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Title: Efficacy and Safety of Neoadjuvant Chemotherapy for Muscle-invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis of RCTs

Running Title: Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer

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Clinical Question Box

Is the combination of chemotherapy and immune checkpoint inhibitors recommended as neoadjuvant chemotherapy for muscle-invasive bladder cancer?

The combination of gemcitabine, cisplatin, and durvalumab is recommended. This combination is emerging as a promising candidate due to strong evidence of its pathological complete response, although it presents moderate overall survival and adverse events. Further studies are required for exploring other combinations of different immune checkpoint inhibitors and chemotherapy.

Abstract

Introduction: Muscle-invasive bladder cancer (MIBC) is a highly aggressive malignancy associated with significant mortality. Neoadjuvant chemotherapy (NAC) has shown improved outcomes by reducing tumor burden and eradicating micrometastases prior to surgery. While platinum-based chemotherapy remains the standard, novel regimens incorporating immune checkpoint inhibitors have emerged, necessitating further investigation into their clinical benefits. Among these, durvalumab in combination with gemcitabine and cisplatin (GC-D) has gained attention for its potential efficacy in MIBC. However, its comparative effectiveness and safety relative to other NAC regimens remain unclear.

Methods: This systematic review and network meta-analysis adhered to PRISMA guidelines and included randomized controlled trials (RCTs) for evaluating NAC in MIBC patients without metastatic disease. Comprehensive searches were conducted in PubMed, Embase, Cochrane Library, and Web of Science till December 2024. The primary outcome was the pathological complete response (pCR), while the secondary outcomes included overall survival (OS) and adverse events (AEs).

Results: Seven RCTs involving 2,529 patients were analyzed. The GC-D achieved the highest pCR rate, with an odds ratio (OR) of 50.6 (95% confidence interval [CI]: 2.7, 927.1) compared to radical cystectomy alone, also outperforming gemcitabine plus cisplatin (GC) (OR 1.5; 95% CI: 1.1, 1.9). As per the 3-year OS, GC-D demonstrated superior outcomes, surpassing GC (OR 0.61; 95% CI: 0.48, 0.78). The AE profiles of GC-D and dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) were comparable to GC, with no significant increase in Grade 3-5 AEs (GC-D: OR 1.08; 95% CI: 0.82, 1.42; ddMVAC: OR 1.27; 95% CI: 0.50, 3.26).

Conclusion: GC-D demonstrates superior pCR rates and OS while maintaining comparable safety to other NAC regimens, establishing it as a promising treatment option for MIBC. However, alternative regimens remain essential for patients for whom GC-D is not applicable.

Keywords: Muscle-invasive bladder cancer, MIBC, neoadjuvant chemotherapy, durvalumab, GC, meta-analysis

Introduction

Bladder cancer is a significant global health concern, ranking among the most common malignancies of the urinary tract.[1] In 2022, bladder cancer was diagnosed in over 600,000 individuals globally, leading to more than 220,000 related deaths.[2] According to recent epidemiological studies, it accounts for a substantial global burden of morbidity and mortality, with higher prevalence rates in men.[3] The global incidence of bladder cancer has been rising steadily, particularly in regions with aging populations and increased exposure to risk factors such as smoking and occupational carcinogens.[4] Muscle-invasive bladder cancer (MIBC), a particularly aggressive form of this disease, poses considerable therapeutic challenges due to its high risk of progression and metastasis. This subtype represents approximately 25% of newly diagnosed bladder cancer cases and is associated with poor prognostic outcomes if not managed effectively.[5] Early and effective treatment is crucial for improving long-term outcomes and survival rates in affected patients, highlighting the clinical importance of investigating optimal therapeutic strategies. The clinical burden of MIBC extends beyond survival statistics, impacting quality of life, healthcare systems, and economic resources.[6]

