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Induction-maintenance intravesical gemcitabine after transurethral resection for intermediate- and selected high-risk non-muscle-invasive bladder cancer: A propensity score-matched cohort study

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Abstract: **Background**: Conventional intravesical chemotherapeutic agents for non-muscle-invasive bladder cancer (NMIBC) are limited by drug resistance and local adverse reactions, which may restrict their clinical benefit. **Objectives**: This study aimed to evaluate the clinical efficacy, urinary and serum concentration indicators, safety and exploratory pharmacoeconomic value of induction-maintenance intravesical gemcitabine as postoperative adjuvant therapy for intermediate- and selected high-risk NMIBC. **Methods**: A retrospective propensity score-matched cohort design was used. A total of 294 patients with intermediate- and selected high-risk NMIBC who underwent transurethral resection of bladder tumor from January 2022 to October 2023 were screened and follow-up records were reviewed through 31 October 2025. After 1:1 nearest-neighbor matching, 100 patients were retained in the induction-maintenance intravesical gemcitabine group and 100 in the conventional intravesical mitomycin group; tumor recurrence, recurrence-free survival, urinary and serum concentration indicators, adverse events and direct medical costs were compared between the two groups. **Results**: The tumor recurrence rates at 12 and 24 months were lower in the gemcitabine group than in the mitomycin group ($p=0.008$) and the mean recurrence-free survival time was longer in the gemcitabine group ($p<0.001$). The overall incidence of adverse events was lower in the gemcitabine group than in the mitomycin group ($p=0.011$) and the completion rate of the instillation course was higher in the gemcitabine group ($p=0.038$). The gemcitabine group showed lower 24-month direct medical costs and higher QALYs, indicating a dominant cost-saving pattern in this exploratory economic analysis. **Conclusion**: Induction-maintenance intravesical gemcitabine was associated with lower recurrence and better treatment completion than mitomycin in this matched cohort, but the study was not designed to compare gemcitabine with Bacillus Calmette-Guérin and should not be interpreted as establishing superiority or non-inferiority to BCG in high-risk NMIBC.

Keywords: Clinical efficacy; Gemcitabine; Intravesical instillation; Non-muscle-invasive bladder cancer; Pharmacoeconomics

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INTRODUCTION

Non-muscle-invasive bladder cancer (NMIBC) is an important clinical subtype of bladder cancer; patients with NMIBC have a high risk of postoperative recurrence and those with intermediate- and high-risk disease in particular require long-term cystoscopic surveillance and adjuvant treatment (Gontero *et al.*, 2024; Dyrskjot *et al.*, 2023). Transurethral resection of bladder tumor (TURBT) is the basis for both diagnosis and treatment of NMIBC (Gontero *et al*., 2024; Holzbeierlein *et al*., 2024); however, surgery alone cannot completely eliminate the risk of recurrence caused by postoperative tumor cell reimplantation, microscopic residual lesions, or carcinoma in situ (Han *et al*., 2021; Dyrskjot *et al*., 2023). For this reason, postoperative intravesical instillation therapy has become an important strategy for reducing recurrence and delaying disease progression (Holzbeierlein *et al.*, 2024; Han *et al.*, 2021).

Commonly used intravesical agents include mitomycin, epirubicin and gemcitabine (Han *et al*., 2021; Chiujdea *et al*., 2024). Previous studies have suggested that gemcitabine may reduce recurrence risk and improve tolerability in selected NMIBC populations and meta-analyses have reported that, compared with mitomycin, gemcitabine may reduce recurrence and chemical cystitis in some clinical settings (Cheng *et al*., 2023; Matloubieh *et al*., 2024). Gemcitabine-based intravesical regimens have also attracted increasing attention in patients with intermediate- and high-risk NMIBC, particularly in settings of Bacillus Calmette-Guerin (BCG) shortage or BCG ineligibility; BCG failure represents a separate salvage setting and was not evaluated in the present treatment-naive cohort (Cheng *et al.*, 2023; Chiujdea *et al.*, 2024; Matloubieh *et al.*, 2024; Michael *et al.*, 2026). In recent years, induction-maintenance intravesical

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regimens have been applied in selected NMIBC populations. Several studies have suggested that maintenance instillation after induction therapy may improve recurrence-free survival and treatment continuity (McElree *et al*., 2022; Ben-David *et al*., 2024), but direct evidence comparing induction-maintenance intravesical gemcitabine monotherapy with conventional intravesical mitomycin remains limited and concentration-related interpretation and long-term economic evaluation are still insufficient (Ben-David *et al.*, 2024; McElree *et al.*, 2022; Kawada *et al.*, 2023; Hentschel *et al.*, 2022).

