

Bladder Preservation With Disitamab Vedotin Plus PD-1 Inhibitors and Local Intensification in Muscle-Invasive Bladder Cancer: A Single-Center Retrospective Cohort of 81 Patients

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Abstract

Purpose

To evaluate the efficacy and safety of disitamab vedotin (DV) plus a PD-1 inhibitors, integrated with various local intensification strategies, for the bladder-preserving management of muscle-invasive bladder cancer (MIBC).

Methods

This single-center retrospective cohort study enrolled patients with MIBC who underwent maximal transurethral resection of bladder tumor (TURBT) followed by DV plus a PD-1 inhibitor between January 1, 2023, and September 30, 2025. According to the local intensification strategy, patients were classified into three groups: group A, maximal TURBT followed by DV plus a PD-1 inhibitor; group B, maximal TURBT followed by DV plus a PD-1 inhibitor combined with intravesical *Bacillus Calmette-Guérin* (BCG); and group C, maximal TURBT followed by DV plus a PD-1 inhibitor combined with radiotherapy. Treatment selection was based on multidisciplinary evaluation of patients' clinical characteristics and treatment accessibility. The primary endpoint was bladder-intact event-free survival (BI-EFS). Secondary endpoints included clinical complete response (cCR), progression-free survival (PFS), overall survival (OS), bladder preservation rate, salvage or delayed radical cystectomy (RC) rate, and safety.

Results

A total of 81 patients were included, comprising 41 in group A, 30 in group B, and 10 in group C. The median follow-up duration was 14.4 months. The 12-month BI-EFS rates were 55.9%, 92.2%, and 90.0% in groups A, B, and C, respectively ($P = 0.003$). Compared with group A, group B showed significantly improved BI-EFS ($P = 0.006$). In multivariable Cox regression analysis, group B was associated with a significantly lower risk of BI-EFS events than group A (adjusted HR, 0.29; 95% CI, 0.11–0.78; $P = 0.015$). The cCR rates were 39.0%, 80.0%, and 60.0% in groups A, B, and C, respectively ($P = 0.002$), while the bladder preservation rates at the last follow-up were 75.6%, 100.0%, and 90.0%, respectively ($P = 0.008$). No significant differences were observed in PFS or OS among the three groups. Any-grade and grade ≥ 3 adverse events occurred in 92.6% and 4.9% of patients, respectively.

Conclusion

DV plus a PD-1 inhibitor combined with local intensification strategies was feasible for the bladder-preserving management of MIBC and demonstrated an acceptable overall safety profile. The addition of intravesical BCG was associated with improved bladder-intact outcomes, whereas the benefit of combined radiotherapy warrants further investigation in larger prospective studies.

Introduction

Muscle-invasive bladder cancer (MIBC) accounts for approximately 20%–25% of newly diagnosed bladder cancers and is associated with a high risk of local recurrence, distant metastasis, and cancer-related mortality, thereby representing a major contributor to bladder cancer-related death[1, 2]. For resectable MIBC, current guidelines continue to recommend a curative treatment strategy centered on radical cystectomy (RC) combined with perioperative systemic therapy[2]. Although this approach has an established role in oncologic control, RC is highly

invasive and is associated with substantial perioperative morbidity, postoperative urinary diversion, sexual dysfunction, and impaired quality of life[2, 3]. Therefore, for patients who are elderly, have substantial comorbidities, are unfit for radical surgery, or strongly desire bladder preservation and are considered appropriate candidates for organ-preserving treatment after careful evaluation, there is a clear clinical need for strategies that better balance oncologic control with organ preservation.

At present, trimodality therapy (TMT), consisting of maximal transurethral resection of bladder tumor (TURBT) followed by concurrent chemoradiotherapy, with salvage cystectomy when necessary, remains one of the most evidence-based bladder-preserving approaches[1, 2, 4]. In carefully selected patients, TMT can achieve oncologic outcomes comparable to those of radical surgery while preserving bladder function. However, TMT requires good performance status, adequate tolerance to chemoradiotherapy, and strict adherence to follow-up, which limits its broader applicability. In addition, because this strategy remains primarily centered on local therapy, its capacity to control occult micrometastatic disease is inherently limited[2, 5, 6]. Accordingly, within the framework of bladder-preserving treatment, optimizing systemic disease control while maintaining effective local control remains a major challenge in MIBC management.

In recent years, immune checkpoint inhibitors (ICIs) and antibody-drug conjugates (ADCs) have substantially reshaped the systemic treatment landscape of urothelial carcinoma[2, 7, 8]. In particular, combinations of ADCs with PD-1/PD-L1 inhibitors have demonstrated promising antitumor activity and manageable safety profiles in locally advanced or metastatic urothelial carcinoma, thereby extending these strategies from advanced disease into perioperative and localized settings. Against this background, organ-preserving approaches based on novel systemic therapies have attracted increasing interest and may offer an alternative to conventional TMT for selected patients with MIBC. However, despite encouraging findings from early studies and real-world reports, robust evidence regarding long-term efficacy, optimal patient selection, and the most effective integration with local therapy remains limited[9–12].

Disitamab vedotin (DV) is a HER2-targeted ADC that has shown promising antitumor activity in urothelial carcinoma. Previous studies have suggested that DV combined with a PD-1 inhibitor can achieve relatively high response rates with an overall manageable toxicity profile in patients with HER2-expressing locally advanced or metastatic urothelial carcinoma. More recently, this strategy has also been explored in perioperative and bladder-preserving settings for localized MIBC. These developments provide a rationale for further investigation of DV plus a PD-1 inhibitor in the bladder-preserving management of MIBC. Nevertheless, the currently available evidence is largely limited to single-arm exploratory studies or early real-world analyses, and it remains unclear whether additional local intensification strategies on top of maximal TURBT and DV plus a PD-1 inhibitor can further improve bladder-intact outcomes[11, 13, 14].