Neoadjuvant chemotherapy (NAC) has emerged as a cornerstone in the management of MIBC, offering several advantages over immediate surgical intervention.[7] By administering systemic chemotherapy before radical cystectomy (RC), NAC aims to reduce tumor burden, eradicate micrometastases, and enhance the likelihood of complete resection. Although questions remain regarding the choice between NAC and adjuvant chemotherapy, particularly in specific racial groups,[8,9] NAC has shown a survival advantage over RC alone, enhancing cancer-specific outcomes in both localized and advanced stages.[10] Among the NAC regimens, dose-dense

methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) and gemcitabine plus cisplatin (GC) are widely recognized as first-choice options due to their proven efficacy and tolerability.[11] This approach is supported by robust evidence from randomized controlled trials (RCTs) and meta-analyses, which demonstrate that NAC can improve overall survival (OS) and disease-free survival (DFS).[12,13] Furthermore, NAC facilitates tumor downstaging, increasing the probability of a pathological complete response (pCR), which is strongly correlated with improved survival outcomes. Despite its well-documented benefits, the adoption of NAC in clinical practice remains suboptimal, partly due to concerns about patient selection, adverse events (AEs), and logistical challenges.[14]

The advent of immunotherapy has transformed the therapeutic landscape for bladder cancer, offering new opportunities to improve outcomes. Immune checkpoint inhibitors (ICIs) targeting the programmed death-1 (PD-1)/programmed death-ligand-1 (PD-L1) axis and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) have shown efficacy in advanced and metastatic bladder cancer.[15] Preliminary evidence suggests that combining ICIs with standard chemotherapy may enhance tumor eradication and immune responses, promising effective treatments for cisplatin-ineligible patients.[16] Ongoing trials are exploring novel combinations and sequencing strategies to optimize immunotherapy in the neoadjuvant setting.[17,18] PD-L1 biomarker expression and tumor mutational burden are being investigated to personalize treatment approaches.[19] Additionally, understanding the interplay between chemotherapy and immunotherapy, as well as the tumor microenvironment's response is crucial for developing protocols that maximize benefits while minimizing adverse effects. Insights into resistance mechanisms and immune modulation will further refine strategies for improving outcomes in MIBC.

Despite numerous clinical trials highlighting the potential of combining ICIs with GC and other regimens, a comprehensive analysis of their efficacy and safety remains limited. This gap is particularly evident in the context of recent study evaluating GC with durvalumab (GC-D), which have shown promising outcomes but require further validation through robust comparative analyses. This systematic review and network meta-analysis (NMA) aims to thoroughly evaluate the efficacy and safety of NAC for MIBC, using data from RCTs. By synthesizing evidence from both direct and indirect comparisons, this study seeks to identify the most effective and safe regimens, provide insights into the role of NAC in modern treatment algorithms, and guide clinical decision-making.

Methods

Study Protocol and Registry

This systematic review and NMA was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] The protocol was registered in the Open Science Framework.[21]

Eligibility Criteria

This study included RCTs that evaluated the efficacy and safety of NAC for MIBC. Eligible studies met the following criteria: (1) enrolled patients had histologically confirmed MIBC without metastatic disease, (2) NAC was administered prior to RC or definitive treatments, (3) reported survival outcomes such as pCR, overall survival (OS), or AEs, and (4) underwent quality assessment using the Cochrane Risk of Bias tool was applicable. Studies were excluded if they met any of the following criteria: (1) not an RCT, (2) published only as abstracts or preclinical data, and (3) lacked sufficient data for analysis. Only peer-reviewed journal articles were considered, with no language restrictions.

Information Sources and Search Strategy

A comprehensive literature search was performed across PubMed, Embase, Cochrane Library, and Web of Science from inception to December 20, 2024. The search strategy combined terms related to (((urothelial carcinoma) OR (bladder cancer)) AND (neoadjuvant chemotherapy)) AND (randomized clinical trial) (Table S1). To ensure a comprehensive review, the reference lists of included studies and relevant reviews were manually screened. Grey literature, including conference proceedings and clinical trial registries, was also searched for additional relevant studies.