Accordingly, the present study retrospectively analyzed the clinical efficacy and safety of induction-maintenance intravesical gemcitabine versus conventional intravesical mitomycin after surgery in patients with intermediate- and selected high-risk NMIBC. This study examined longitudinal oncological outcomes, urinary and serum concentration indicators, treatment completion, adverse events and direct medical costs in a propensity score-matched cohort. The novelty of this study lies in the integrated evaluation of clinical outcomes, concentration-related indicators, safety and exploratory cost-utility findings within the same real-world NMIBC cohort, rather than in claiming a new drug combination or superiority over BCG. These findings may provide mitomycin-comparator evidence for postoperative adjuvant intravesical chemotherapy, while conclusions for high-risk NMIBC should remain limited because BCG was not included as a comparator.

MATERIALS AND METHODS

Study design and participants

This was a retrospective cohort study using propensity score matching (PSM). Patients with NMIBC who underwent TURBT at Affiliated Hospital of North Sichuan Medical College between January 2022 and October 2023 were included as the study population. Follow-up records were reviewed through 31 October 2025 and the analysis dataset was finalized after verification of recurrence, treatment completion and cost records. According to the postoperative adjuvant instillation regimen, patients were divided into the induction-maintenance intravesical gemcitabine group (observation cohort) and the conventional intravesical mitomycin group (control cohort). The study protocol was reviewed and approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (approval No. 2025ER110-1). Because this retrospective study used de-identified clinical records, the ethics committee waived the requirement for additional written informed consent for data analysis.

Inclusion and exclusion criteria

Inclusion criteria: patients were pathologically diagnosed with primary NMIBC after surgery and met the intermediate- or high-risk criteria of the European Organization for Research and Treatment of Cancer (EORTC)/European Association of Urology risk-stratification framework, as referenced in the 2024 EAU guideline update (Gontero *et al*., 2024). Patients were required to be 18 to 80 years old, regardless of sex and to have undergone TURBT for the first time without receiving any form of antitumor treatment before surgery. The upper age limit reflected the institutional protocol for standardized intravesical chemotherapy and follow-up, but its potential impact on generalizability to very elderly NMIBC patients is acknowledged in the Limitations section. Patients also needed to complete standardized postoperative intravesical chemotherapy, with a treatment completion rate of at least 80% and to provide complete clinical and follow-up data, with a minimum follow-up duration of 24 months.

PSM

PSM was performed using 1:1 nearest-neighbor matching without replacement, with the matching order randomized before matching. The treatment cohort (observation cohort versus control cohort) was used as the dependent variable in a prespecified main-effects logistic regression model. Clinically relevant pretreatment covariates were entered as independent variables, including age, sex, body mass index (BMI), smoking history, tumor size, tumor number, tumor grade, tumor stage, concomitant carcinoma in situ and Charlson comorbidity index. Tumor size was analyzed as a continuous variable and categorized when required; tumor number was categorized as single or multiple; tumor grade was defined according to the WHO 2004/2016 low-grade/high-grade classification; and tumor stage was assigned according to routine TNM pathological reporting. Drinking history was retained only as a descriptive baseline variable and was not entered into the propensity-score model because it was not prespecified as a recurrence-related confounder. Primary onset was not entered into the model because all enrolled patients were primary, treatment-naïve cases by definition. Operative time, intraoperative blood loss and postoperative hospital stay were presented descriptively but were not included in the propensity-score model because they were perioperative or post-treatment variables rather than pretreatment covariates. The caliper width was set at 0.05 on the propensity-score scale and covariate balance after matching was assessed using standardized mean differences (SMDs), with SMD<0.1 considered excellent balance and SMD<0.2 considered acceptable balance. Among 294 potential candidates, 100 pairs of patients were successfully matched.

Treatment regimens

The observation cohort received induction-maintenance intravesical therapy with gemcitabine hydrochloride for injection at a dose of 1000 mg per dose, dissolved in 50 mL of 0.9% sodium chloride injection. The instillation

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regimen consisted of two stages: induction and maintenance. The first instillation was performed immediately after surgery when clinically appropriate and when bladder perforation or extensive resection was not suspected. Subsequent induction instillation was started after postoperative recovery according to the institutional protocol, administered once weekly for 8 sessions and then maintained monthly from the completion of induction until 12 months after TURBT. The immediate postoperative instillation was recorded separately from the scheduled induction course.

