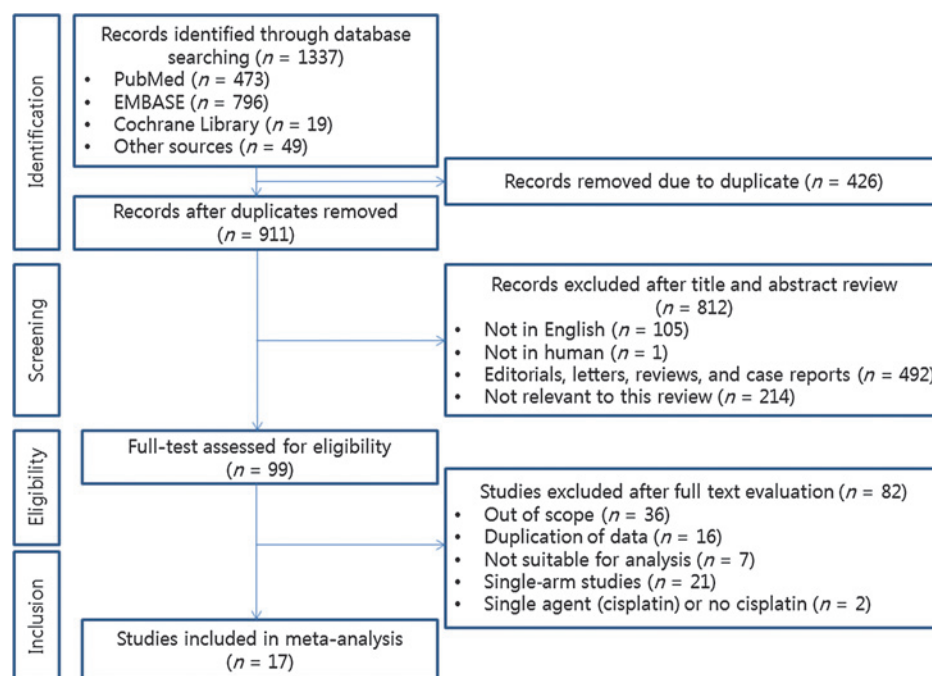
Outcome: pCR rate.

Study design: Retrospective or prospective.

Published studies were included if they (i) included patients with muscle-invasive urothelial carcinoma of the bladder; (ii)

Figure 1.

A flowchart of the literature search approach that was used in this meta-analysis.



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Table 1. Study characteristics of the eligible studies

Study	Year	Country	No. of centers	Type of study	Recruitment period	Median age, range (y)	No. of gender (male/female)	Median follow-up, range (mo)
Logothetis (30)	1996	USA	1	Prospective	1986-1994	RC: 64 (mean). 35-79 MVAC: 67 (mean), 32-79	72/28	31.7, NA
ICT (31)	1999	Multination	106	Prospective	1989-1995	NA	863/113	NA
Sherif (32)	2002	Multination	NA	Prospective	1991-1997	RC: 67, 41-84 CM: 66, 31-90	249/60	NA
Grossman (14)	2003	USA	126	Prospective	1987-1998	RC: 63, 39-84 MVAC: 63, 36-79	251/56	8.7 years, 3.1-13 years
Dash (18)	2008	USA	1	Retrospective	2000-2006	GC: 64, 56-70 MVAC: 63, 58-67	75/21	NA
Kaneko (19)	2011	Japan	1	Retrospective	2007-2011	GC: 69 (mean), 53-78 MVAC: 62 (mean), 53-74	24/7	18, 1-80
Pal (21)	2012	USA	1	Retrospective	1995-2012	GC: 68.6, 64.4-71.4 (IQR) MVAC: 60.1, 52.7-68.1 (IQR)	39/7	28.7, NA
Scosyrev (20)	2012	USA	1	Retrospective	1999-2009	RC: 70, NA GC: 65, NA	126/34	32, NA
Yeshchina (22)	2012	USA	1	Retrospective	1988-2010	GC: 66.0, NA MVAC: 62.9, NA	77/37	GC: 25, 1-120 MVAC: 30, 1-216
Fairey (26)	2013	USA	1	Retrospective	1985-2011	GC: 67, 43-85 MVAC: 63: 34-82	90/26	NA
Kitagawa (24)	2013	Japan	1	Retrospective	1997-2010	RC: 71.1 (mean), NA MVAC: 64.3 (mean), NA	45/7	41.2 (mean), 4-170
Lee (25)	2013	USA	1	Retrospective	2003-2011	NA	136/42	NA
Matsubara (23)	2013	Japan	1	Retrospective	2005-2010	RC: 64, 50-76 GC: 67, 47-79	31/11	28.6, 3.4-64.9
El-Gehani (27)	2014	Canada	1	Retrospective	2007-2011	RC: 72, 50-89 GC: 65, 48-89	120/40	RC: 22.1, 1.7-74.6 GC: 34, 6.4-84.6
Kitamura (33)	2014	Japan	28	Prospective	2003-2009	RC: 63, 35-74 MVAC: 63, 40-75	117/13	55, NA
Gandhi (29)	2015	USA	1	Retrospective	2000-2013	RC: 63.7, 34-88 GC: 62.5, 39-82	222/49	NA
Zargar (28)	2015	Multination	19	Retrospective	2000-2013	GC: 65, 57-71 (IQR) MVAC: 62, 57-69 (IQR)	617/168	11, 3-27 (IQR)