Study Selection

Two independent reviewers (P.E. and F.J.) screened titles and abstracts for potential inclusion. Full-text articles were assessed for eligibility based on the predefined criteria. Discrepancies were resolved through discussion or consultation with a third reviewer (U.M.). A standardized data extraction form was used to collect information on study characteristics (e.g., author, year, sample size, and setting), patient demographics, intervention details, comparator arms, and reported outcomes. Data were independently extracted by two reviewers and cross-verified to ensure accuracy.

Outcomes

The primary outcome was pCR, defined as T0. Secondary outcomes included OS and AEs. OS was defined as a 3-year OS to maximize the inclusion of available studies. AEs were categorized as Grade 3 to Grade 5, based on the Common Terminology Criteria for Adverse Events (CTCAE).[22] The treatment regimens evaluated in the included studies were ddMVAC; GC; methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC); methotrexate and cisplatin (MC); gemcitabine and cisplatin; and GC-D.

Data Synthesis

All statistical analyses were performed using R (Version 4.4, R Foundation for Statistical Computing, Vienna, Austria), utilizing the 'meta' and 'netmeta' packages. Visualizations were generated through forest plots and league tables to illustrate relative treatment effects. Pairwise meta-analyses were conducted for direct comparisons using random-effects models to address heterogeneity, with odds ratios (ORs) and 95% confidence intervals (CIs) either extracted or calculated as needed. A NMA was conducted to compare multiple NAC regimens simultaneously

by integrating direct and indirect evidence. Model consistency was evaluated, and results were reported as relative treatment effects with 95% confidence intervals.

Heterogeneity and Consistency Assessment

Statistical heterogeneity was evaluated using the I^2 statistic, with values greater than 25% indicating low heterogeneity, above 50% representing moderate heterogeneity, and over 75% suggesting high heterogeneity. Consistency between direct and indirect evidence in the NMA was evaluated using the node-splitting method. Potential inconsistencies were investigated through subgroup and sensitivity analyses. Subgroup analyses were performed based on factors such as cisplatin eligibility, age, performance status, and geographical location. Sensitivity analyses involved the exclusion of studies with a high risk of bias and application of alternative statistical models to evaluate the robustness of the findings. The risk of bias in individual studies was assessed using the Cochrane Risk of Bias tool, which evaluates domains including the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Each domain was rated as low risk, high risk, or some concerns, with overall risk categorized accordingly.[23] Publication bias was examined through funnel plots of asymmetry.

Evidence Level Assessment

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the level of evidence for direct, indirect, and network comparisons for each outcome.[24,25] Direct comparisons from head-to-head RCTs were prioritized over indirect comparisons. The evidence quality was categorized as high, moderate, low, or very low, considering factors such as study bias, result consistency, evidence directness, estimate precision,

and potential publication bias. The evidence quality was reduced when study limitations were identified or upgraded in cases of robust effect sizes or large sample sizes, following GRADE guidelines.

Results

Study Selection and Characteristics

An initial search of the databases identified 1,633 studies. Following duplication removal, primary and secondary screening, 489, 1,018, and 119 studies were excluded, respectively (Figure S1). Ultimately, seven RCTs were included in this systematic review and network meta-analysis, comprising a total of 2,529 patients with MIBC. These studies, conducted between 2002 and 2024, targeted diverse demographics, including the USA, Japan, Egypt, France, Sweden, and the UK. The patient demographics, study characteristics, and treatment arms are detailed in Table 1. Most of the studies included patients with disease stages up to T4aN0M0, while one study also included patients with T4bN0M0. The majority of patients were approximately 60 years old, with a predominance of males. The evaluated regimens comprised ddMVAC, MVAC, MC, GC, and GC-D, with neoadjuvant chemotherapy courses ranging from two to six cycles.

