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Analysis of the efficacy and safety of immunotherapy combined with targeted therapy in postoperative muscle-invasive bladder cancer: a retrospective cohort study

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Abstract

Objective

To compare the survival outcomes and safety of immunotherapy combined with targeted therapy versus immunotherapy alone in postoperative patients with muscle-invasive bladder cancer (MIBC) in the real-world setting.

Methods

This single-center retrospective cohort study enrolled 47 patients with MIBC who underwent surgery and received immunotherapy-based regimens at the Department of Urology, The First Affiliated Hospital of Nanchang University, from July 2022 to September 2025. Patients were divided into two groups: Group A (immunotherapy combined with targeted therapy, n = 25) and Group B (immunotherapy alone, n = 22). PFS and OS were evaluated using Kaplan-Meier analysis and Cox proportional hazards models. Treatment-related adverse events were assessed according to CTCAE version 5.0.

Results

The median PFS was 29 months in Group A and 10 months in Group B, with a statistically significant difference (P = 0.024); the median OS was 29 months in Group A and 21 months in Group B, with a statistically significant difference (P = 0.034). In multivariable Cox regression analysis, immunotherapy combined with targeted therapy was associated with longer PFS compared with immunotherapy alone (HR = 0.412, 95% CI 0.171–0.993, P = 0.048). Most adverse events were grade 1–2, and no statistically significant difference in the overall incidence of AEs was observed between the groups (52.0% vs 72.7%, P = 0.145).

Conclusion

In postoperative patients with MIBC, immunotherapy combined with targeted therapy was associated with longer PFS and OS compared with immunotherapy alone. The observed safety profile was also manageable, and most AEs can be alleviated with appropriate support care. These findings provide preliminary real-world evidence supporting further investigation of combination therapy in prospective studies with larger cohorts.

1. INTRODUCTION

Bladder cancer is one of the most common malignancies of the urinary system. According to statistics, there were approximately 573,000 new cases and 213,000 deaths worldwide in 2020, and these numbers are projected to more than double by 2040[1],[2]. Based on whether the cancer has invaded the muscle

layer, bladder cancer can be classified into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), with NMIBC accounting for approximately 70% and MIBC for approximately 20% to 30%[3]. Treatment for NMIBC primarily involves transurethral resection of bladder tumors and instillation therapy; however, the recurrence rate remains above 50%, and approximately 30% of cases progress to MIBC. MIBC is characterized by high invasiveness with significant rates of recurrence and metastasis. The standard treatment regimen consists of radical cystectomy (RC) combined with pelvic lymph node dissection (PLND) and cisplatin-based adjuvant chemotherapy[4]; however, this strategy has clear limitations: on the one hand, the overall survival benefit derived from chemotherapy is limited; on the other hand, the chemotherapy drugs are highly toxic, and a significant proportion of patients cannot tolerate cisplatin due to renal insufficiency or other factors; these factors collectively limit the clinical application of chemotherapy.

In recent years, with the advancement of research and clinical application of immune checkpoint inhibitors (ICIs, such as PD-1/PD-L1 inhibitors), these agents have been approved worldwide for the treatment of various solid tumors, including renal cell carcinoma, lung cancer, breast cancer, and melanoma[5], and have also opened an entirely new avenue for the clinical management of MIBC. ICI monotherapy can activate and enhance the function of T-cell-mediated immune effector cells, reactivating the body's antitumor immune response, and have demonstrated durable efficacy and survival benefits in advanced bladder cancer[6]. Based on the above findings, immunotherapy alone has been explored as adjuvant treatment for postoperative patients with MIBC, aiming to reduce the risk of postoperative tumor recurrence and metastasis. However, clinical practice has also demonstrated that not all patients can achieve a deep and durable response to immunotherapy alone, and its efficacy exhibits significant population heterogeneity. This has prompted us to explore more optimized combination therapeutic strategies.

Meanwhile, as a novel class of antitumor agents with prominent targeting properties and relatively low toxicity, antibody-drug conjugates (ADCs) are opening new avenues for the treatment of various malignant tumors and showing promising prospects for clinical application[7]. ADCs can precisely deliver cytotoxic drugs to HER2-expressing tumor cells, achieving "precision destruction". More importantly, studies have shown that in addition to directly killing tumor cells, ADCs can also induce immunogenic cell death (ICD) and remodel the tumor microenvironment, thereby exerting synergistic effects with PD-1/PD-L1 inhibitors[8],[9]. Theoretically, such a combination therapy is expected to overcome the limitations of immunotherapy alone. Through the synergy of multiple mechanisms and pathways, this approach aims to achieve a synergistic therapeutic effect, providing patients with deeper remission and superior survival benefits.

However, clinical data on the application of immunotherapy combined with targeted therapy regimens in the adjuvant setting following surgery for MIBC remain limited. It is unclear whether such combination therapy can significantly improve efficacy over immunotherapy alone, or whether the safety profile of the combination therapy is manageable. Therefore, this study aimed to systematically compare the efficacy

and safety of PD-1/PD-L1 inhibitors plus ADCs versus PD-1/PD-L1 inhibitor monotherapy after radical resection of MIBC through a retrospective cohort study, with the goal of providing real-world clinical evidence to optimize postoperative adjuvant treatment strategies for MIBC.