Abbreviations: ICT, international collaboration of trialists; IQR, interquartile range; NA, not available.

evaluated neoadjuvant cisplatin-based combination chemotherapy; and (iii) reported pCR following RC. The exclusion criteria were the following: non-human studies, review articles, letters, editorial comments, case reports, and articles that did not include raw data. Studies that included neoadjuvant radiotherapy, single-agent cisplatin chemotherapy, carboplatin-based chemotherapy, or studies in which chemotherapy was delivered non-intravenously were also excluded. If multiple publications from the same study or institution were available, we included the publication with the largest number of cases and the most applicable information.

Data extraction

Two authors (C. Kwak and H.H. Kim) completed an independent review of 1,337 articles. A total of 1,238 articles were excluded on the basis of the titles and abstracts, and the full-text versions of 99 articles were evaluated. In accordance with the inclusion criteria, a final selection of 17 articles was performed (14, 18-33) and any discrepancies were resolved. A PRISMA flowchart depicting the process for the systematic literature search and selection of the studies is shown in Fig. 1.

The following information was recorded for each eligible trial: author name, year of publication, geographic location, period of recruitment, study design, total number of patients, median age,

percentage of patients achieving pCR, and systemic NACH regimen administered.

Statistical analysis

If two or more studies compared the same regimen, a direct meta-analysis was conducted and the random effects OR was calculated, according to the methods described by DerSimonian and Laird. The χ^2 and I^2 tests were used to assess heterogeneity of the ORs between studies. Significant differences were defined as <0.1 for the χ^2 P value and $>50\%$ for the I^2 test. Publication bias was evaluated for the OR analysis using Egger's linear regression, the Begg rank correlation, and funnel plots. A $P < 0.05$ for either test was considered to indicate significant statistical publication bias.

For indirect comparisons between regimens, a Bayesian random effects model using Markov chain Monte Carlo methods was used (34). We modeled the binary outcomes for every treatment group of every study, and specified the relationship between the ORs with 95% confidence intervals (CIs) across studies. Each analysis was based on noninformative priors for effect size and precision. The surface under the cumulative ranking curve (SUCRA) that represented the cumulative ranking probabilities was used to provide a hierarchy of the treatments and accounted for both the location and the variance of all the relative treatment