pCR

All RCTs reported pCR findings; the network graph is presented in Figure S2. A direct comparison with RC using a random-effects model indicated that GC-D achieved the highest pCR, with an OR of 50.6 (95% CI: 2.7, 927.1), followed by ddMVAC, GC, and MVAC (Figure 2A). A ranking based on 1,000 simulations for each treatment also confirmed GC-D as the most effective regimen (Figure S3). The results of the network meta-analysis are detailed in Table 2. GC-D was superior to GC and RC, with ORs of 1.5 (95% CI: 1.1, 1.9) and 50.6 (95% CI: 2.8, 927.1), respectively. However, no statistically significant differences were observed when compared with ddMVAC, MVAC, and MC, with ORs of 1.3 (95% CI: 0.8, 1.9), 11.1 (95% CI: 0.6, 214.5), and 18.3 (95% CI: 0.9, 360.1), respectively.

OS

Five RCTs reported OS results; the network graph is presented in Figure S4. A direct comparison with RC using a random-effects model indicated that GC-D achieved the longest OS, with an OR of 0.41 (95% CI: 0.14, 1.17), followed by MVAC, GC, and MC (Figure 2B). A ranking based on 1,000 simulations for each treatment also confirmed GC-D as the most effective regimen (Figure S5). The results of the network meta-analysis are detailed in Table 3. GC-D was superior to GC, with ORs of 0.61 (95% CI: 0.48, 0.78). However, no statistically significant differences were observed when compared with MVAC, MC, and RC, with ORs of 0.70 (95% CI: 0.23, 2.14), 0.56 (95% CI: 0.18, 1.75), and 0.41 (95% CI: 0.14, 1.17), respectively.

AEs

Only three studies compared AEs among ddMVAC, GC-D, and GC (Figure 2). Pooled analysis showed that ddMVAC had an OR of 1.27 (95% CI: 0.50–3.26; $p = 0.62$; $I^2 = 88\%$), while GC-D had an OR of 1.08 (95% CI: 0.82–1.42; $p = 0.57$). These results did not indicate a significant increase in AEs for ddMVAC and GC-D compared to GC. Sensitivity analysis and network meta-analysis were not feasible due to the limited number of studies.

Bias and Certainty of Evidence

The risk of bias is presented in Figure S6. High risk of bias was not identified in the included studies; however, two studies showed an uncertain risk in performance and detection bias. A significant publication bias was also not observed. According to the GRADE approach, the overall certainty of the evidence was high for pCR but moderate for OS and AEs, downgraded due to evidence directness and heterogeneity, respectively.

Discussion

This meta-analysis provides a comprehensive evaluation of the efficacy and safety of neoadjuvant chemotherapy regimens for MIBC, offering critical insights into treatment outcomes. Among the regimens assessed, GC-D demonstrated the highest pCR rates, reinforcing its superior efficacy relative to RC alone. Furthermore, while GC-D showed the longest OS outcomes among the analyzed regimens, these differences were not statistically significant when compared to alternatives such as ddMVAC and MVAC. Interestingly, ddMVAC achieved better pCR rates compared to GC, which remains a widely used regimen due to its balance of efficacy and safety, consistent with previous studies. Notably, the AE profiles of GC-D and ddMVAC were comparable to those of GC, supporting their acceptability from a safety perspective. While GC-D demonstrated modest OS advantages, an extended follow-up is imperative to confirm its long-term survival benefits. From a safety standpoint, the comparable AE profiles of GC-D, ddMVAC, and GC validate their feasibility in clinical practice, reinforcing the integration of GC-D into routine therapeutic protocols. The National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines currently recommend cisplatin-based neoadjuvant chemotherapy as the standard of care.[26,27] However, our results suggest that GC-D may offer an alternative option with comparable efficacy and safety profiles.