2. METHODS

2.1. Clinical data

This was a retrospective cohort study. Clinical data were collected from patients with MIBC who received immunotherapy-based combination therapy in the Department of Urology, the First Affiliated Hospital of Nanchang University, between July 2022 and September 2025. The inclusion criteria satisfied the following requirements: (1) Age ≥ 18 years; (2) Pathologically diagnosed with MIBC (T2-4N0-2M0) after cystectomy; (3) Initiated immune checkpoint inhibitor (ICI)-based therapy (monotherapy or combined targeted therapy) within 90 days postoperatively and completed at least one cycle of treatment. (4) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Exclusion criteria: (1) Concurrent diagnosis of other malignancies; (2) Severe cardiac, pulmonary or cerebrovascular diseases; (3) Autoimmune diseases or immunodeficiency; (4) Received neoadjuvant therapy prior to surgery; (5) Incomplete clinical data.

Patients enrolled in the study were divided into Group A and Group B according to different treatment regimens. Group A received immunotherapy combined with targeted therapy, whereas Group B received immunotherapy alone. Clinical data on patients were collected through the electronic medical record system, including age, sex, weight, HER2 expression, serum creatinine clearance rate, smoking history, history of transurethral resection, clinical T and N stage, surgical approach, history of prior immunotherapy, history of chemotherapy, and surgical history. All laboratory baseline values were obtained from the results of the patients' final preoperative examination for bladder cancer and were used as baseline values for prognostic analysis. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University (IIT [2025] Clinical Ethics Review No. 397).

2.2. Therapeutic drugs and routes of administrations

The immunotherapy agents included in the combination treatment regimens in this study primarily consist of nivolumab, toripalimab, serplulimab, penpulimab, tislelizumab, and sintilimab. The targeted therapy drug was disitamab vedotin. All agents were administered intravenously. In clinical practice, the treating physician will make a comprehensive decision regarding whether to reduce the dose, temporarily suspend, or permanently discontinue the drug based on the patient's physical condition, biochemical markers and treatment-related adverse reactions. Treatment for all patients continues until disease progression, loss of clinical benefit, or the occurrence of intolerable treatment-related adverse reactions.

2.3. Efficacy assessment

Progression-free survival (PFS) was defined as the time from the date of surgery to the first occurrence of tumor recurrence, metastasis, or all-cause death, whichever occurred first. Tumor recurrence or metastasis was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST). The PFS was the primary endpoint of this study. The secondary endpoint was overall survival (OS), defined as the time from the date of surgery to death from any cause.

2.4. Safety assessment

All treatment-related adverse events (trAEs) occurring in all patients in Group A and Group B during the treatment period were statistically analyzed in this study. The grading of trAEs was performed in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 issued by the U.S. Department of Health and Human Services[10]. trAEs were graded from 1 to 5 according to severity: grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life-threatening; and grade 5, treatment-related death. The management of all trAEs followed relevant domestic and international clinical practice guidelines, and all trAEs leading to dose reduction, treatment interruption, or permanent drug discontinuation were fully documented.

2.5. Statistical methods

Statistical analysis was conducted using SPSS 26.0 software. Normally distributed continuous variables were reported as mean ± standard deviation (SD); comparisons between groups were performed using t-tests. Categorical variables were presented as numbers and proportions (%); comparisons between groups were performed using the chi-square test. Survival curves were plotted using the Kaplan-Meier method; differences between groups were compared with the log-rank test. The Cox proportional hazards regression model was used to estimate hazard ratios (HR) and their corresponding 95% confidence intervals (95%CI) for both univariate and multivariate analyses. A p-value < 0.05 was considered statistically significant.

3. RESULTS

3.1. Baseline patient characteristics

A total of 47 patients diagnosed with MIBC were retrospectively enrolled in this study. All patients received immunotherapy-based combination regimens at the Department of Urology in our hospital between July 2022 and September 2025. The detailed patient screening and enrollment flowchart is illustrated in Fig. 1. According to the different therapeutic protocols administered, patients were divided into two groups. Group A included 25 patients (22 males and 3 females), with a mean age of (67.28 ± 5.21) years. Group B consisted of 22 patients (21 males and 1 female), with a mean age of (71.41 ± 9.83) years. Comparison of baseline characteristics between the two groups revealed no statistically significant differences in age, sex, body weight, HER-2 expression, serum creatinine clearance, smoking history, history of transurethral resection, clinical T stage, clinical N stage, surgical approach, history of prior immunotherapy, history of chemotherapy, and surgical history (P > 0.05), indicating good balance

between the two groups at enrollment. Baseline characteristics of the two groups are summarized in Table 1.

Table 1
Comparison of baseline characteristics between the two groups

Demographic characteristics		**Group A**	**Group B**	***P***
Age*		67.28 ± 5.21	71.41 ± 9.83	0.088
Gender	Male	22(88.0)	21(95.5)	0.361
	Female	3(12.0)	1(4.5)	
HER-2 Expression	Positive	22(88.0)	15(68.2)	0.098
	Negative	3(12.0)	7(31.8)	
Serum creatinine clearance rate*		86.36 ± 18.93	126.52 ± 156.84	0.269
Weight*		63.60 ± 12.49	57.97 ± 7.96	0.076
Smoking history	Yes	13(52.0)	15(68.2)	0.259
	No	12(48.0)	7(31.8)	
N stage	N0	19(76.0)	13(59.1)	0.328
	N1	4(16.0)	4(18.2)	
	N2	2(8.0)	5(22.7)	
T stage	T1	3(12.0)	2(9.1)	0.622
	T2	12(48.0)	14(63.6)	
	T3	7(28.0)	3(13.6)	
	T4	3(12.0)	3(13.6)	
Surgical approach	Partial Cystectomy	1(4.0)	1(4.5)	0.433
	RC+Ileocystoplasty	8(32.0)	3(13.6)	
	RC+Ureterostomy	10(40.0)	9(40.9)	
	TURBT	6(24.0)	9(40.9)	
History of transurethral resection	Yes	13(52.0)	11(50.0)	0.891
	No	12(48.0)	11(50.0)	
History of immunotherapy	Yes	0(0)	1(4.5)	0.281
	No	25(100.0)	21(95.5)	
History of chemotherapy	Yes	6(24.0)	1(4.5)	0.918
	No	25(100.0)	21(95.5)	

Demographic characteristics		Group A	Group B	*P*
Surgical history	Yes	19(76.0)	13(59.1)	0.215
	No	6(24.0)	9(40.9)	

*Quantitative data is expressed as mean ± standard (SD), while count data is expressed as cases (%).