The control cohort received conventional intravesical therapy with mitomycin for injection at a dose of 40 mg each time, dissolved in 50 mL of 0.9% sodium chloride injection according to the institutional comparator regimen and the treatment frequency was the same as that used for gemcitabine. Available clinical records did not allow uniform reconstruction of pre-instillation urine pH management in all mitomycin-treated patients; therefore, the absence of standardized urine pH documentation was acknowledged as a limitation when interpreting the comparator protocol. Patients were instructed to empty the bladder before instillation. A disposable urethral catheter was inserted, the drug solution was slowly infused and the catheter was then removed. Patients were then asked to rotate through the supine, left lateral, right lateral and prone positions, maintaining each position for 15 minutes. The planned intravesical retention time was 60 minutes for both cohorts, per the institutional protocol and patients were instructed to avoid excessive fluid intake before instillation when clinically feasible. After the retention period, patients were asked to void and increase fluid intake to facilitate the elimination of residual drug.

During treatment, adverse reactions were graded according to CTCAE v5.0. Patients with grade I–II bladder irritation were given symptomatic treatment, including hydration and clinically indicated urinary alkalization. For patients with grade III or higher adverse reactions, instillation was suspended for 1–2 sessions and resumed only after symptoms improved to CTCAE grade 0–1 and blood counts and renal and hepatic function were clinically acceptable. Intravesical treatment was permanently discontinued in cases of CTCAE grade 3–4 bone marrow suppression, serious allergic reaction, biopsy-proven recurrence, progression to muscle-invasive disease, severe hemorrhagic cystitis, serious adverse events, or patient withdrawal.

Observation indicators and detection methods

Clinical efficacy outcomes

The primary endpoint of this study was the 24-month postoperative recurrence-free survival (RFS) rate. Secondary endpoints included tumor recurrence rates at 3, 6, 12 and 18 months after surgery, as well as recurrence-free survival time. Tumor recurrence was defined as pathologically confirmed urothelial carcinoma detected during follow-up, including papillary recurrence, carcinoma in situ, prostatic urethral recurrence, or upper urinary tract urothelial recurrence when clinically confirmed. Recurrence-free survival was calculated from the date of TURBT to the date of first pathologically confirmed recurrence or last documented follow-up. Patients without recurrence were right-censored at the last follow-up, whereas deaths unrelated to bladder cancer and progression to muscle-invasive disease were recorded as censoring events in sensitivity interpretation.

In routine clinical practice, cystoscopic surveillance was recommended every 3 months for the first 2 years after surgery, then every 6 months thereafter. Actual follow-up dates were extracted from medical records and deviations from the planned schedule were recorded when available. At each follow-up visit, routine urine testing, liver and renal function tests and urinary system ultrasonography were also performed. For patients with suspected recurrence, computed tomography urography (CTU) was further performed to clarify the diagnosis.

Urinary and serum concentration indicators

Urine samples were collected at 0.5, 1, 2 and 4 hours after the 1st and 6th instillations in both groups and peripheral venous blood samples were collected at 1 hour after the 1st instillation for descriptive comparison of serum concentrations at a prespecified time point. Systemic Cmax, Tmax, AUC, or elimination half-life were not derived from this single serum sample. High-performance liquid chromatography (HPLC) was used to measure drug concentrations in urine and serum according to the institutional bioanalytical procedure (Eksborg *et al*., 1983; Freeman *et al*., 1995).. Testing was performed using a high-performance liquid chromatograph (Agilent), with matched chromatographic columns and reagent kits (Waters). Calibration standards and quality-control samples were included in each analytical batch and samples were reanalyzed when chromatographic separation or quality-control acceptance was unsatisfactory (Viswanathan *et al*., 2007). The calibration curves were linear over the prespecified analytical ranges, with correlation coefficients above 0.995; intra- and inter-day precision was controlled within 10%; and extraction recovery remained within the acceptable range for clinical bioanalytical testing. For urine samples, peak concentration, apparent urinary concentration-decay half-life and the sixth-to-first instillation peak concentration ratio were summarized descriptively from the recorded concentration data. Peak concentration was defined as the highest observed value, the apparent concentration-decay half-life was estimated from the log-linear decline in urinary concentration as $t1/2=\ln 2/k$ and the sixth-to-first ratio was calculated as $C_{max,6}/C_{max,1}$ (Dalton *et al*., 1991; Noe, 2020).

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Table 1: Baseline characteristics and post-matching covariate balance after PSM.