The clinical implications of these findings are considerable. The superior pCR rates of GC-D, position it as a potential preferred neoadjuvant regimen for MIBC. Combining ICIs with chemotherapy as a neoadjuvant approach for MIBC offers a promising strategy to enhance therapeutic outcomes. Preliminary studies and ongoing trials, such as the PURE-01 and NABUCCO studies, have demonstrated the potential of ICI-based regimens to improve pCR rates and enhance immune responses against residual tumor cells.[17,28] Similarly, other studies have

discussed pembrolizumab's and nivolumab's efficacy as neoadjuvant MIBC therapies.[29-31] However, the absence of a controlled arm precludes their inclusion in a meta-analysis. The results of ongoing phase 3 trials are eagerly awaited. Evidence suggests that PD-L1 expression, tumor mutational burden, and DNA damage response gene mutations may influence GC-D response.[32] However, variability in biomarker assessment and limited standardized data precluded a comprehensive analysis. While GC remains widely used due to its balanced efficacy and safety, ddMVAC has demonstrated superior pCR rates, suggesting its potential as a more effective option for tumor downstaging.[33] The integration of ICIs with regimens like ddMVAC merits further investigation given its superior pCR outcomes and the potential synergy between cytotoxic and immunotherapeutic mechanisms.

This meta-analysis synthesizes data from diverse RCTs through rigorous network meta-analysis, establishing a robust ranking of neoadjuvant chemotherapy regimens for MIBC. Unlike prior studies that focused on individual regimens or direct comparisons, this study offers a comprehensive perspective on the comparative efficacy and safety of various treatments.[34,35] However, the lack of standardization in the number of chemotherapy cycles introduces variability, highlighting the need for consensus on treatment protocols to optimize outcomes. Observed discrepancies, such as variations in OS outcomes, may result from various study designs, patient demographics, and treatment protocols.[36] High heterogeneity was observed in AEs, which can be attributed in part to differences in regimen compositions. Standardizing treatment protocols and incorporating a common add-on therapy in future studies may help reduce this heterogeneity. The variability in chemotherapy cycles across studies remains a significant limitation, potentially contributing to inconsistencies in treatment efficacy and adverse event profiles. Future clinical

trials should aim to standardize the number and duration of chemotherapy cycles to improve comparability.

This study has several limitations. Firstly, variability in study designs, patient populations, and outcome measures across the included trials introduces uncertainty into the pooled estimates. Only one study directly compared the effectiveness of GC and RC, and its small sample size resulted in wide confidence intervals for GC in NMA. Additionally, only one RCT reported on ICIs combined with chemotherapy, leaving the efficacy of other ICIs unclear. Furthermore, OS calculations were based on a three-year follow-up period, which is shorter than that used in most RCTs. This limited follow-up duration may impact the comprehensiveness of survival outcome evaluation, underscoring the necessity for long-term data to fully assess treatment efficacy.

Conclusion

This meta-analysis offers a nuanced evaluation of neoadjuvant chemotherapy regimens for MIBC, with GC-D emerging as a promising candidate due to its efficacy and safety profile. By synthesizing diverse evidence and addressing critical gaps, this study provides a strong foundation for both clinical decision-making and future research aimed at improving outcomes for MIBC patients. Further research is warranted to refine patient selection criteria and optimize NAC strategies to maximize clinical benefits.

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Data Availability: The corresponding author shall make the datasets available upon reasonable request.

Ethical Statement: Institutional Review Board approval was waived due to the nature of the meta-analysis.

Conflict of Interest: The authors report no conflicts of interest in this work.

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Table 1: Characteristics of Enrolled Patients

Author Year	Stage	Nation	Cases	Age	Male	Cycles	Regimen 1	Regimen 2
Flaig 2021	T2-T4a	USA	167	65	139	4/4	ddMVAC	GC
Grossman 2003	T2-T4a	USA	307	63	251	3	MVAC	RC
Kitamura 2014	T2-T4	Japan	130	63	117	2	MVAC	RC
Osman 2014	T2-T4a	Egypt	60	51	57	3	GC	RC
Pfister 2020	T2-T4a	France	493	63	408	4/6	ddMVAC	GC
Powles 2024	T2-T4a	UK	1063	65	870	4/4	GC-D	GC
Sherif 2002	T2-T4b	Sweden	309	65	249	3	MC	RC

ddMVAC: dose- dense methotrexate, vinblastine, doxorubicin, and cisplatin; MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin; GC: gemcitabine and cisplatin; MC: methotrexate and cisplatin; RC: radical cystectomy