We screened 164 patients with muscle-invasive bladder cancer who were treated at our hospital between July 2022 and September 2025.

3.2. Efficacy analysis

3.2.1. PFS outcomes in two groups of patients

As shown in the PFS survival curve (Fig. 2), the median PFS in Group A and Group B was 29 months (95% CI: 14.697–43.303) and 10 months (95% CI: 6.204–13.796), respectively. The log-rank test revealed a statistically significant difference in PFS between the two groups (P = 0.024). To further quantify intergroup differences in progression risk, univariate Cox analysis revealed that combination therapy was associated with a lower risk of disease progression compared with immunotherapy alone(HR = 0.391, 95% CI: 0.164–0.929, P = 0.033). The result indicated that Patients receiving combination therapy had longer PFS than those receiving immunotherapy alone. (Fig. 2).

3.2.2. OS outcomes in two groups of patients

The median OS for patients in Group A and Group B was 29 months (95% CI: 19.798–38.202) and 21 months (95% CI: 4.993–37.007), respectively. The log-rank test revealed a statistically significant difference in overall survival curves between the two groups (P = 0.034), indicating a superior OS benefit associated with treatment regimen in Group A. To further quantify the difference in mortality risk between the two groups, we performed an analysis using the Cox proportional hazards regression model, which showed that combination therapy was associated with a significantly lower risk of death compared with immunotherapy alone (HR = 0.311, 95% CI: 0.100-0.968, P = 0.044). This suggests that immunotherapy combined with targeted therapy confers a superior long-term survival benefit over immunotherapy alone in postoperative patients with MIBC. (Fig. 3).

3.2.3 Analysis of factors associated with FPS-related in patients with MIBC after immunotherapy combined with targeted therapy.

In this study, univariate analysis was performed using the Cox proportional hazards regression model. The results showed that demographic characteristics (gender, age, body weight), clinical baseline indicators (smoking history, history of transurethral resection, HER-2 expression, serum creatinine clearance rate), and tumor-related indicators (clinical T stage, clinical N stage, surgical approach, history of chemotherapy, and surgical history) had no statistically significant effects on PFS in patients (all P >

0.05). However, a history of prior immunotherapy and immunotherapy combined with targeted therapy were factors associated with postoperative PFS in patients with MIBC ($P < 0.05$). To further identify independent influencing factors, multivariate analysis was subsequently conducted using the Cox proportional hazards regression model. The results demonstrated that immunotherapy combined with targeted therapy was an independent protective factor for prolonged postoperative PFS in patients with MIBC ($P < 0.05$), with a significant therapeutic advantage, suggesting that it can serve as an important strategy for clinical treatment. Details were shown in Table 2.

Table 2
Cox analysis of PFS factors in MIBC patients after immune-combined targeted therapy

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
Age	1.049	0.992–1.102	0.093			
Gender(Male vs Female)	2.345	0.681–8.073	0.177			
Smoking history(Yes vs No)	1.618	0.665–3.939	0.289			
Transurethral resection history(Yes vs No)	0.740	0.317–1.728	0.486			
HER-2 Expression (Positive vs Negative)	1.446	0.558–3.745	0.447			
Weight	0.984	0.951–1.018	0.354			
Serum reatinine clearance	1.002	0.999–1.005	0.194			
T stage						
T2 vs T1	2.649	0.350-20.064	0.346			
T3 vs T1	1.054	0.109–10.233	0.946			
T4 vs T1	1.258	0.114–13.930	0.851			
N stage						
N1 vs N0	1.436	0.510–4.046	0.493			
N2 vs N0	1.145	0.330–3.971	0.831			
Surgical approach						
RC+Ureterostomy vs TURBT	2.185	0.910–5.246	0.080			
RC+Ileocystoplasty vs TURBT	0.834	0.112–6.242	0.860			

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
History of chemotherapy (Yes vs No)	1.500	0.607–3.702	0.379			
Prior immunotherapy history (No vs Yes)	0.333	0.114–0.973	0.045	0.405	0.137–1.198	0.102
Surgical history (No vs Yes)	1.371	0.543–3.462	0.504			
Treatment regimens (Immune-combined targeted therapy vs Immunotherapy)	0.391	0.164–0.929	0.033	0.412	0.171–0.993	0.048

3.3. Safety analysis

In this study, the severity of trAEs in the enrolled patients was predominantly grade 1–2, indicating that the overall safety of both treatment regimens was manageable. The common AEs in Group A included lymphocytopenia in 4 cases (16.0%), anemia in 4 cases (16.0%), and urinary tract infection in 2 cases (8.0%). The common AEs in Group B included anemia in 8 cases (36.4%), urinary tract infection in 6 cases (27.3%), and lymphocytopenia in 5 cases (21.7%). With regard to serious AEs, Group A reported 2 cases of grade 3 or higher AEs, namely secondary tumor and intestinal obstruction; Group B reported 3 cases of grade 3 or higher AEs, including decreased A/G ratio, renal insufficiency, and multiple organ failure. In summary, the incidence of AEs was 52.0% among the 25 patients in Group A and 72.7% among the 22 patients in Group B. A chi-square test revealed no statistically significant difference in the overall incidence of AEs between the two groups ($\chi^2 = 2.218$, $P = 0.145$). The trAEs in both groups were predominantly grade 3 or lower, which were effectively controlled after corresponding symptomatic interventions, indicating favorable and manageable overall safety. The detailed distribution of trAEs in each group was shown in Table 3.