Table 2. Treatment characteristics of the eligible studies

Study	Clinical stage	Chemotherapy regimens (mg/m ²)	No. of planned cycles	No. of patients	No. of pCR
Logothetis (30)	T3b-4a, N0, M0	MVAC (M 30, V 3, D 30, C 70)	2	RC: 48 MVAC: 51	RC: 1 (2.1%) MVAC: 14 (27.5%)
ICT (31)	T2-4a, N0, M0	CMV (M 30, V 4, C 100)	3	RC: 211 CMV: 206	RC: 26 (12.3%) CMV: 67 (32.5%)
Sherif (32)	T2-4a, N0, M0	CM (M 250, C 100)	3	RC: 139 CM: 140	RC: 16 (11.5%) CM: 37 (26.4%)
Grossman (14)	T2-4a, N0, M0	MVAC (M 30, V 3, D 30, C 70)	3	RC: 121 MVAC: 126	RC: 18 (14.9%) MVAC: 48 (38.1%)
Dash (18)	T2-4a, N0, M0	GC (G 1000, C 35) MVAC (M 30, V 3, D 30, C 70)	GC: 4 MVAC: 4	GC: 42 MVAC: 33	GC: 11 (26.2%) MVAC: 9 (27.3%)
Kaneko (19)	T1-4, Nany, M0	GC (G 1000, C 70) MVAC (M 30, V 3, D 30, C 70)	GC: 2 MAVC: 2	GC: 22 MVAC: 9	GC: 10 (45.5%) MVAC: 2 (22.2%)
Pal (21)	NA	GC (NA) MVAC (NA)	GC: 3-4 MVAC: 3-4	GC: 24 MVAC: 22	GC: 6 (25%) MVAC: 4 (18.2%)
Scosyrev (20)	T2-4, Nany, M0	GC (G 2000, C 70)	2-4	RC: 135 GC: 25	RC: 7 (5.2%) GC: 5 (20%)
Yeshchina (22)	T2-4a, N0-2, M0	GC (NA) MVAC (NA)	GC: NA MVAC: NA	GC: 16 MVAC: 45	GC: 4 (25%) MVAC: 14 (31.1%)
Fairey (26)	T2-4, N0, M0	GC (NA) MVAC (NA)	GC: 4 MVAC: 4	GC: 58 MVAC: 58	GC: 12 (20.7%) MVAC: 6 (10.3%)
Kitagawa (24)	T2-4, N0, M0	MVAC (M 30, V 3, D 30, C 70)	2	RC: 25 MVAC: 58	RC: 0 (0%) MVAC: 15 (25.9%)
Lee (25)	T2-4, N0, M0	GC (NA) MVAC (NA)	GC: NA MVAC: NA	RC: 91 GC: 41 MVAC: 31	RC: 8 (8.8%) GC: 12 (29.3%) MVAC: 7 (22.6%)
Matsubara (23)	T2-4, N0-2, M0	GC (G 1000, C 70)	4	RC: 17 GC: 25	RC: 0 (0%) GC: 10 (40%)
El-Gehani (27)	T2-4, N0, M0	GC (G 1250, C 70)	4	RC: 69 GC: 91	RC: 2 (2.9%) GC: 19 (20.9%)
Kitamura (33)	T2-4a, N0, M0	MVAC (M 30, V 3, D 30, C 70)	2	RC: 65 MVAC: 59	RC: 6 (9.2%) MVAC: 22 (37.3%)
Gandhi (29)	T1-4, N0-2, M0	GC (G 1000, C 70)	Variable	RC: 121 GC: 150	RC: 8 (6.6%) GC: 34 (22.7%)
Zargar (28)	T2-4a, N0, M0	GC (NA) MAVC (NA)	Variable	GC: 602 MVAC: 183	GC: 144 (23.9%) MVAC: 45 (24.6%)

Abbreviations: ICT, international collaboration of trialists; NA, not available.

effects (35). The larger the SUCRA value, the better the rank of the treatment. A subgroup analysis was performed that only included prospective, randomized controlled trials.

The meta-analysis was performed using Review Manager v.5.1 (The Nordic Cochrane Center, The Cochrane Collaboration; 2008) and R 2.13.0 (R development Core Team, Vienna, <http://www.R-project.org>). The Bayesian framework meta-analyses were performed by using WinBUGS 1.4 (MRC Biostatistics Unit) and NetMetaXL, which provided an interface using WinBUGS from within Microsoft Excel (36). Two-sided *P* values <0.5 were considered statistically significant except for in the heterogeneity test, in which a one-sided *P* value <0.1 was used.