Table 2: Network Meta-Analysis of Pathological Complete Response Using a Random-Effects Model

GC-D					
1.3 [0.8; 1.9]	**ddMVAC**				
1.5 [1.1; 1.9]	1.3 [0.8; 1.6]	**GC**			
11.1 [0.6; 214.6]	8.8 [0.5; 171.3]	7.6 [0.4; 145.0]	**MVAC**		
18.3 [0.9; 360.1]	14.6 [0.7; 287.5]	12.5 [0.7; 243.3]	1.7 [0.7; 3.8]	**MC**	
50.6[2.8; 927.1]	40.2[2.2; 740.4]	34.6[1.9; 626.2]	4.5 [2.6; 7.8]	2.8 [1.5; 5.2]	**RC**

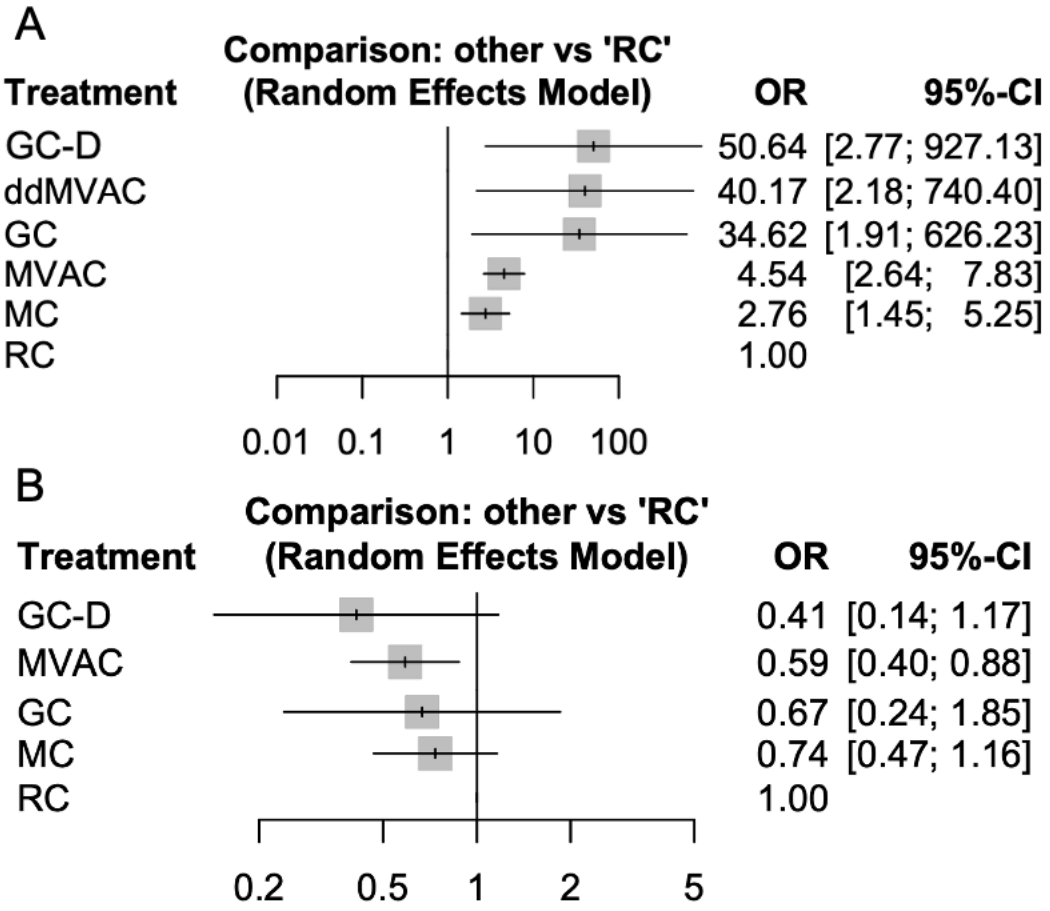
GC-D: gemcitabine, cisplatin, and durvalumab; ddMVAC: dose- dense methotrexate, vinblastine, doxorubicin, and cisplatin; MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin; GC: gemcitabine and cisplatin; MC: methotrexate and cisplatin; RC: radical cystectomy