	Observation cohort, n (%) or mean ± SD (n=100)	Control cohort, n (%) or mean ± SD (n=100)	Statistics	*p* value	SMD
Age (years)	62.38±8.75	62.13±8.97	0.200	0.842	0.028
Male	72	69	0.216	0.642	0.066
BMI (kg/m²)	24.30±3.12	24.10±3.21	0.456	0.649	0.063
Smoking	56	52	0.322	0.570	0.080
Drinking	39	36	0.192	0.661	0.062
Tumor size (cm)	2.30±0.80	2.20±0.81	0.869	0.386	0.124
Tumor number ⩾3	32	30	0.094	0.76	0.043
High-grade tumor	64	59	0.528	0.468	0.103
T1 stage tumor	48	43	0.504	0.478	0.101
Concomitant carcinoma in situ	25	20	0.717	0.397	0.120
Charlson comorbidity index	1.24±0.83	1.17±0.89	0.576	0.566	0.081
TURBT operative time (min)	45.23±12.34	44.48±12.16	0.433	0.666	0.061
Intraoperative blood loss (ml)	32.55±15.71	31.83±15.27	0.329	0.743	0.046
Postoperative hospital stay (days)	3.19±1.13	3.09±1.17	0.613	0.541	0.087

Note: Values are presented as n (%) for categorical variables and mean ± standard deviation for continuous variables. Operative time, intraoperative blood loss and postoperative hospital stay are presented descriptively and were not used in the propensity-score model. The available revision dataset contained matched patients only; therefore, Table 1 reports post-matching balance.

Safety and quality-of-life indicators

All adverse events occurring during intravesical treatment were recorded and graded according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 5.0 (CTCAE v5.0) (National Cancer Institute, 2017). The overall incidence of adverse events, the incidence of local adverse events (bladder irritation, hematuria, urinary frequency and urgency), the incidence of systemic adverse events (bone marrow suppression, gastrointestinal reactions and abnormal liver function) and treatment discontinuation due to adverse events were calculated. Because detailed severity strata, event duration and causality categories were not uniformly available in the retrospective dataset, the safety analysis was mainly based on recorded local, systemic, overall and discontinuation events. At 1, 3 and 6 months after surgery, maximum bladder capacity was measured using a urodynamic system (Laborie). The International Prostate Symptom Score (IPSS) (Yao & Green, 2022) was used as a descriptive measure of lower urinary tract symptoms after intravesical therapy, rather than as a direct toxicity scale for chemotherapy-induced cystitis.

Pharmacoeconomic indicators

Direct medical costs in the two groups were calculated from the perspective of the healthcare system (Sanders *et al*., 2016). These costs included drug acquisition, instillation procedure-related costs, cystoscopic surveillance and follow-up examinations, imaging when clinically indicated, adverse-event management and retreatment after tumor recurrence. Costs were extracted from hospital billing records and expressed in Chinese yuan. Quality-adjusted life years (QALYs) were calculated using the EQ-5D-3L scale with utility values derived from the Chinese population-based value set (Zhuo *et al*., 2018), based on available QALY records at 12 and 24 months after surgery. Because baseline utility was not available in the retrospective dataset, the QALY estimates and cost-utility findings were interpreted as exploratory. The incremental cost-utility result was interpreted on the cost-effectiveness plane; when the gemcitabine group showed lower costs and higher QALYs, the regimen was described as dominant rather than solely by a negative ICUR value.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 software. Normally distributed continuous variables were expressed as mean ± standard deviation; between-group differences were evaluated using the independent-samples t test, while longitudinal outcomes across different time points were compared using repeated-measures analysis of variance, with treatment group, time and the group-by-time interaction assessed when repeated measurements were available. Count data were expressed as frequency (percentage) and between-group differences were analyzed using the χ^2 test or Fisher's exact test when expected cell counts were insufficient. Risk differences with 95% confidence intervals were added for key adverse-event comparisons. Exploratory uncertainty in the cost-utility analysis was assessed using bootstrap resampling (Briggs *et al*., 1997). All statistical tests were two-sided and $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics and balance after PSM

After matching, a total of 200 eligible patients with intermediate- and selected high-risk NMIBC were included in the final analysis; the SMDs for all baseline characteristics in the observation and control cohorts were less than 0.2, indicating acceptable between-group balance (Table 1).

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Table 2: Comparison of tumor recurrence and recurrence-free survival at different postoperative time points.

	Observation cohort, n (%) or mean ± SD (n=100)	Control cohort, n (%) or mean ± SD (n=100)	Statistic	*p* value
Recurrence rate at 3 months after surgery	3 (3.0)	5 (5.0)	Fisher's exact test	0.721
Recurrence rate at 6 months after surgery	7 (7.0)	14 (14.0)	2.607	0.106
Recurrence rate at 12 months after surgery	12 (12.0)	26 (26.0)	6.368	0.012
Recurrence rate at 18 months after surgery	17 (17.0)	32 (32.0)	6.082	0.014
Recurrence rate at 24 months after surgery	21 (21.0)	38 (38.0)	6.948	0.008
Recurrence-free survival time (months)	21.65±4.27	18.35±5.76	4.602	<0.001

Note: Values are presented as n (%) for categorical variables and mean ± standard deviation for continuous variables. Fisher's exact test was used when expected cell counts were insufficient for the chi-square test; otherwise, the chi-square test statistic is reported.