Results

Overview of the included studies

Individual data regarding the characteristics of the 17 included studies and patient populations are shown in Table 1 (14, 18–33). The studies were published between 1994 and 2014, and patients were recruited between 1986 and 2013. Five studies were prospective randomized trials (14, 30–33). Additional characteristics of the eligible studies are summarized in Table 1.

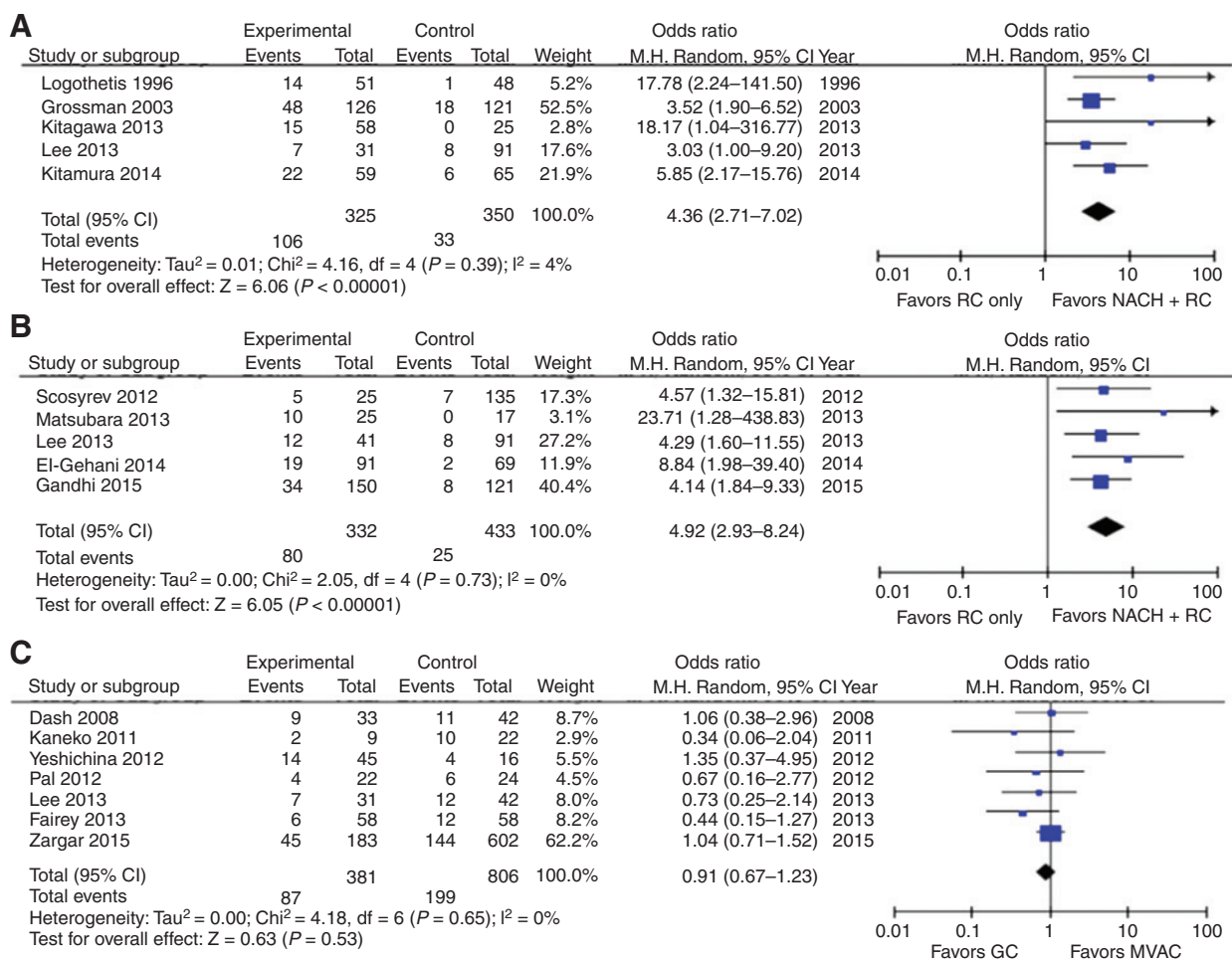
Details regarding the treatment characteristics of the 17 studies that were included in the meta-analysis are shown in Table 2. Clinical staging was generally performed for muscle-invasive or locally advanced (cN+) disease. Chemotherapy consisted of the MVAC or GC regimens in all except two publications in which cisplatin/methotrexate (CM, one trial) and cisplatin/methotrexate/vinblastine (CMV, one trial) were used. The number of cycles was variable but ranged from 2 to 4 in most studies. The pCR rates ranged from 0% to 14.9% in the RC only arms and 10.3% to 45.5% in the NACH followed by RC arms.