Table 3: Network Meta-Analysis of Overall Survival Using a Random-Effects Model

GC-D				
0.70 [0.23; 2.14]	**MVAC**			
0.61 [0.48; 0.78]	0.88 [0.29; 2.64]	**GC**		
0.56 [0.18; 1.75]	0.80 [0.44; 1.47]	0.91 [0.30; 2.78]	**MC**	
0.41 [0.14; 1.17]	0.59 [0.40; 0.88]	0.67 [0.24; 1.85]	0.74 [0.47; 1.16]	**RC**

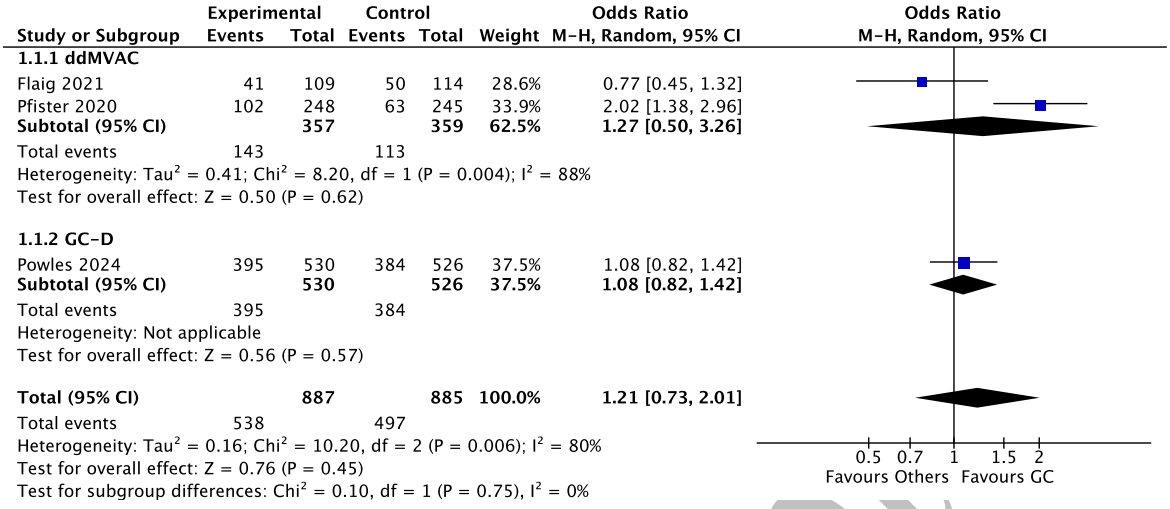
GC-D gemcitabine, cisplatin, and durvalumab; MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin; GC: gemcitabine and cisplatin; MC: methotrexate and cisplatin; RC: radical cystectomy

Figure 1: Direct Comparison of Pathological Complete Response and Overall Survival



A: Pathological Complete Response; B: Overall Survival; GC-D: gemcitabine, cisplatin, and durvalumab; ddMVAC: dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC: gemcitabine and cisplatin; MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin; MC: methotrexate and cisplatin; RC: radical cystectomy

Figure 2: Direct Comparison of Adverse Events with Gemcitabine and Cisplatin Regimen



ddMVAC: dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC-D: gemcitabine, cisplatin, and durvalumab; CI: confidence interval