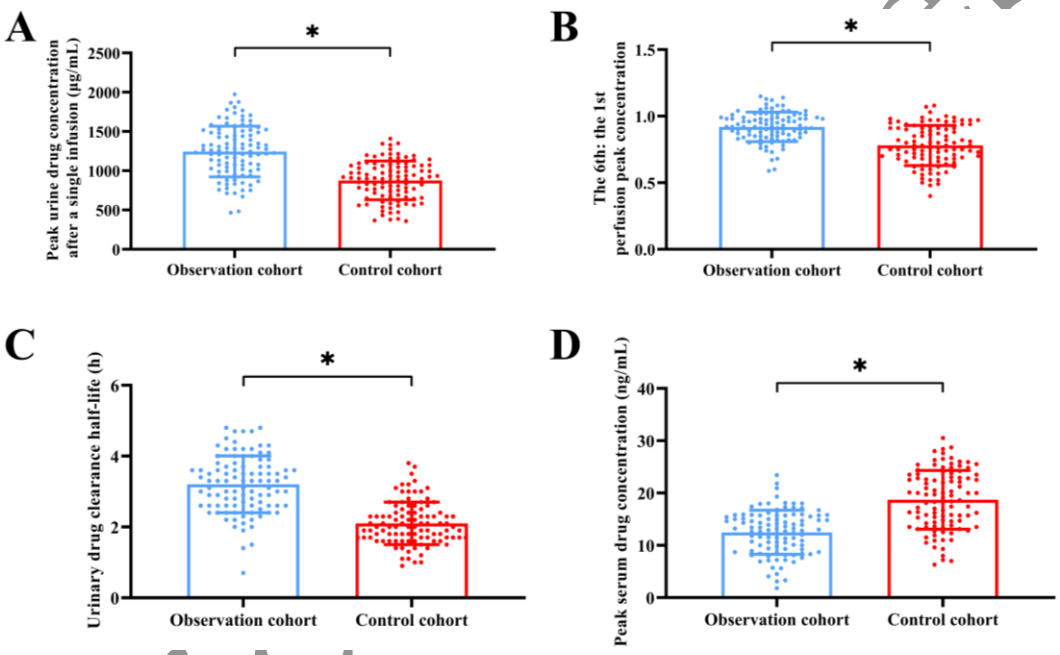


Fig. 1: Descriptive urinary and serum concentration indicators of induction-maintenance intravesical gemcitabine versus conventional mitomycin instillation. (A) Urinary peak drug concentration after intravesical instillation; (B) sixth-to-first instillation peak concentration ratio; (C) apparent urinary elimination half-life after intravesical instillation; (D) 1-hour serum drug concentration after intravesical instillation. *p<0.05.*

Comparison of clinical efficacy outcomes at different time points

In the early postoperative period, namely at 3 and 6 months, the recurrence rates were similar between the two groups (p>0.05). However, from 12 months after surgery, the recurrence rate was lower in the gemcitabine cohort than in the mitomycin cohort (12.0% vs. 26.0%, p=0.012) and this difference persisted until the end of follow-up (21.0% vs. 38.0%, p=0.008). In addition, patients in the gemcitabine cohort had a longer mean recurrence-free survival time than those in the mitomycin cohort (21.65±4.27 vs. 18.35±5.76 months, p<0.001) (Table 2).

Comparison of urinary and serum concentration indicators

After a single instillation, the gemcitabine cohort showed higher urinary peak concentration (1245.60±323.02 vs. 876.30±246.93 μg/mL, p<0.001) and a longer apparent urinary elimination half-life (3.21±0.80 vs. 2.10±0.60 h, p<0.001) than the mitomycin cohort. After six consecutive instillations, the sixth-to-first instillation peak concentration ratio was higher in the gemcitabine cohort than in the mitomycin cohort (3.15±0.55 vs. 2.05±0.50, p<0.001), suggesting a smaller reduction in urinary peak concentration. The gemcitabine cohort also showed a lower 1-hour serum concentration than the mitomycin cohort (12.50±4.23 vs. 18.70±5.62 ng/ml, p<0.001), but this finding was interpreted descriptively and not as direct proof of superior systemic safety or tissue exposure. Mean residence time and tissue penetration depth were not interpreted as validated endpoints because they were not supported by direct tissue drug quantification or full systemic pharmacokinetic modeling (Fig. 1).

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Table 3: Dynamic changes in therapeutic outcomes across different intravesical instillation cycles.