With respect to local intensification, radiotherapy and intravesical instillation represent two distinct therapeutic approaches with different mechanisms and potential clinical roles. Radiotherapy is a core component of current bladder-preserving treatment paradigms. Beyond its direct local cytotoxic effects, radiotherapy may synergize with immunotherapy by promoting tumor antigen release, enhancing antigen presentation, and remodeling the tumor immune microenvironment. In the context of expanding ADC applications, the potential radiosensitizing interaction between radiotherapy and ADCs has also attracted increasing attention[15–17]. By contrast, intravesical Bacillus Calmette-Guérin (BCG) is well established in high-risk non-muscle-invasive bladder cancer, but its role in bladder-preserving treatment pathways for MIBC has not been established, and it is not included in current guideline-recommended standard management[4, 18, 19]. In particular, in the setting of ADC plus immunotherapy, whether

BCG can further control microscopic residual disease within the bladder, reduce bladder-preservation failure, and improve bladder-intact outcomes remains unsupported by high-quality clinical evidence[4, 20, 21].

Against this background, we retrospectively evaluated three bladder-preserving strategies based on a common treatment backbone of maximal TURBT followed by DV plus a PD-1 inhibitor: DV plus a PD-1 inhibitor alone, DV plus a PD-1 inhibitor combined with intravesical BCG, and DV plus a PD-1 inhibitor combined with radiotherapy. We compared their efficacy and safety, with particular emphasis on the association between different local intensification strategies and BI-EFS. Using real-world data, we sought to provide preliminary clinical evidence for comprehensive bladder-preserving management of MIBC based on ADC plus immunotherapy and to inform the design of future prospective studies.

Materials and Methods

3.1 Study design and patient selection

This single-center retrospective cohort study was conducted at Lanzhou University Second Hospital. Consecutive patients with pathologically confirmed MIBC who underwent maximal TURBT followed by DV plus a PD-1 inhibitor between January 1, 2023, and September 30, 2025, were included. Clinical data were collected from electronic medical records, imaging archives, and outpatient or telephone follow-up records. The study protocol was approved by the Ethics Committee of Lanzhou University Second Hospital (approval No. 2026A-097), and the requirement for written informed consent was waived because the study used de-identified retrospective data and involved no additional intervention beyond routine care. Maximal TURBT was defined as resection of all visible tumors to the greatest extent safely feasible, with an effort to obtain specimens containing muscularis propria for pathological assessment.

3.2 Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) age ≥ 18 years; (2) pathologically confirmed MIBC with clinical stage T2-T4aN0-1M0, according to the AJCC 8th edition TNM staging system; (3) receipt of maximal TURBT followed by DV plus a PD-1 inhibitor as part of a bladder-preserving treatment pathway; (4) completion of at least two cycles of combination therapy; and (5) availability of evaluable baseline and follow-up data.

The exclusion criteria were as follows: (1) prior or concurrent radical cystectomy; (2) distant metastasis (M1); (3) prior treatment with a similar ADC plus PD-1 inhibitor regimen; (4) missing key information precluding efficacy or safety evaluation; and (5) other conditions judged by the investigators to make the patient unsuitable for inclusion, such as severe immune disorders or uncontrolled infection.

3.3 Treatment regimens

Patients were classified into three groups according to the local intensification strategy. Group A received DV plus a PD-1 inhibitor alone after maximal TURBT. Group B received the same systemic therapy combined with intravesical BCG. Group C received the same systemic therapy combined with radiotherapy.

DV was administered at 2.0 mg/kg every 2 weeks. PD-1 inhibitors included toripalimab at 3 mg/kg every 2 weeks or tislelizumab at 200 mg every 3 weeks. In group B, intravesical BCG was administered at 120 mg once weekly for 6 consecutive weeks as induction therapy, followed by maintenance instillation every 2 weeks, with a planned total of up to 19 instillations. All patients in group B completed at least the 6-week induction course, whereas subsequent maintenance instillations were individualized according to clinical response, tolerability, and follow-up findings. In

group C, radiotherapy was delivered to the local bladder lesion after completion of two cycles of systemic therapy, using individualized fractionation schedules with a total dose of 50–66 Gy. The radiotherapy target volume, fractionation schedule, sequencing relative to systemic therapy, and treatment completion were determined by radiation oncologists and the multidisciplinary team after comprehensive evaluation. The number of DV and PD-1 inhibitor treatment cycles was adjusted individually according to treatment response, tolerability, and follow-up assessments.

3.4 Data collection and follow-up

Baseline clinicopathological variables included age, sex, body mass index (BMI), ECOG performance status, age-adjusted Charlson comorbidity index (ACCI), clinical T stage, clinical N stage, tumor grade, multifocality, HER2 expression status, Ki-67 level, and liver and renal function. HER2 expression was assessed by immunohistochemistry (IHC) according to the Chinese expert consensus on the clinicopathological evaluation of urothelial carcinoma; IHC 2+/3+ was defined as positive and IHC 0/1+ as negative[22]. Routine blood tests, biochemical panels, coagulation tests, electrocardiography, and imaging assessments were performed before and during treatment. Follow-up was generally scheduled every 2–3 months and included imaging, cystoscopy, and biopsy when clinically indicated. Post-treatment response was evaluated according to routine clinical practice. The data cutoff date was January 31, 2026.

3.5 Endpoints

The primary endpoint was BI-EFS, defined as the time from initiation of systemic therapy to the first occurrence of any of the following events: local muscle-invasive recurrence ($\geq T2$), regional nodal recurrence, distant metastasis, salvage or delayed RC, or bladder cancer-specific death.

Secondary endpoints included cCR, PFS, OS, bladder preservation rate, salvage or delayed RC rate, local invasive recurrence rate, and safety. cCR was defined as no visible tumor on post-treatment cystoscopy, negative biopsy when performed, and no evidence of local residual disease, regional nodal progression, or distant metastasis on imaging[12, 23]. Because all patients underwent maximal TURBT before systemic therapy, cCR mainly reflected the combined effect of initial local resection and subsequent combination treatment and was therefore interpreted as a supplementary efficacy endpoint.

3.6 Safety assessment

Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Particular attention was paid to treatment-related toxicities, immune-related adverse events (irAEs), intravesical instillation-related local adverse reactions, and radiotherapy-related toxicities.