Table 3
Treatment-related adverse events (trAEs) in Group A and Group B

Adverse events	Total(47)		Group A(25)		Group B(22)	
	All Grades	Grade 3–4	All Grades	Grade 3–4	All Grades	Grade 3–4
Anemia	12(25.5)	0(0)	4(16.0)	0(0)	8(36.4)	0(0)
Decreased A/G Ratio	4(8.5)	1(2.1)	1(4.0)	0(0)	3(13.6)	1(4.5)
Decreased Lymphocytes	9(19.1)	0(0)	4(16.0)	0(0)	5(22.7)	0(0)
Decreased Neutrophils	2(4.3)	0(0)	1(4.0)	0(0)	1(4.5)	0(0)
Urinary Tract Infection	8(16.7)	0(0)	2(8.0)	0(0)	6(27.3)	0(0)
Allergic Dermatitis	4(8.5)	0(0)	1(4.0)	0(0)	3(13.6)	0(0)
Thyroiditis	1(2.1)	0(0)	1(4.0)	0(0)	0(0)	0(0)
Renal Insufficiency	2(4.3)	1(2.1)	1(4.0)	0(0)	1(4.5)	1(4.5)
Secondary Tumor	1(2.1)	1(2.1)	1(4.0)	1(4.0)	0(0)	0(0)
Intestinal Obstruction	1(2.1)	1(2.1)	1(4.0)	1(4.0)	0(0)	0(0)
Multiple Organ Failure	1(2.1)	1(2.1)	0(0)	0(0)	1(4.5)	1(4.5)
Limb Numbness	1(2.1)	0(0)	1(4.0)	0(0)	0(0)	0(0)
Rash	1(2.1)	0(0)	0(0)	0(0)	1(4.5)	0(0)
Abdominal Pain	1(2.1)	0(0)	1(4.0)	0(0)	0(0)	0(0)
Drug Allergic Reaction	1(2.1)	0(0)	1(4.0)	0(0)	0(0)	0(0)
Peritonitis	1(2.1)	0(0)	1(4.0)	0(0)	0(0)	0(0)

4. DISCUSSION

With the development of ICIs and ADCs, the therapeutic landscape of MIBC has evolved substantially. Although most clinical evidence for Disitamab Vedotin (DV) has been generated in locally advanced or metastatic urothelial carcinoma, increasing evidence has begun to explore DV-based strategies in localized MIBC[11]. DV is a HER2-targeted ADC that delivers the cytotoxic payload monomethyl auristatin E (MMAE) to HER2-expressing tumor cells [12]. Previous phase II studies demonstrated clinically meaningful antitumor activity of DV in patients with HER2-positive locally advanced or metastatic urothelial carcinoma, providing a clinical basis for further evaluation of DV-based combination strategies[13]. More recently, clinical studies evaluating DV in combination with ICIs have reported encouraging antitumor activity in locally advanced or metastatic urothelial carcinoma. For example, a

phase Ib/II study of DV plus the PD-1 inhibitor toripalimab reported a confirmed objective response rate (ORR) of 76.1%, with a median PFS of 13.1 months and a median OS of 31.5 months, supporting further investigation of this combination strategy [14]. However, whether these findings can be translated into the localized and postoperative setting of MIBC remains unclear.

Evidence supporting DV-based combination therapy in earlier-stage MIBC is also emerging, although the available studies have largely focused on neoadjuvant or bladder-preserving treatment settings. A multicenter real-world study evaluated DV combined with PD-1 inhibitors as neoadjuvant therapy for localized MIBC and reported a pathological complete response (pCR) rate of 48.0% and a pathological downstaging rate of 88.0%; the 12-month disease-free survival (DFS) and OS rates were 91.5% and 100%, respectively [15]. Another retrospective study comparing DV combined with immunotherapy with a gemcitabine-cisplatin-based regimen combined with immunotherapy reported a higher pCR rate in the DV-based combination group (82.35% vs. 47.62%, P = 0.043), with no significant difference in grade 3 adverse events [16]. In addition, a real-world study of DV alone or in combination with PD-1 inhibitors in bladder-preserving treatment for MIBC reported an ORR of 81.8% and a bladder preservation rate of 72.7% at 16 months [17]. These findings collectively support the potential antitumor activity of DV-based combination therapy in localized MIBC. However, these studies primarily evaluated neoadjuvant or bladder-preserving strategies and focused on pathological response, objective response, or bladder preservation, whereas the present study specifically examined postoperative systemic therapy and compared long-term survival outcomes between immunotherapy combined with DV and immunotherapy alone. In our cohort, the combination group demonstrated longer median PFS and OS than the immunotherapy-alone group (29 vs. 10 months, P = 0.024; 29 vs. 21 months, P = 0.034), and multivariable Cox regression analysis showed that combination therapy was associated with longer PFS (HR = 0.412, 95% CI: 0.171–0.993, P = 0.048). Although these results cannot be directly compared with the pathological response rates reported in previous neoadjuvant studies because of differences in treatment setting, patient population, and endpoints, they provide additional real-world evidence regarding the potential role of DV-based combination therapy in the postoperative setting.