Supplementary Fig. S1 illustrates the network of studies that were included according to the comparisons of the different regimens. Nodes in a network that were not well connected (i.e., CM and CMV), should be interpreted with caution.

Pair-wise meta-analysis

There were five studies that focused on the comparison between RC alone and MVAC NACH. The present meta-analysis indicated that MVAC NACH was associated with better pCR compared with RC alone (OR, 4.36; 95% CI, 2.71–7.02; *P* < 0.001). There was no significant heterogeneity among these studies (*P* = 0.39; *I*² = 4%; Fig. 2A). Five studies reported the data for a comparison between RC alone and GC NACH. The GC NACH regimen was

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**Figure 2.**

Forest plots of pCR. The horizontal lines correspond to the study-specific ORs and 95% CIs. The area of the squares reflects the study-specific weight. The diamond represents the results for the pooled HRs and 95% CIs. A, RC alone versus MVAC NACH. B, RC alone versus GC NACH. C, comparison between MVAC NACH and GC NACH.

significantly associated with better pCR (OR, 4.92; 95% CI, 2.93–8.24; *P* < 0.001). Interstudy heterogeneity was not significant (*P* = 0.73; *I*² = 0%; Fig. 2B). Seven studies were included in the analysis for the comparison between GC NACH versus MVAC NACH. The pooled OR value was 0.91 (95% CI, 0.67–1.23; *P* = 0.53), which indicated that there was no difference between the two regimens. There was also no obvious interstudy heterogeneity (*P* = 0.65; *I*² = 0%; Fig. 2C).

Funnel plots showed no evidence of significant asymmetry. The Egger and Begg tests were not significant (all *P* > 0.05; Supplementary Fig. S2).

Bayesian framework network meta-analysis

The results of the network meta-analysis are shown in Fig. 3. When RC alone was used as the reference for the comparison, the GC (OR, 5.86; 95% CI, 3.68–9.90), MVAC (OR, 5.11; 95% CI, 3.42–8.54), CMV (OR, 3.49; 95% CI, 1.71–7.97), and CM (OR, 2.69; 95% CI, 1.21–6.51) regimens were associated with a statistically significant increase in the pCR rate. There was no significant difference in the pCR rate between NACH regimens (Fig. 3A). The summary league table of comparisons is shown

in Fig. 3B. These data suggest that the GC regimen was generally better than the MVAC regimen in terms of the pCR rate.

The SUCRA values provided the hierarchy for the five active regimens and were 0.2%, 36.5%, 46.9%, 75.7%, and 90.6%, for RC only, CM, MVAC, and GC, respectively. Supplementary Fig. S3 demonstrates that the share of probabilities among the competing regimens ranked at a specific place. The GC regimen predominantly populated the first two ranks whereas the MVAC regimen had a high probability of ranking second or third.

We performed a subgroup analysis that included five prospective, randomized controlled trials. When no NACH was considered as the reference for the comparison, MVAC regimen was associated with a statistically significant increase in the pCR rate (OR, 5.75; 95% CI, 1.96–24.18; Fig. 4A). When compared with RC alone, the summary league table demonstrated that the only MVAC regimen was significantly related to the achievement of pCR (OR, 5.75; 95% CI, 1.96–24.18), whereas the CM (OR, 2.70 95% CI, 0.34–26.57) and CMV (OR, 3.31 95% CI, 0.41–28.11) regimens had no significant effect on the achievement of pCR (Fig. 4B).