3.7 Statistical analysis

Continuous variables were presented as mean $\pm$ standard deviation or median (interquartile range), as appropriate, and categorical variables as number (percentage). Between-group comparisons of continuous variables were performed using one-way analysis of variance or the Kruskal-Wallis test, whereas categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. OS, PFS, and BI-EFS were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards regression models were used to explore factors associated with BI-EFS, and HRs with 95% CIs were calculated. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using R software (version 4.5.2) and GraphPad Prism (version 10.1.2). Given the limited sample size and number of events, the number of covariates included in multivariable models was restricted; therefore, these analyses were intended to

explore associations with BI-EFS rather than establish causality. Only patients with complete key baseline and follow-up data sufficient for efficacy and safety evaluation were included, and no imputation was performed for missing data. Given the observational design and treatment selection through multidisciplinary clinical decision-making, all findings should be interpreted as exploratory associations rather than causal effects.

Results

4.1 Patient screening and baseline characteristics

During the study period, 94 patients with MIBC were screened. Thirteen patients were excluded because they did not meet the eligibility criteria or lacked sufficient data for efficacy or safety evaluation, leaving 81 patients for the final analysis, including 41 in group A, 30 in group B, and 10 in group C. Most baseline characteristics were comparable across the three groups, although clinically meaningful imbalances could not be excluded given the limited sample size. The median ages were 72, 69, and 69 years in groups A, B, and C, respectively ($P=0.789$). No statistically significant between-group differences were observed in sex, BMI, comorbidities, ECOG performance status, ACCI, clinical T stage, clinical N stage, tumor grade, multifocality, PD-1 inhibitor type, disease status at study entry, HER2 expression, or Ki-67 level. The only variable showing a significant between-group difference was transaminase abnormality ($P=0.046$), with a relatively higher proportion of liver function abnormality in group C (Figure 1 and Table 1).

Table 1 Baseline characteristics of patients by treatment group.

Characteristic	Group A N = 41	Group B N = 30	Group C N = 10	p-value
Age	72 (60, 77)	69 (61, 77)	69 (66, 71)	0.789
Sex				0.074
Female	4 (9.8%)	8 (26.7%)	0 (0.0%)	
Male	37 (90.2%)	22 (73.3%)	10 (100.0%)	
Body mass index, kg/m2	24.0 (4.0)	23.3 (3.7)	25.4 (3.3)	0.265
Comorbidities	19 (46.3%)	11 (36.7%)	4 (40.0%)	0.737
ECOG performance status				0.821
0	21 (51.2%)	14 (46.7%)	6 (60.0%)	
≥1	20 (48.8%)	16 (53.3%)	4 (40.0%)	
Age-adjusted Charlson comorbidity index (ACCI)				0.730
0-2	14 (34.1%)	13 (43.3%)	4 (40.0%)	
≥3	27 (65.9%)	17 (56.7%)	6 (60.0%)	
Clinical T stage				0.963
T2	35 (85.4%)	27 (90.0%)	10 (100.0%)	
T3	3 (7.3%)	1 (3.3%)	0 (0.0%)	
T4	3 (7.3%)	2 (6.7%)	0 (0.0%)	
Clinical N stage				0.872
N0	36 (87.8%)	28 (93.3%)	9 (90.0%)	
N1	5 (12.2%)	2 (6.7%)	1 (10.0%)	
Tumor grade				0.712
High	40 (97.6%)	28 (93.3%)	10 (100.0%)	
Low	1 (2.4%)	2 (6.7%)	0 (0.0%)	
Multifocality	9 (22.0%)	12 (40.0%)	4 (40.0%)	0.199
PD-1 inhibitor				0.819
Tislelizumab	18 (43.9%)	15 (50.0%)	5 (50.0%)	
Toripalimab	23 (56.1%)	15 (50.0%)	5 (50.0%)	
Disease status				0.694
Initial diagnosis	31 (75.6%)	24 (80.0%)	9 (90.0%)	
Recurrence	10 (24.4%)	6 (20.0%)	1 (10.0%)	
Transaminase status				0.046
Impaired	9 (22.0%)	6 (20.0%)	6 (60.0%)	

Characteristic	Group A N = 41	Group B N = 30	Group C N = 10	p-value
Normal	32 (78.0%)	24 (80.0%)	4 (40.0%)	
Creatinine, $\mu\text{mol/L}$	74 (64, 92)	66 (60, 87)	83 (72, 97)	0.058
HER2 status (IHC)				0.323
Negative (0/1+)	2 (4.9%)	4 (13.3%)	0 (0.0%)	
Positive (2+/3+)	39 (95.1%)	26 (86.7%)	10 (100.0%)	
Ki67, %	60 (40, 60)	60 (30, 70)	65 (40, 70)	0.656

Abbreviations: Data are presented as median (Q1, Q3), mean (SD), or n (%); P values were calculated using the Kruskal-Wallis test, chi-square test, or Fisher's exact test, as appropriate.

4.2 Treatment exposure

The number of DV plus a PD-1 inhibitor treatment cycles varied according to treatment response, tolerability, and follow-up assessment. The median numbers of treatment cycles were 4.0 (IQR, 3.0-6.0), 5.5 (IQR, 4.0-6.0), and 5.5 (IQR, 4.0-6.0) in groups A, B, and C, respectively; the corresponding ranges were 2-8, 2-8, and 3-8 cycles. In the overall cohort, the median number of treatment cycles was 5.0 (IQR, 3.0-6.0; range, 2-8).

In group B, intravesical BCG was administered at 120 mg once weekly for 6 weeks as induction therapy, followed by maintenance instillation every 2 weeks, with a planned total of up to 19 instillations. All 30 patients in group B completed at least the 6-week induction course. The median total number of BCG instillations was 11 (IQR, 8-14; range, 6-18), and 25 of 30 patients (83.3%) received more than 6 instillations, indicating continuation into the maintenance phase. Patients in group C received individualized radiotherapy regimens with total doses ranging from 50 to 66 Gy according to target delineation, fractionation schedule, and sequencing relative to systemic therapy.