Several potential biological mechanisms may, at least in part, underlie the activity of the combination therapy, including the distinct but potentially complementary mechanisms of ADCs and immune checkpoint blockade. DV is a HER2-targeted ADC that selectively delivers the cytotoxic payload MMAE to HER2-expressing tumor cells. Following binding to HER2 on the surface of tumor cells, DV is internalized and subsequently releases MMAE, resulting in cytotoxic effects and tumor cell death [18]. Beyond its direct cytotoxic effects, DV may also modulate the tumor immune microenvironment. Preclinical and translational studies suggest that DV may reduce tumor-cell PD-L1 expression through the Hippo-TAZ/TEAD4 pathway and may promote the infiltration and activation of $CD8^+$ T cells, potentially contributing to antitumor immune responses[9]. In addition, DV can induce immunogenic cell death(ICD), which may enhance antigen presentation and T-cell infiltration, thereby further promoting antitumor immune responses [15]. These immunomodulatory effects provide a potential biological rationale for combining DV with immune checkpoint blockade, although their contribution to clinical outcomes in

postoperative MIBC remains to be established. Clinical evidence has provided further support for this potential complementary effect. The phase III RC48-C016 trial further demonstrated the efficacy of DV plus toripalimab in previously untreated HER2-expressing locally advanced or metastatic urothelial carcinoma, with significantly longer PFS and OS than platinum-based chemotherapy[19]. These findings provide further clinical support for the potential activity of combining HER2-targeted ADC therapy with immune checkpoint blockade.

Regarding safety, most adverse events (AEs) observed in our study were grade 1–2, and no statistically significant difference was observed in the overall incidence of AEs between the two groups. In the immunotherapy-alone group, the most frequently observed AEs were anemia (8 cases, 36.4%), urinary tract infection (6 cases, 27.3%), decreased lymphocyte count (5 cases, 21.7%), decreased albumin-to-globulin ratio (A/G ratio) (3 cases, 13.6%), and allergic dermatitis (3 cases, 13.6%). In the immunotherapy plus targeted therapy group, the most common AEs were decreased lymphocyte count (4 cases, 16.0%), anemia (4 cases, 16.0%), and urinary tract infection (2 cases, 8.0%). These findings were generally consistent with findings from previous studies[20][21]. Previous studies have shown that ICI monotherapy can cause immune-related adverse events (irAEs) of varying degrees, involving almost all organs and systems of the body[22][23]. Common examples include immune-related myocarditis and liver injury[24]. In terms of targeted therapy, a pooled analysis of two phase II trials involving 107 patients with HER2-positive locally advanced or metastatic urothelial carcinoma reported that the most common TRAEs associated with DV were peripheral sensory neuropathy (68.2%), leukopenia (50.5%), increased AST levels (42.1%), and neutropenia (42.1%). Grade ≥ 3 trAEs occurred in 54.2% of patients, with peripheral sensory neuropathy (18.7%) and neutropenia (12.1%) being the most common. No grade 4 or 5 trAEs were reported, suggesting a manageable safety profile of DV[13]. Regarding immunotherapy combined with targeted therapy, a real-world comparative study of RC48 plus PD-1 inhibitors versus GC plus PD-1 inhibitors in bladder-preserving multimodal therapy for MIBC reported that the RC48-based regimen had a lower incidence of grade 3–4 trAEs (7.7% vs 19.2%) and fewer treatment discontinuations due to toxicity (1.9% vs 9.6%) [25]. In our cohort, the incidence of AEs in the combination group was not significantly higher than that in the immunotherapy-alone group. This finding may be partly explained by the distinct toxicity profiles and mechanisms of action of the two treatment modalities. ICIs enhance T-cell-mediated antitumor immune responses by blocking inhibitory immune checkpoint signaling, but may also disrupt peripheral immune tolerance and activate autoreactive immune responses, potentially resulting in immune-mediated injury to normal tissues[26]. Although DV is designed to preferentially deliver its cytotoxic payload to HER2-expressing cells, systemic toxicities remain possible. The absence of a significant difference in overall AE incidence in our cohort suggests that the addition of DV did not result in an apparent increase in overall toxicity; however, this finding should be interpreted cautiously given the small sample size. The potential risks associated with combination therapy should nevertheless be considered, and comprehensive monitoring throughout treatment is warranted to facilitate early recognition and prompt management of AEs.

Several limitations should be acknowledged in this study. First, this was a retrospective study conducted at a single institution, with a relatively small sample size of 47 patients. Treatment allocation was not randomized and may have been influenced by clinical characteristics, physician preference, HER2 status, and other factors, potentially resulting in confounding by indication and selection bias. Second, the relatively small number of patients and outcome events limited the statistical power of the study and may have resulted in unstable estimates in the multivariable Cox regression analysis. Third, heterogeneity may have existed in both the study population and treatment regimens. Differences in the specific immune checkpoint inhibitors used, treatment duration, and subsequent therapies may have influenced survival outcomes.

5. CONCLUSION

Overall, our findings suggest that postoperative immunotherapy combined with DV may be associated with improved survival outcomes in patients with MIBC. However, given the retrospective design and small sample size, these findings should be interpreted cautiously and require validation in larger, multicenter prospective studies. Future studies should also investigate predictive biomarkers to identify patients who may derive greater benefit from this combination regimen and to inform individualized treatment of MIBC.

Declarations

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Data availability The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Conflict of interest The authors have no competing interests to declare.

Clinical Trail Number: Not applicable.

Ethical approval The collection of clinical data and study protocol were approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University. The study was conducted in accordance with the principles of the Declaration of Helsinki and relevant guidelines and regulations.