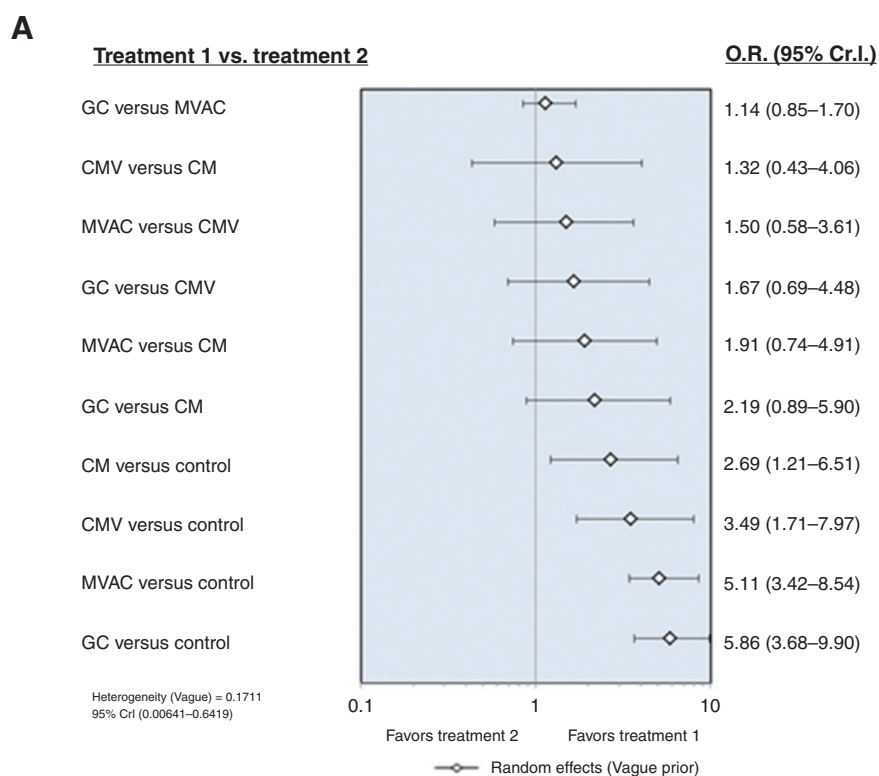


Figure 3. Bayesian framework network meta-analysis. A, pooled OR and 95% CIs for pCR. B, league tables for the comparisons. An OR >1 indicated that the regimen in the top left was better.

B

GC				
1.14 (0.85–1.70)	MVAC			
1.67 (0.69–4.48)	1.50 (0.58–3.61)	CMV		
2.19 (0.89–5.90)	1.91 (0.74–4.91)	1.32 (0.43–4.06)	CM	
5.86 (3.68–9.90)	5.11 (3.42–8.54)	3.49 (1.71–7.97)	2.69 (1.21–6.51)	Control

Discussion

Patients with locally advanced bladder cancer are at a significant risk for occult distant micrometastasis, despite locally successful management with complete resection of the tumor, such as RC with bilateral pelvic lymphadenectomy. Bladder cancer is moderately chemosensitive, and therefore the use of NACH for the treatment of MIBC may have several potential benefits given that: (i) by reducing the primary tumor burden, effective local surgery is possible, (ii) occult metastatic disease can be treated as early as possible, (iii) compliance with planned chemotherapy is more likely, and (iv) improved survival outcomes may be attained. According to the current international guidelines, cisplatin-based NACH is the preferred treatment for patients with T2 or greater (T2-T4a) disease based on level 1 evidence (37, 38). An updated meta-analysis based on 11 randomized controlled trials reported that platinum-based NACH was associated with a 5% absolute improvement in 5-year OS and a 9% absolute improvement in 5-year disease-free survival (5).