4.3 Primary endpoint: BI-EFS

At the data cutoff, the median follow-up for the overall cohort was 14.4 months. Kaplan-Meier analysis showed a significant difference in BI-EFS among the three groups. The 12-month BI-EFS rates were 55.9% (95% CI, 42.0%-74.5%), 92.2% (95% CI, 82.4%-100.0%), and 90.0% (95% CI, 73.2%-100.0%) in groups A, B, and C, respectively, with a significant overall difference ($P=0.003$) (Table 2). The BI-EFS event rates were 46.3%, 16.7%, and 20.0%, respectively ($P=0.020$). Pairwise comparisons showed that group B had significantly better BI-EFS than group A ($P=0.006$), whereas the differences between groups A and C and between groups B and C were not statistically significant (Figure 2).

4.4 Multivariable Cox analysis of BI-EFS

In the multivariable Cox proportional hazards model including treatment group, age, ECOG performance status, clinical T stage, and clinical N stage, group B remained associated with a lower risk of BI-EFS events than group A (adjusted HR, 0.29; 95% CI, 0.11-0.78; $P=0.015$). Group C also showed a trend toward a lower risk than group A, although the difference did not reach statistical significance (adjusted HR, 0.16; 95% CI, 0.02-1.20; $P=0.075$). In

addition, higher clinical T stage (cT3-4 vs T2) was independently associated with a higher risk of BI-EFS events (adjusted HR, 3.15; 95% CI, 1.02-9.74; P=0.046). Age, ECOG performance status, and clinical N stage were not significantly associated with BI-EFS in the multivariable model (Figure 3).

Table 2 Oncologic and bladder preservation outcomes

Outcome	A (n=41)	B (n=30)	C (n=10)	Overall (n=81)	P value
Follow-up					
Median follow-up, months (IQR)	13.8 (8.0-21.9)	13.6 (8.7-19.0)	18.2 (15.3-22.1)	14.4 (8.8-21.5)	
Primary endpoint					
12-month BI-EFS rate, % (95% CI)	55.9 (42.0-74.5)	92.2 (82.4-100.0)	90.0 (73.2-100.0)	74.0 (64.8-84.6)	0.003
BI-EFS events, n (%)	19 (46.3%)	5 (16.7%)	2 (20.0%)	26 (32.1%)	0.020
Secondary endpoints					
Clinical complete response (cCR), n/N (%)	16/41 (39.0%)	24/30 (80.0%)	6/10 (60.0%)	46/81 (56.8%)	0.002
12-month progression-free survival, % (95% CI)	80.3 (68.1-94.7)	89.1 (78.0-100.0)	100.0 (100.0-100.0)	86.3 (78.7-94.6)	0.426
12-month overall survival, % (95% CI)	88.9 (79.0-100.0)	93.2 (84.6-100.0)	100.0 (100.0-100.0)	91.9 (85.8-98.4)	0.830
Bladder preservation at last follow-up, n (%)	31 (75.6%)	30 (100.0%)	9 (90.0%)	70 (86.4%)	0.008
Salvage or delayed radical cystectomy, n (%)	9 (21.9%)	0 (0.0%)	1 (10.0%)	10 (12.3%)	0.010
Local invasive recurrence, n (%)	4 (10.0%)	2 (6.7%)	0 (0.0%)	6 (7.4%)	0.857
Regional nodal recurrence, n (%)	2 (4.9%)	1 (3.3%)	0 (0.0%)	3 (3.7%)	1.000
Distant metastasis, n (%)	2 (4.9%)	1 (3.3%)	0 (0.0%)	3 (3.7%)	1.000
Bladder cancer-specific death, n (%)	2 (4.9%)	2 (6.7%)	1 (10.0%)	5 (6.2%)	0.819

Abbreviations: BI-EFS, bladder-intact event-free survival; CI, confidence interval; cCR, complete clinical response; IQR, interquartile range. BI-EFS was defined as the time from treatment initiation to the first occurrence of local muscle-invasive recurrence, regional nodal recurrence, distant metastasis, salvage or delayed radical cystectomy, or bladder cancer-specific death. Time-to-event endpoints were estimated using the Kaplan-Meier method and compared using the log-rank test. Categorical variables with sparse cell counts were compared using the Fisher-Freeman-Halton exact test; otherwise, the chi-square test was used as appropriate. Percentages are shown in parentheses unless otherwise indicated.

4.5 Secondary endpoints

The cCR rates were 39.0% (16/41), 80.0% (24/30), and 60.0% (6/10) in groups A, B, and C, respectively, with a significant overall difference (P=0.002). At the last follow-up, the bladder preservation rates were 75.6%, 100.0%, and 90.0%, respectively (P=0.008), whereas the salvage or delayed RC rates were 21.9%, 0.0%, and 10.0%, respectively (P=0.010). The 12-month PFS rates were 80.3%, 89.1%, and 100.0%, respectively, with no significant overall difference (P=0.426). Similarly, the 12-month OS rates were 88.9%, 93.2%, and 100.0%, respectively, with no significant between-group difference (P=0.830). No significant between-group differences were observed in local invasive recurrence, regional nodal recurrence, distant metastasis, or bladder cancer-specific death (Table 2).

4.6 Safety

Overall, treatment-related adverse events were manageable, and no new safety signals were identified. Among the 81 patients, 75 (92.6%) experienced at least one any-grade adverse event, and 4 (4.9%) experienced grade 3 or higher adverse events. The incidences of any-grade adverse events in groups A, B, and C were 85.4%, 100.0%, and 100.0%, respectively, whereas the incidences of grade 3 or higher adverse events were 2.4%, 3.3%, and 20.0%, respectively (Table 3).

The most common adverse events were alopecia (44.4%), nausea and vomiting (38.3%), hypoalbuminemia (33.3%), leukopenia (29.6%), drug-related rash (27.2%), fatigue (23.5%), and decreased appetite (21.0%). Urinary irritative symptoms, including dysuria, were more frequent in group B, whereas leukopenia, drug-related rash, and cystitis were more common in group C.

Serious adverse events were uncommon overall. Interstitial pneumonia occurred in 3 patients (3.7%), including 2 with grade 3 or higher events. In addition, one patient developed grade 3 or higher drug-related rash, and one developed grade 3 or higher transaminase elevation. Overall, DV plus a PD-1 inhibitor combined with local therapy showed acceptable tolerability in patients with MIBC, although toxicity profiles differed across local intensification strategies.

Table 3 Treatment-related adverse events by treatment group.