Given the retrospective nature of this study, the requirement for informed consent was waived by the Ethics Committee.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries [J]. Cancer J Clin. 2021;71(3):209–49. 10.3322/caac.21660.
2. Filho AM, Briganti A, Jemal A, Bray F. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. Eur Urol Published online Dec. 2025;19. 10.1016/j.eururo.2025.12.011.
3. Patel VG, Oh WK, Galsky MD. Treatment of muscle-invasive and advanced bladder cancer in 2020. CA Cancer J Clin. 2020;70(5):404–23. 10.3322/caac.21631.
4. de Jong, Joep J et al. Re: EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. European urology vol. 86,5 (2024): 480–1. 10.1016/j.eururo.2024.07.023
5. Zhang M, Wu J, Zhang Y, et al. Recent advances of neoadjuvant immunotherapy for urothelial bladder cancer. Ann Surg Oncol. 2024;31(9):5851–9. 10.1245/s10434-024-15725-8. Epub 2024 Jul 12. PMID: 38995447.
6. Zhang F, Li YY, Shi ZZ, et al. Progress in treatment of PD-1/PD-L1 inhibitors for bladder cancer. Chin J Surg. 2021;59(11):952–5. 10.3760/cma.j.cn112139-20210805-00358.
7. Aggarwal D, Yang J, Salam MA, et al. Antibody-drug conjugates: the paradigm shifts in the targeted cancer therapy. Front Immunol. 2023;14:1203073. 10.3389/fimmu.2023.1203073. Published 2023 Aug 21.
8. Coats S, Williams M, Kebble B, et al. Antibody-Drug Conjugates: Future Directions in Clinical and Translational Strategies to Improve the Therapeutic Index. Clin Cancer Res. 2019;25(18):5441–8.
9. Xiao J, Liu J, Zhang C, et al. Overcoming immunotherapy resistance in bladder cancer with a novel antibody-drug conjugate RC48. J Immunother Cancer. 2025;13(8):e011881. 10.1136/jitc-2025-011881. Published 2025 Aug 11.
10. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. CTCAE versión 5.0. Evaluación. Actas Dermosifiliogr (Engl Ed). 2021;112(1):90–2. 10.1016/j.ad.2019.05.009. de la gravedad de los eventos adversos dermatológicos de las terapias antineoplásicas.
11. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017;376(11):1015–26. 10.1056/NEJMoa1613683.
12. Jiang W, Zhu D, Wang C, Zhu Y. An immune relevant signature for predicting prognoses and immunotherapeutic responses in patients with muscle-invasive bladder cancer (MIBC). Cancer Med. 2020;9(8):2774–90. 10.1002/cam4.2942.

13. Sheng X, Wang L, He Z, et al. Efficacy and Safety of Disitamab Vedotin in Patients With Human Epidermal Growth Factor Receptor 2-Positive Locally Advanced or Metastatic Urothelial Carcinoma: A Combined Analysis of Two Phase II Clinical Trials. J Clin Oncol. 2024;42(12):1391–402. 10.1200/JCO.22.02912.
14. Zhou L, Yang KW, Zhang S, et al. Disitamab vedotin plus toripalimab in patients with locally advanced or metastatic urothelial carcinoma (RC48-C014): a phase Ib/II dose-escalation and dose-expansion study. Ann Oncol. 2025;36(3):331–9. 10.1016/j.annonc.2024.12.00219.
15. Guo X, Wang S, Ma Y et al. Disitamab vedotin (RC48-ADC) combined with immunotherapy as neoadjuvant therapy for localized muscle-invasive bladder cancer: a multicenter real-world study. NPJ Precis Oncol. 2025;10(1):11. Published 2025 Dec 3. 10.1038/s41698-025-01211-1
16. Zhang C, Yu Y, Zhou Q, Ouyang J, Zhang Z. Disitamab vedotin *vs*. gemcitabine-cisplatin regimen with immunotherapy: a comparative analysis of efficacy and safety in muscle-invasive bladder cancer. Front Immunol. 2025;16:1549647. 10.3389/fimmu.2025.1549647. Published 2025 Feb 27.
17. Wang A, Chen M, Li D, et al. Disitamab Vedotin Alone or in Combination With Immune Checkpoint Inhibitors in Bladder-Sparing Treatment of Muscle-Invasive Bladder Cancer: A Real-World Study. Clin Genitourin Cancer. 2024;22(3):102085. 10.1016/j.clgc.2024.102085.
18. Shi F, Liu Y, Zhou X, Shen P, Xue R, Zhang M. Disitamab vedotin: a novel antibody-drug conjugates for cancer therapy. Drug Deliv. 2022;29(1):1335–44. 10.1080/10717544.2022.2069883.
19. Sheng X, Zeng G, Zhang C, et al. Disitamab Vedotin plus Toripalimab in HER2-Expressing Advanced Urothelial Cancer. N Engl J Med. 2025;393(23):2324–37. 10.1056/NEJMoa2511648.
20. Yao JM, Zhong JL, Zhou Q, Guo J. Efficacy and safety of disitamab vedotin in combination with immune checkpoint inhibitors in patients with locally advanced or metastatic urothelial carcinoma. World J Urol. 2025;43(1):154. Published 2025 Mar 9. 10.1007/s00345-025-05544-1
21. Xu J, Zhang H, Zhang L, et al. Real-world effectiveness and safety of RC48-ADC alone or in combination with PD-1 inhibitors for patients with locally advanced or metastatic urothelial carcinoma: A multicenter, retrospective clinical study. Cancer Med. 2023;12(23):21159–71. 10.1002/cam4.6680.
22. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23. 10.1056/NEJMoa1003466.
23. Powles T, Kockx M, Rodriguez-Vida A, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. Nat Med. 2019;25(11):1706–14. 10.1038/s41591-019-0628-7.
24. Feng Z, Zhang YZ, Xie C. A case analysis of multiple immune-related adverse event induced by toripalimab[J]. China Pharm. 2025;36(01):96–100.
25. Ruan ZT, Lin YZ, Ke ZB. Efficacy and safety of Disitamab Vedotin compared with GC regimen combined with immunotherapy in the bladder-preserving treatment of bladder cancer.[J]. Clin Urol (China). 2024;39(11):1000–7.

26. Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. IntImmunopharmacol.2018;62:29–39. 10.1016/j.intimp.2018.06.001

Figures

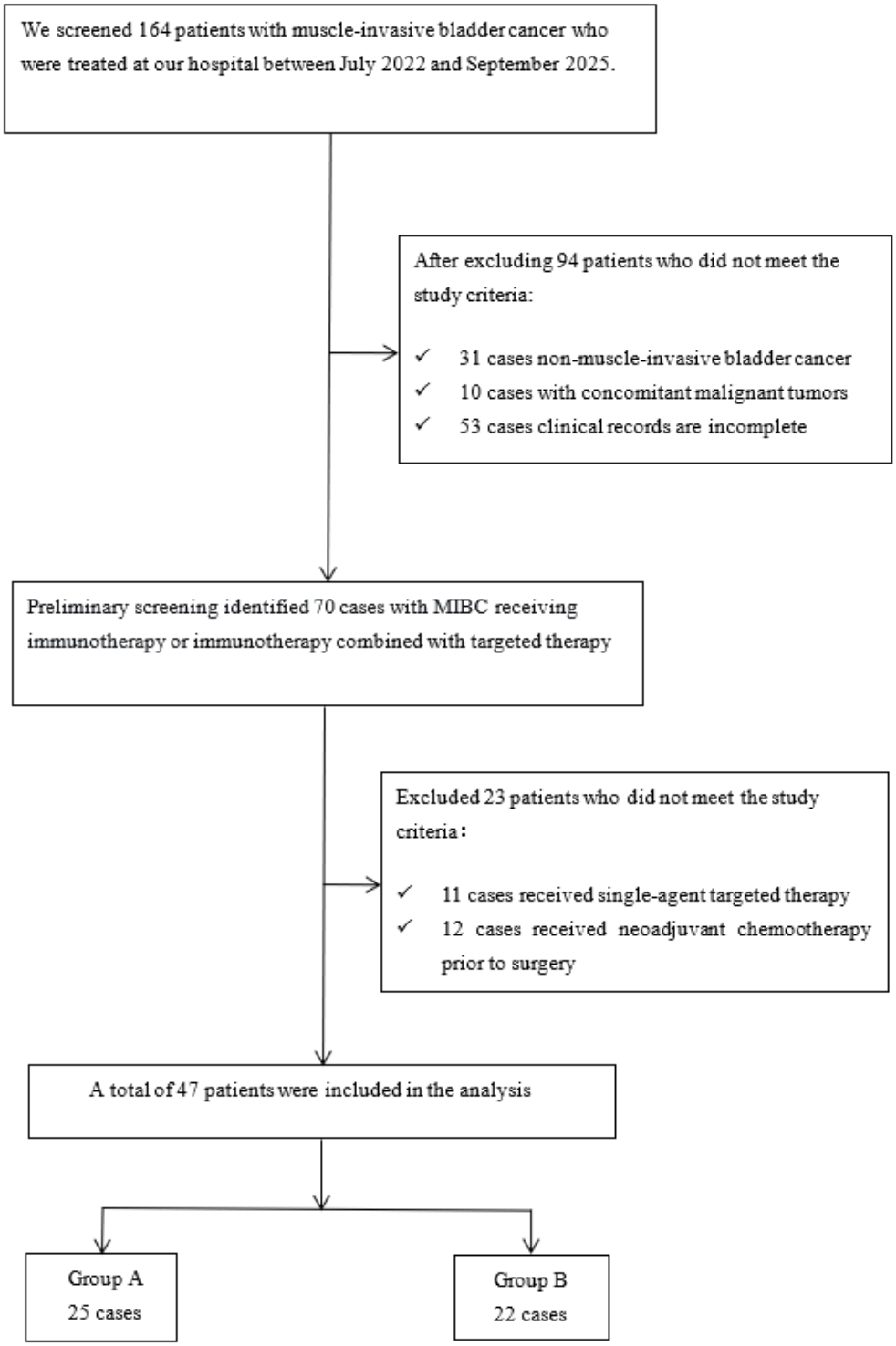

Figure 1

Flowchart of patient selection for the study