	Observation cohort, n (%) or mean ± SD (n=100)	Control cohort, n (%) or mean ± SD (n=100)	Statistic	*p* value
Recurrence rate during induction phase	5 (5.0)	8 (8.0)	0.74	0.39
Recurrence rate in the first 6 months of the maintenance phase	4 (4.0)	11 (11.0)	Fisher's exact test	0.105
Recurrence rate in the second 6 months of the maintenance phase	12 (12.0)	19 (19.0)	1.871	0.171
Completion rate of instillation course	94 (94.0)	85 (85.0)	4.31	0.038

Note: Values are presented as n (%) for categorical variables and mean ± standard deviation for continuous variables. Fisher's exact test was used when expected cell counts were insufficient for the chi-square test; otherwise, the chi-square test statistic is reported.

Table 4: Comparison of adverse events and treatment discontinuation between the induction-maintenance intravesical gemcitabine and conventional intravesical mitomycin cohorts.

Indicator	Observation cohort, n (%) (n=100)	Control cohort, n (%) (n=100)	Statistic	*p* value
Overall incidence of adverse events	38 (38.0)	56 (56.0)	6.503	0.011
Incidence of local adverse events	32 (32.0)	48 (48.0)	5.333	0.021
Incidence of systemic adverse events	8 (8.0)	16 (16.0)	3.03	0.082
Incidence of adverse events during induction vs maintenance phase (observation cohort)	26 (26.0) vs 12 (12.0)	-	6.368	0.012
Incidence of adverse events during induction vs maintenance phase (control cohort)	-	38 (38.0) vs 18 (18.0)	9.921	0.002
Treatment discontinuation rate due to adverse events	6 (6.0)	15 (15.0)	4.31	0.038

Note: Values are presented as n (%).

Dynamic changes in efficacy across different instillation cycles

During the induction and maintenance phases, the two groups had similar dosing frequencies and no significant difference in recurrence rate was observed ($p>0.05$). Moreover, the completion rate of the instillation course was higher in the gemcitabine cohort than in the mitomycin cohort (94.0% vs. 85.0%, $p=0.038$) (Table 3).

Comparison of safety indicators

The overall adverse-event rate was lower in the gemcitabine cohort than in the mitomycin cohort (38.0% vs. 56.0%; risk difference, −18.0%; 95% CI, −31.0% to −4.4%; $p=0.011$) and local adverse events were also less frequent (32.0% vs. 48.0%; risk difference, −16.0%; 95% CI, −29.4% to −2.6%; $p=0.021$). However, there was no statistically significant difference in systemic adverse events between the two groups (8.0% vs. 16.0%; risk difference, −8.0%; 95% CI, −17.5% to 1.5%; $p=0.082$). In both groups, adverse events were concentrated mainly in the induction phase, while their incidence decreased during the maintenance phase. The proportion of patients who discontinued treatment because of adverse events was lower in the gemcitabine cohort than in the mitomycin cohort (6.0% vs. 15.0%, $p=0.038$) (Table 4).

Comparison of bladder function and quality of life

Follow-up of bladder function showed that maximum bladder capacity gradually recovered after surgery in both groups, but the recovery was faster in the gemcitabine cohort. At 1, 3 and 6 months after surgery, maximum bladder capacity was higher in the gemcitabine cohort than in the mitomycin cohort, while IPSS at 1 and 3 months was lower and the 6-month QoL score was better in the gemcitabine cohort ($p<0.05$), suggesting milder lower urinary tract symptoms and better postoperative quality-of-life recovery (Fig. 2).

Comparison of direct medical cost components

The 24-month total direct medical cost was lower in the gemcitabine cohort than in the mitomycin cohort (8724.29±527.81 vs. 16251.48±756.10 CNY, $p<0.001$), with lower drug costs, follow-up examination costs, adverse-event management costs and retreatment costs after recurrence ($p<0.05$), whereas instillation procedure-related costs were similar between the two groups ($p>0.05$) (Fig. 3).

Exploratory cost-utility analysis

Cost-utility analysis showed that QALYs were higher in the gemcitabine cohort than in the mitomycin cohort ($p<0.05$).