Adverse Events	A (N=41)		B (N=30)		C (N=10)		Total (N=81)	
	Any grade	Grade≥3	Any grade	Grade≥3	Any grade	Grade≥3	Any grade	Grade≥3
Patients with at least one adverse event	35 (85.4%)	1 (2.4%)	30 (100.0%)	1 (3.3%)	10 (100.0%)	2 (20.0%)	75 (92.6%)	4 (4.9%)
Alopecia	14 (34.1%)	0 (0.0%)	16 (53.3%)	0 (0.0%)	6 (60.0%)	0 (0.0%)	36 (44.4%)	0 (0.0%)
Nausea and vomiting	13 (31.7%)	0 (0.0%)	13 (43.3%)	0 (0.0%)	5 (50.0%)	0 (0.0%)	31 (38.3%)	0 (0.0%)
Hypoalbuminemia	10 (24.4%)	0 (0.0%)	14 (46.7%)	0 (0.0%)	3 (30.0%)	0 (0.0%)	27 (33.3%)	0 (0.0%)
Leukopenia	7 (17.1%)	0 (0.0%)	9 (30.0%)	0 (0.0%)	9 (90.0%)	0 (0.0%)	25 (29.6%)	0 (0.0%)
Drug-related rash	4 (9.8%)	0 (0.0%)	11 (36.7%)	0 (0.0%)	7 (70.0%)	1 (10.0%)	22 (27.2%)	1 (1.2%)
Fatigue	8 (19.5%)	0 (0.0%)	11 (36.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	19 (23.5%)	0 (0.0%)
Decreased appetite	7 (17.1%)	0 (0.0%)	8 (26.7%)	0 (0.0%)	2 (20.0%)	0 (0.0%)	17 (21.0%)	0 (0.0%)
Thrombocytopenia	5 (12.2%)	0 (0.0%)	7 (23.3%)	0 (0.0%)	4 (40.0%)	0 (0.0%)	16 (19.8%)	0 (0.0%)
Transaminase elevation	7 (17.1%)	0 (0.0%)	5 (16.7%)	0 (0.0%)	3 (30.0%)	1 (10.0%)	15 (18.5%)	1 (1.2%)
Urinary tract infection	8 (19.5%)	0 (0.0%)	6 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (17.3%)	0 (0.0%)
Creatinine elevation	5 (12.2%)	0 (0.0%)	4 (13.3%)	0 (0.0%)	2 (20.0%)	0 (0.0%)	11 (13.6%)	0 (0.0%)
Anemia	5 (12.2%)	0 (0.0%)	3 (10.0%)	0 (0.0%)	3 (30.0%)	0 (0.0%)	11 (13.6%)	0 (0.0%)
Peripheral neuropathy	3 (7.3%)	0 (0.0%)	8 (26.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (13.6%)	0 (0.0%)
Dysuria	0 (0.0%)	0 (0.0%)	9 (30.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (11.1%)	0 (0.0%)
Abdominal distension	1 (2.4%)	0 (0.0%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (6.2%)	0 (0.0%)
Cystitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (40.0%)	0 (0.0%)	4 (4.9%)	0 (0.0%)
Interstitial pneumonia	1 (2.4%)	1 (2.4%)	2 (6.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	3 (3.7%)	2 (2.5%)
Thyroiditis	1 (2.4%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.5%)	0 (0.0%)

Abbreviations: Data are presented as n (%). Grade ≥ 3 indicates adverse events of grade 3 or higher; Adverse events were graded according to CTCAE version 5.0.

Discussion

In this retrospective study, we compared three bladder-preserving strategies for MIBC based on a common treatment backbone of maximal TURBT followed by DV plus a PD-1 inhibitor. In this real-world cohort, the strategy incorporating intravesical BCG was associated with superior BI-EFS compared with systemic therapy alone, whereas the radiotherapy-containing strategy showed potential value but did not demonstrate a statistically significant advantage. Overall, all three strategies showed acceptable safety, although the toxicity profiles differed according to the local intensification approach.

The clinical relevance of this study lies in its comparison of different local intensification strategies within the same framework of novel systemic therapy. Previous studies of bladder preservation in MIBC have largely centered on TMT, and current international consensus continues to regard TMT as the most established and evidence-based bladder-preserving option aside from RC, while emphasizing that alternative organ-preserving approaches should generally be limited to carefully selected patients. In contrast, bladder-preserving strategies based on ADCs combined with PD-1 inhibitors remain exploratory. Although early clinical studies and real-world reports have emerged, mature high-quality evidence in this setting remains limited[1, 4, 11, 14].

As a HER2-targeted ADC, DV combined with a PD-1 inhibitor may theoretically support organ preservation by contributing to both local tumor control and the management of occult micrometastatic disease[11, 13]. Previous studies have demonstrated antitumor activity of DV in locally advanced or metastatic urothelial carcinoma, and early clinical studies of DV plus PD-1 inhibitors have reported favorable response rates with an overall manageable safety profile[14, 24]. In parallel, ADC-immunotherapy regimens represented by enfortumab vedotin plus pembrolizumab have shown robust activity in advanced urothelial carcinoma and have stimulated increasing interest in extending such systemic strategies into perioperative and localized MIBC settings[9, 12]. These developments provide a clinical rationale for the present treatment framework, although its long-term value in bladder-preserving management still requires further validation.

BI-EFS was selected as the primary endpoint because the goal of bladder-preserving treatment is not only to delay disease progression but also to preserve bladder integrity and avoid transition to RC whenever possible. In this context, endpoints such as PFS or local recurrence alone may not adequately capture whether an organ-preserving strategy has truly succeeded. Therefore, this study defined BI-EFS to include local muscle-invasive recurrence, regional nodal recurrence, distant metastasis, salvage or delayed RC, and bladder cancer-specific death, thereby integrating both oncologic control and organ preservation into a single clinically relevant outcome. From this perspective, BI-EFS represents a reasonable primary endpoint in studies of bladder-preserving management for MIBC.