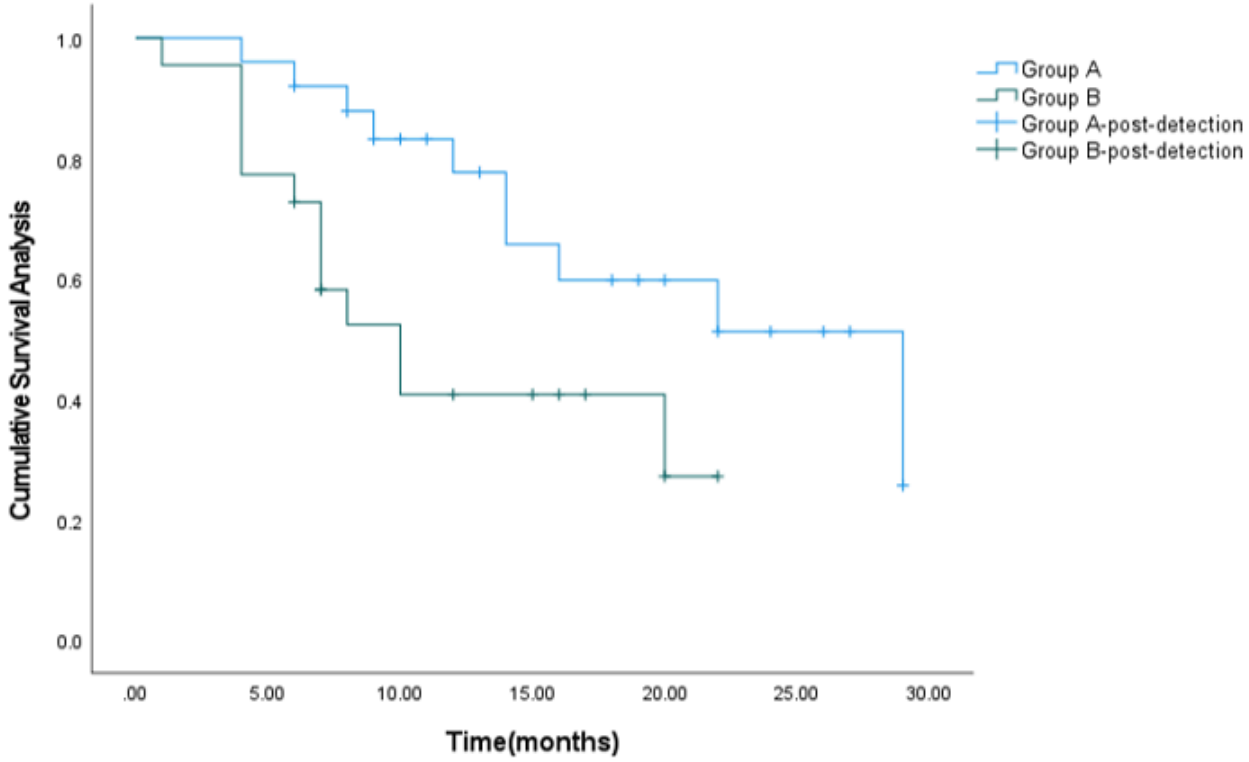

Figure 2

Kaplan-Meier curves for PFS in two groups of MIBC patients

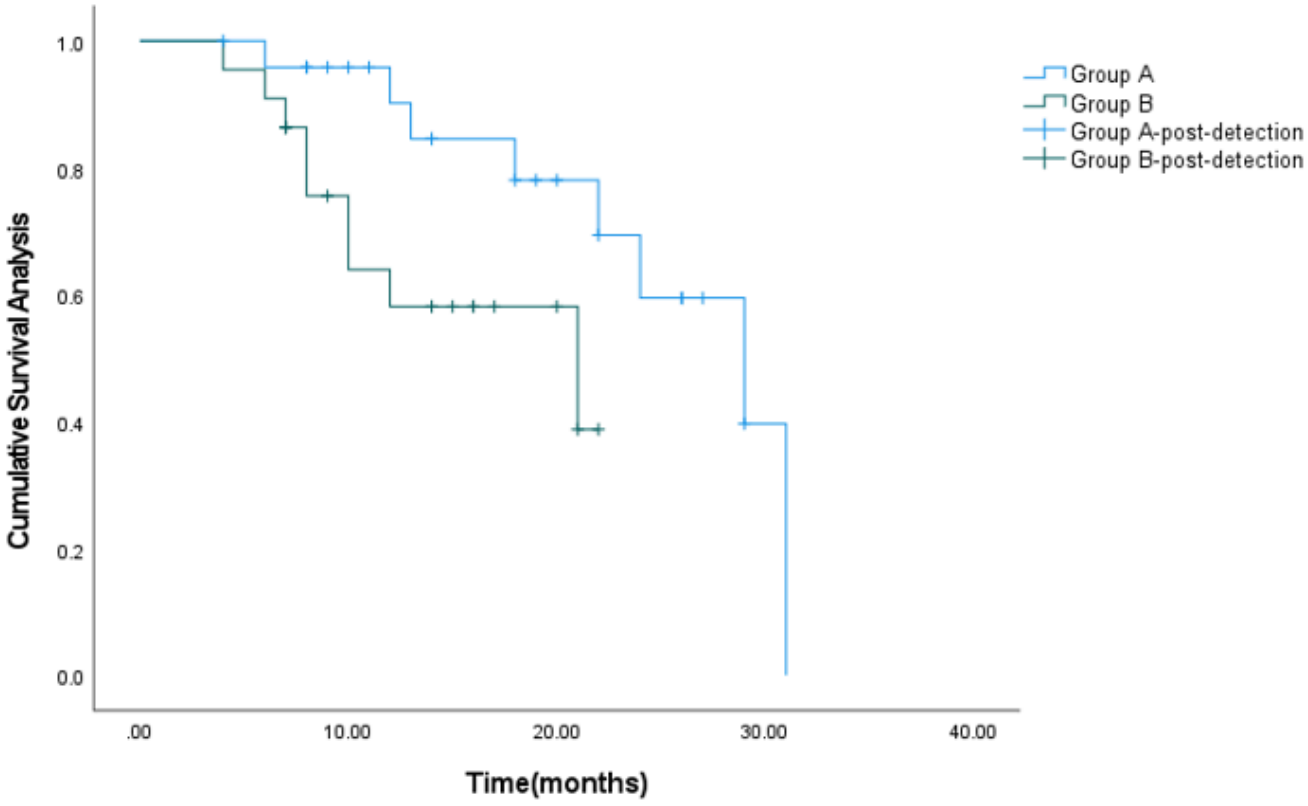

Figure 3

Kaplan-Meier curves for OS in two groups of MIBC patients