In general, pathologic tumor stage following RC is a crucial predictor of survival in patients with bladder cancer. In particular, chemo-induced tumor downstaging is considered to be a useful and potential surrogate marker that has been associated with favorable survival outcomes among patients treated with subsequent RC (11, 13–16). The impact of various NACH regimens including CM, CMV, MVAC, and GC, on the achievement of pCR and on survival outcomes has been evaluated by many investigators, both retrospectively and prospectively (14, 18–33). There was only one prospective trial that evaluated the CMV (31) and CM (32) regimens. The survival benefit achieved with the NACH with MVAC regimen in patients with MIBC was prospectively assessed in several phase III studies (14, 30, 33), and MVAC has been considered to be an effective regimen in a neoadjuvant setting. Although the GC regimen has not been studied in a prospective setting, it has been the most commonly used and acceptable alternative to MAVC in clinical practices based on the results of several retrospective comparative studies that were conducted in patients with locally advanced bladder cancer (18, 19, 21, 22, 25, 26, 28).

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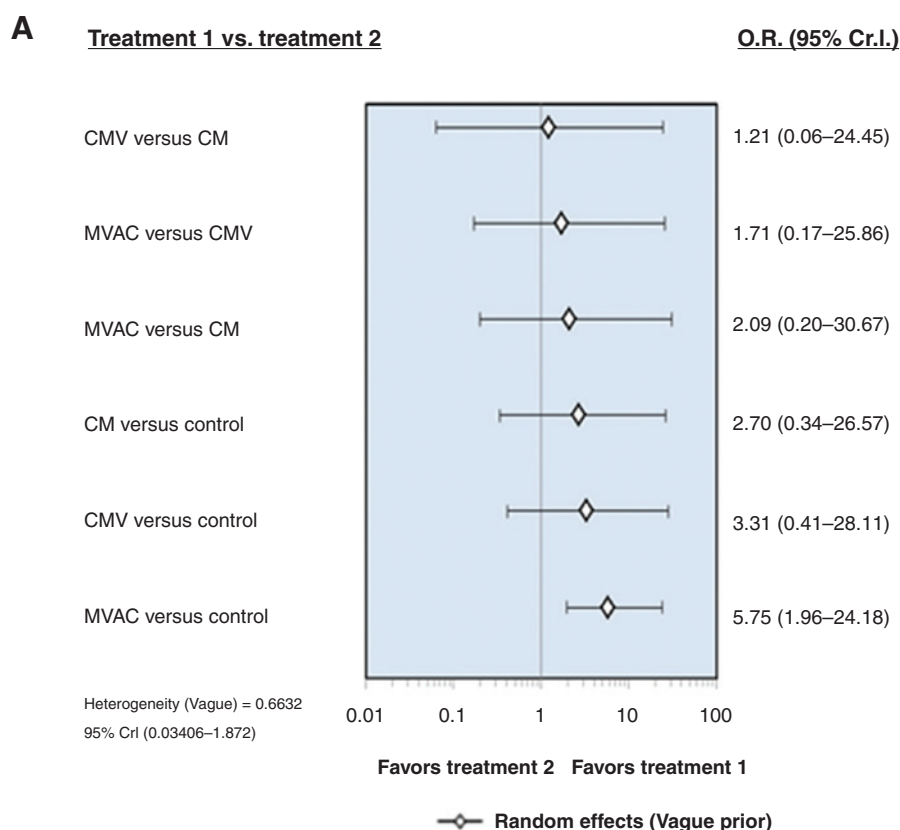


Figure 4. Subgroup analysis of prospective randomized, controlled trials. A, pooled OR and 95% CIs for pCR. B, league tables of comparisons. An OR >1 indicated that the regimen in the top left was better.