At the same time, BI-EFS is a composite endpoint and should not be interpreted as equivalent to a purely biological measure of tumor progression. In particular, salvage or delayed RC may be influenced by physician judgment, patient preference for bladder preservation, local symptom burden, adherence to follow-up, and institutional treatment patterns. Its clinical meaning is therefore not identical to that of recurrence, metastasis, or bladder cancer-specific death. Accordingly, BI-EFS in this study should be understood as a composite outcome reflecting both failure of disease control and failure of organ preservation. This also highlights the importance of reporting the individual components of composite endpoints in bladder-preservation studies.

In the present cohort, local invasive recurrence, regional nodal recurrence, distant metastasis, salvage or delayed RC, and bladder cancer-specific death occurred in 6 (7.4%), 3 (3.7%), 3 (3.7%), 10 (12.3%), and 5 (6.2%) patients, respectively. Among these events, salvage or delayed RC was one of the most frequent components, suggesting that BI-EFS in this study captured not only recurrence or metastasis risk, but also whether bladder preservation could ultimately be maintained. In this sense, an improvement in BI-EFS may reflect not only better disease control but also a lower likelihood of transition to RC and a greater probability of sustained bladder preservation. Therefore, the superior BI-EFS observed in group B compared with group A suggests that intravesical BCG may have contributed to improved bladder-intact outcomes.

The multivariable Cox analysis was consistent with the primary analysis. After adjustment for age, ECOG performance status, clinical T stage, and clinical N stage, group B remained associated with a lower risk of BI-EFS events than group A, indicating that the observed association was not fully explained by these baseline variables. In addition, the cT3-4 stage was independently associated with a higher risk of BI-EFS events, underscoring the importance of local tumor burden in determining the success of bladder-preserving treatment. Although group C showed a trend toward lower risk in the multivariable model, the potential benefit remains uncertain because of the small sample size and wide confidence interval.

The improved BI-EFS observed in group B suggests that intravesical BCG may provide additional local disease control on top of maximal TURBT and systemic therapy. One possible explanation is that maximal TURBT followed by DV plus a PD-1 inhibitor may already substantially reduce tumor burden, whereas subsequent intravesical BCG may further control microscopic residual disease within the bladder, thereby delaying local recurrence or bladder-preservation failure[13, 15, 25]. Notably, all patients in the BCG group completed the 6-week induction course, and most proceeded to maintenance instillation, supporting the practical feasibility of incorporating BCG into this treatment framework. However, compared with TMT, the evidence supporting BCG as a local intensification strategy in MIBC remains insufficient, and it should still be considered exploratory rather than established standard care[4, 9, 25]. Accordingly, the present findings should be interpreted as hypothesis-generating rather than as evidence supporting treatment substitution.

By contrast, group C did not show superior BI-EFS compared with group A or group B, and this finding should be interpreted with caution. First, only 10 patients were included in group C, resulting in limited statistical power. Second, the proportion of baseline transaminase abnormality was higher in group C, raising the possibility of selection bias. Third, radiotherapy dose, target delineation, and sequencing relative to systemic therapy may all have influenced efficacy. Therefore, the present findings are insufficient to negate the role of radiotherapy in bladder-preserving treatment for MIBC and should instead be regarded as exploratory observations. Current reviews and consensus statements continue to consider radiotherapy integrated with maximal TURBT and chemotherapy a core component of bladder-preserving treatment, indicating that the optimal incorporation of radiotherapy in the setting of ADC plus immunotherapy warrants further investigation[4, 15, 26, 27].

From a safety perspective, the incidence of grade 3 or higher adverse events in the overall cohort was 4.9%, suggesting generally good tolerability of this treatment framework. Different treatment strategies showed distinct toxicity patterns: intravesical BCG was mainly associated with local urinary irritative symptoms, whereas radiotherapy was more often accompanied by leukopenia, cystitis, and rash. Severe immune-related adverse events were uncommon overall, although interstitial pneumonia remained a toxicity of particular concern. Notably, perioperative enfortumab vedotin plus pembrolizumab studies and prior DV-related studies have also suggested that, although ADC plus immunotherapy is generally manageable, pulmonary toxicity, skin toxicity, and immune-related adverse events require close monitoring. These observations are broadly consistent with our findings[9, 24].

This study has several limitations. First, as a single-center retrospective analysis, it is inherently subject to selection bias and residual confounding. Second, the sample sizes across the three groups were imbalanced, particularly the very small radiotherapy group, which limited the stability of between-group comparisons. Third, treatment regimens were heterogeneous, including the type of PD-1 inhibitor, the number of DV treatment cycles, and local treatment parameters. Fourth, exposure to maintenance intravesical BCG varied among patients, introducing additional within-group heterogeneity in the BCG cohort. Fifth, because systemic treatment duration was individualized according to treatment response and tolerability, potential time-dependent bias cannot be excluded. Sixth, follow-up was relatively short, and endpoints such as OS remained immature. Finally, because all patients underwent maximal TURBT, the cCR endpoint was influenced to some extent by the effect of initial local resection and should therefore be interpreted cautiously. In addition, the choice of local intensification strategy was driven by clinical decision-making and may still have been affected by confounding by indication.

Overall, our findings suggest that a comprehensive bladder-preserving strategy based on DV plus a PD-1 inhibitor combined with local intensification merits further evaluation in MIBC. Among the strategies examined, the addition of intravesical BCG was associated with better bladder-intact outcomes, whereas the potential value of radiotherapy requires further clarification in larger prospective studies using more standardized protocols. Future multicenter prospective studies incorporating biomarkers such as HER2 expression, dynamic ctDNA changes, and features of the tumor immune microenvironment are warranted to optimize patient selection, treatment sequencing, and treatment duration.

Conclusion

DV plus a PD-1 inhibitor combined with local intensification strategies after maximal TURBT appears feasible for the bladder-preserving management of MIBC and shows an overall acceptable safety profile. Compared with systemic therapy alone, the addition of intravesical BCG may be associated with improved bladder-intact outcomes, whereas the clinical benefit of combined radiotherapy requires further clarification in larger prospective studies with standardized protocols. These findings provide preliminary support for further investigation of ADC-plus-immunotherapy-based organ-preserving strategies in MIBC; however, given the single-center retrospective design and limited sample size, further validation is needed.