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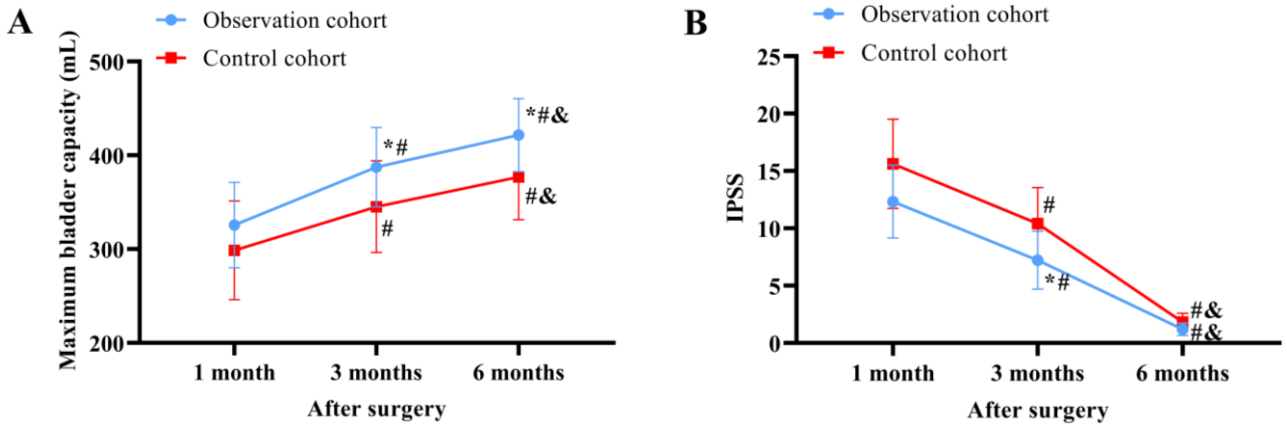


Fig. 2: Postoperative bladder function and lower urinary tract symptom recovery after intravesical treatment. (A) Changes in maximum bladder capacity at 1, 3 and 6 months after surgery; (B) changes in IPSS at 1 and 3 months after surgery. #p<0.05 compared with 1 month after surgery, &p<0.05 compared with 3 months after surgery and p<0.05 compared with the mitomycin cohort.

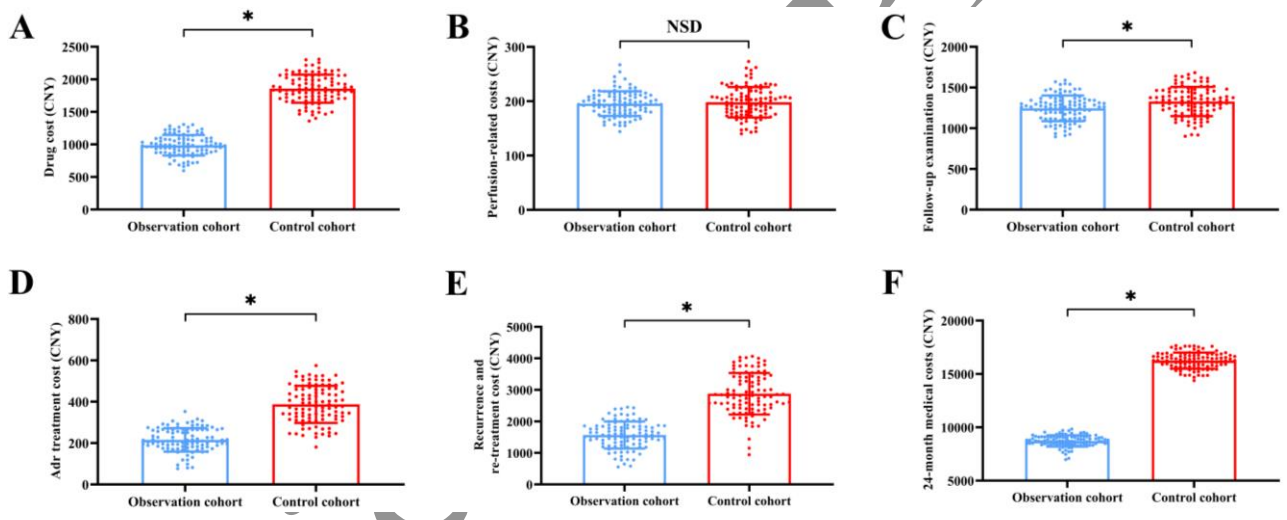


Fig. 3: Direct medical cost components over 24 months in the induction-maintenance gemcitabine and conventional mitomycin cohorts. (A) Drug costs; (B) instillation procedure-related costs; (C) follow-up examination costs; (D) adverse reaction management costs; (E) retreatment costs after tumor recurrence; (F) total direct medical costs over 24 months. p<0.05; NS, p>0.05.

Table 5: Comparison of QALYs between the two cohorts.

Indicator	Observation cohort, mean ± SD (n=100)	Control cohort, mean ± SD (n=100)	t-test	*p* value
QALY at 12 months	0.81±0.11	0.75±0.15	3.449	<0.001
QALY at 24 months	1.58±0.21	1.36±0.28	6.230	<0.001

Note: Mean ± standard deviation for continuous variables.