B

MVAC				
1.71 (0.17–25.86)	CMV			
2.09 (0.20–30.67)	1.21 (0.06–24.45)	CM		
5.75 (1.96–24.18)	3.31 (0.41–28.11)	2.70 (0.34–26.57)	Control	

In the current meta-analysis, we aimed to determine which type of NACH regimen was optimal in terms of pCR achievement among patients with MIBC who underwent subsequent RC. To the best of our knowledge, this is the first meta-analysis that has focused on the correlation between each NACH regimen and pCR. We evaluated a total of 17 eligible studies, which consisted of 12 retrospective and five prospective studies. There were five prospective studies of the MVAC, CM, and CMV regimens (14, 40–33). The overall pCR rate was higher for patients treated with NACH plus RC than for those treated with RC alone (10.5%–45.5% vs. 0%–14.9%). In a direct pair-wise meta-analysis of publications that compared the same regimens, both the MVAC and GC NACH regimens were associated with better pCR compared with RC alone (all $P < 0.001$), but there was no significant difference between the MVAC and GC regimens for the achievement of pCR ($P = 0.53$). On the basis of the results of the indirect

network meta-analysis that compared the various regimens, all regimens (including the GC, MVAC, CMV, and CM regimens) were significantly correlated with a higher pCR rate than RC alone. In particular, of all the regimens, GC was the most effective NACH regimen for achieving pCR on the basis of the summary league table and the SUCRA values (90.6%). In contrast, in a subgroup network meta-analysis that included only five prospective randomized trials, the MVAC regimen showed a significant association with the achievement of pCR relative to RC alone. Because no prospective studies regarding GC NACH were included, it was impossible to assess the impact of GC on pCR in a prospective setting.

The strengths of the present study are as follows. First, our study is the first systematic review and meta-analysis to evaluate the efficacy of the NACH regimen with a focus on pCR achievement, which may provide basic evidence to select an appropriate

chemotherapy regimen in neoadjuvant setting. Second, to compare the different NACH regimens, we conducted a network meta-analysis based on a Bayesian random effect model using a Microsoft Excel-based tool called NetMetaXL (36), and therefore, we could obtain the information with reference to a hierarchy and the relative variance of the effects of each NACH regimen. Third, the articles included in this analysis were relatively consistent in terms of the treatment cycles (ranged from 2 to 4 cycles) and clinical stage. Finally, our study results can be regarded as sound, given that publication bias and interstudy heterogeneity, which can be major problems in all types of meta-analyses, were not significant in our analysis.

In addition to these strengths, there are a number of limitations of our study. Above all, the trials that were included were heterogeneous in design in that they included both retrospective and prospective studies, and therefore there was inherent bias due to the retrospective design of the individual reports. To avoid this bias, we performed a subgroup network meta-analysis that targeted only prospective randomized trials. Second, because this study was based on a previously published trial level meta-analysis, the correlation between NACH regimen and pCR could not be adjusted in a multivariable analysis with other prognostic factors, such as chemotherapy-related toxicity, which is known to be an important cause of withholding chemotherapy. Third, the primary endpoint of interest in this analysis was pCR achievement, and thus we did not evaluate the correlation of between pCR after NACH and survival outcomes. The ultimate goal of NACH is to improve the survival times of patients. As mentioned earlier, tumor downstaging following NACH closely correlated with survival (11, 13–16). Although we did not directly assess the association between pCR and survival, it was expected that pCR after NACH would positively affect survival outcomes among patients with MIBC. Fourth, we did not investigate the clinical outcomes of patients who did not respond to NACH. These patients generally experienced poorer survival outcomes than NACH responders or patients who were treated with RC alone (12). Given that a substantial portion (>50%) of patients after

NACH remained as nonresponders in this study, delay of RC in nonresponders might result in a failure to cure and may compromise the final outcome. Finally, we only included studies that were published in English, which may have resulted in language bias, even in the absence of publication bias in the present study.

Conclusions

Because GC is a well-tolerated chemotherapy regimen, NACH with GC is widely used for MIBC without level I evidence. In the present study, retrospective data demonstrated that GC produced definitive clinical activity in a neoadjuvant setting, with a pCR rate that was similar to or slightly better than that of MVAC. However, MVAC, but not GC, has been proven to be effective in prospective randomized controlled trials. Furthermore, no randomized trials have directly compared neoadjuvant MVAC with neoadjuvant GC. Larger prospective comparative trials of neoadjuvant GC and MVAC may help establish this regimen as the gold standard in terms of NACH.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.H. Ku
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H.S. Kim, C.W. Jeong, C. Kwak
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.H. Ku
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