Declarations

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This retrospective study was approved by the Ethics Committee of Lanzhou University Second Hospital (Approval No. 2026A-097). All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate

The requirement for written informed consent was waived by the Ethics Committee of Lanzhou University Second Hospital because of the retrospective nature of the study and the use of de-identified data.

Consent for publication

Not applicable.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available because they contain potentially identifiable patient information but are available from the corresponding author on reasonable request and subject to institutional and ethical approval.

Author contributions

Conceptualization: Yan Chen, Wei Wang; Methodology: Yan Chen, Wenqiang An; Data curation: Ruonan Qu, Chao Chen, Zhong Wang, Fangqiu Yu, Yixuan Li, Shenbao He; Formal analysis: Yan Chen, Wenqiang An; Investigation: Yan Chen, Wenqiang An, Ruonan Qu, Chao Chen, Zhong Wang, Fangqiu Yu, Yixuan Li, Shenbao He; Writing—original draft: Yan Chen; Writing—review and editing: all authors; Supervision: Wei Wang. All authors read and approved the final manuscript.

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Figures

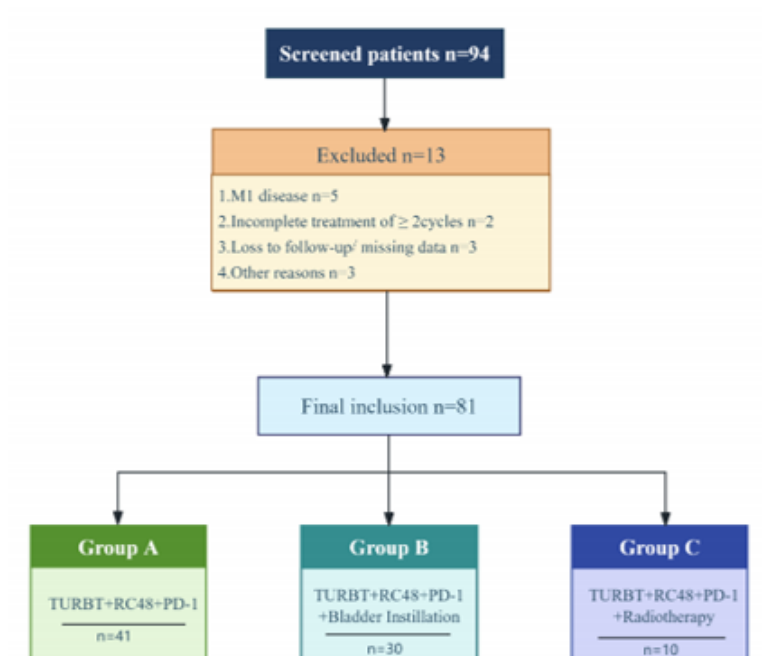


Figure 1

Flowchart of patient selection.

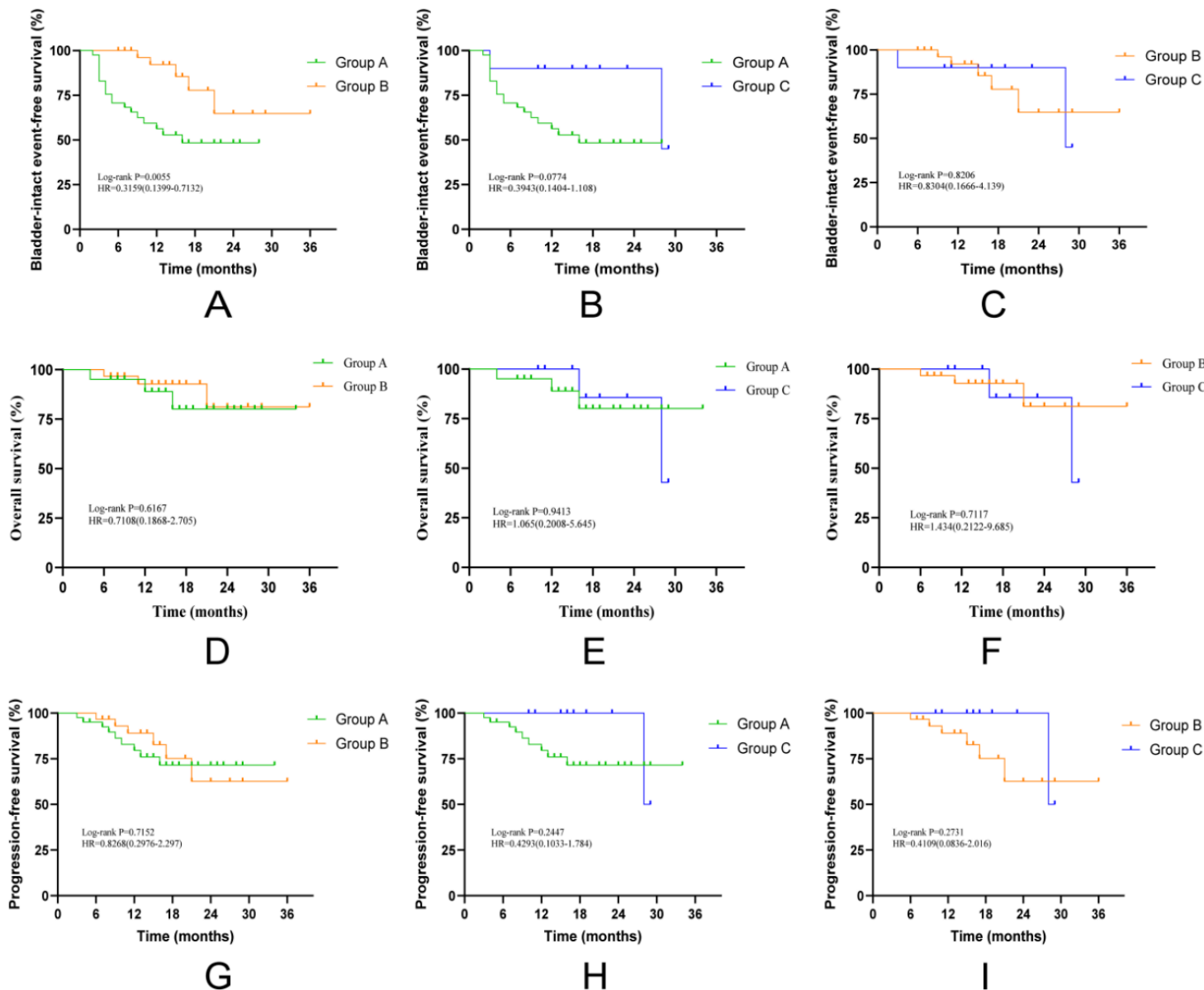


Figure 2

Pairwise Kaplan-Meier curves for bladder-intact event-free survival, progression-free survival, and overall survival among the treatment groups.