The gemcitabine cohort had lower total direct medical costs and higher 24-month QALYs than the mitomycin cohort (cost difference, approximately −7528 CNY; QALY difference, approximately 0.220), indicating a dominant cost-saving pattern in this exploratory analysis. Bootstrap analysis supported this interpretation, with sampled estimates falling in the lower-cost and higher-QALY quadrant (Table 5).

DISCUSSION

The between-group difference became more apparent after 12 months rather than during the early postoperative period. This pattern suggested that the observed benefit may be related to cumulative maintenance treatment, treatment completion and delayed recurrence prevention,

rather than immediate eradication of residual tumor cells alone..As pharmacological background, gemcitabine is a deoxycytidine analogue that requires intracellular activation and inhibits DNA synthesis; however, the present study did not measure intracellular drug activation, target inhibition, apoptosis markers, DNA-repair markers, or resistance-related genetic variants and mechanistic explanations should therefore be interpreted only as contextual evidence rather than as directly demonstrated findings (Han *et al.*, 2022).

The urinary and serum concentration results showed different descriptive exposure patterns between the two cohorts. Because gemcitabine and mitomycin were administered at different mass doses, serum sampling was limited to one prespecified time point and direct bladder-wall drug quantification was not performed, these findings should not be interpreted as direct evidence of intrinsic pharmacokinetic superiority, superior tissue exposure, or a favorable local therapeutic index (Li *et al.*, 2024). Recent studies on intravesical drug delivery indicate that urinary dilution, voiding-related washout, the urothelial barrier, mucosal permeability, concentration, retention time and mode of administration can all influence local drug exposure (Marchenko & Trushina, 2023).

In terms of safety, the lower aggregate adverse-event rate suggested better observed tolerability in this cohort; however, this interpretation should be considered with caution because detailed severity strata and causality data were not uniformly available. The pharmacoeconomic analysis suggested a dominant cost-saving pattern for gemcitabine in this matched cohort, but this finding should be viewed as exploratory single-center evidence and should not be used alone to support broad clinical adoption, clinical pathway revision, or reimbursement decisions.

Finally, the exploratory pharmacoeconomic analysis suggested that induction-maintenance intravesical gemcitabine was economically favorable in this cohort; however, this finding requires confirmation before it can inform routine clinical use.

Limitations

However, although PSM was used to control known baseline confounders, residual confounding from unmeasured factors and information bias related to retrospective data cannot be fully excluded. Second, this was a single-center study with a relatively limited sample size and the upper age limit of 80 years may restrict generalizability to very elderly NMIBC patients. Third, the comparator was mitomycin rather than Bacillus Calmette-Guerin and therefore the findings should not be interpreted as evidence that gemcitabine is superior or non-inferior to BCG in high-risk NMIBC. Fourth, the requirement for treatment completion and complete 24-month follow-up data may have introduced selection or survivorship bias. Fifth, urinary and serum concentration indicators were analyzed descriptively; systemic multi-time-point pharmacokinetic modeling, direct bladder-wall drug quantification, tissue AUC measurement and validated tissue penetration assessment were not performed. In addition, routine H&E staining was not used to directly evaluate drug penetration. Sixth, pre-instillation urine pH management in the mitomycin cohort and detailed CTCAE severity strata were not uniformly documented in the retrospective dataset. Finally, the pharmacoeconomic analysis was exploratory because baseline utility, prospective health-state valuation, discounting and full probabilistic sensitivity analysis were not available. Further prospective studies with a BCG comparator, standardized pharmacokinetic sampling, direct tissue drug measurement and formal economic modeling are needed.

CONCLUSION

Induction-maintenance intravesical gemcitabine was associated with lower recurrence and better treatment completion than mitomycin in this matched cohort. However, because BCG was not included as a comparator and the concentration-related and economic analyses were exploratory, these findings should be interpreted as mitomycin-comparator evidence rather than as proof that gemcitabine is a preferred regimen for the overall high-risk NMIBC population.

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Authors' contributions

YG.L: Conceived and designed the study; JQ.G. and CM.W: Wrote and revised the manuscript; CL.T: Collected and analyzed data; D.L and J.H: Supervised the study; JQ.G and CM.W: Made equal contributions in this work as co-first authors. All authors read and approved the final submitted manuscript.

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Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Ethical approval

The study involving human subjects complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (approval No. 2025ER110-1). Because this retrospective study used de-identified clinical records, the requirement for additional written informed consent for data analysis was waived by the ethics committee. This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Consent to publish

All authors gave final approval of the version to be published.

Conflicts of interest

The authors report no conflict of interest.

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