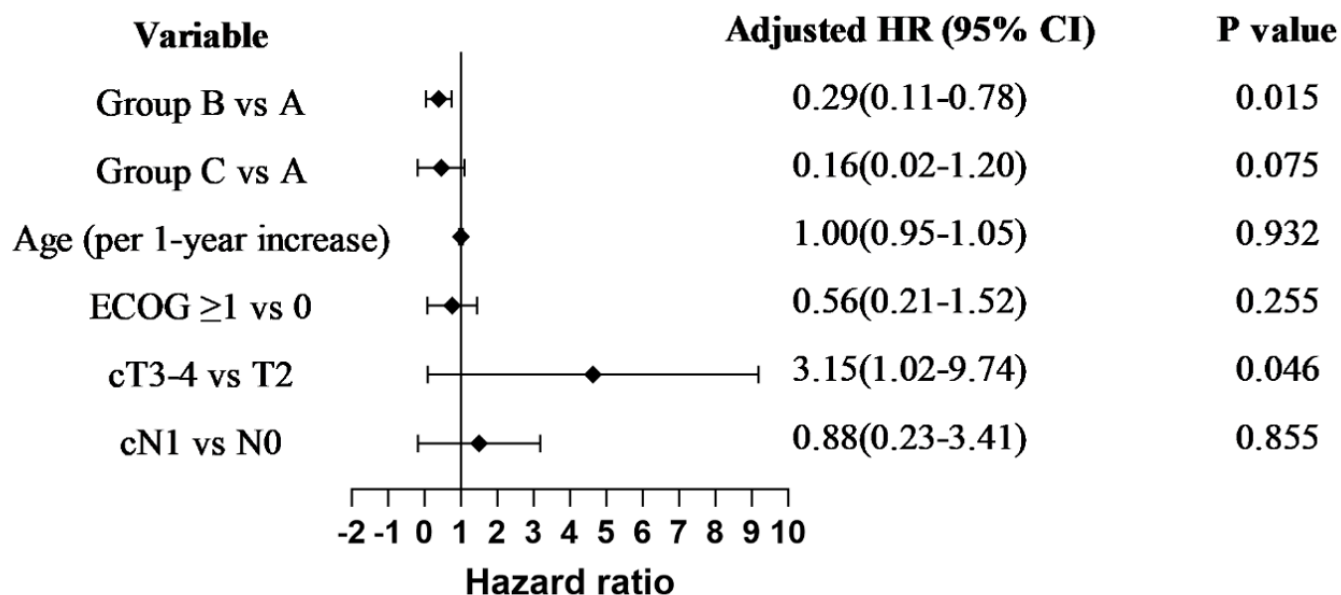


Figure 3

Forest plot of multivariable Cox proportional hazards analysis for bladder-intact event-free survival.

Distribution of BI-EFS Component Events

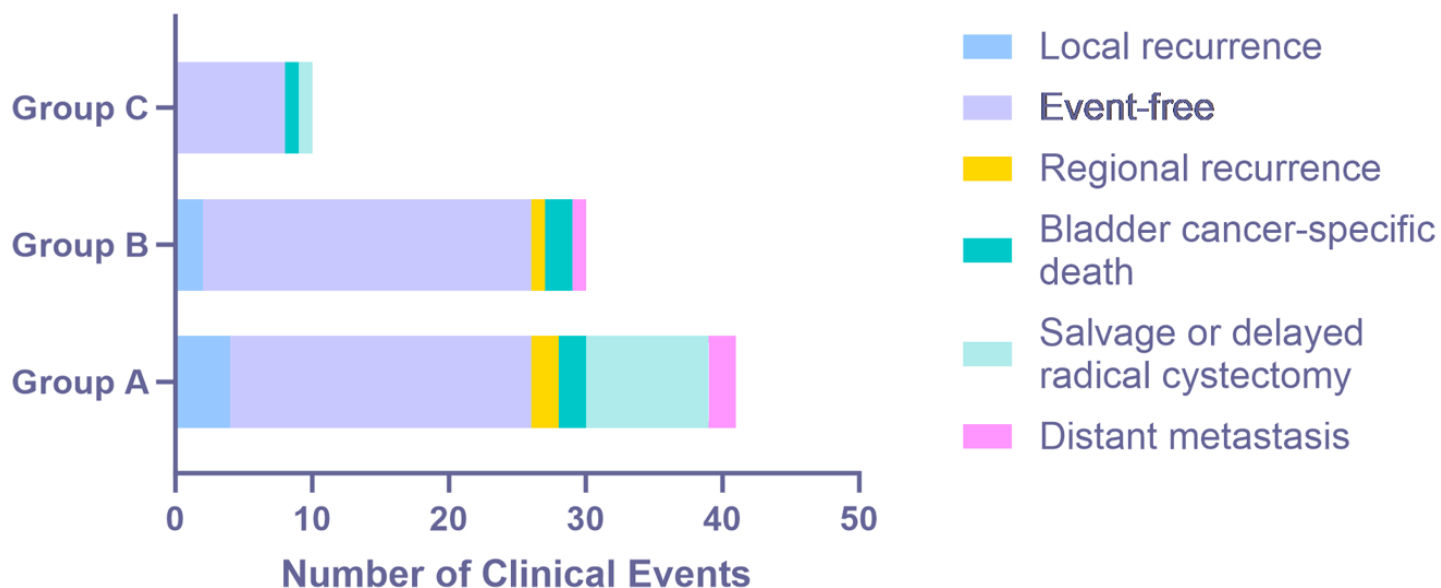


Figure 4

Distribution of bladder-intact event-free survival component events.