

Original Article

Outcomes of maintenance BCG versus gemcitabine/docetaxel following BCG induction in NMIBC

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Objectives

To compare the oncologic outcomes and safety profiles of Bacillus Calmette–Guérin (BCG) versus gemcitabine/docetaxel (Gem/Doce) maintenance following BCG induction in treatment-naïve non-muscle-invasive bladder cancer (NMIBC).

Methods

We identified patients with treatment-naïve NMIBC who received induction BCG followed by maintenance BCG per the Southwest Oncology Group Cancer Research Network protocol or Gem/Doce monthly for 1 year (2016–2026). Oncological outcomes included recurrence-free survival (RFS), high-grade RFS, progression-free survival, and metastasis-free survival. Adverse events were systematically assessed to evaluate treatment tolerability.

Results

Overall, 128 patients received BCG induction followed by either BCG maintenance ($n = 98$; 76.6%) or Gem/Doce maintenance ($n = 30$; 23.4%). After a median follow-up of 75.0 months (interquartile range [IQR] 66.7–86.5) in the BCG group and 22.5 months (IQR 14.8–42.9) in the Gem/Doce group ($P < 0.001$), 3-year RFS (80.0% vs. 83.8%; $P = 0.8$), 3-year high-grade RFS (83.4% vs. 92.2%; $P = 0.7$), 3-year progression-free survival (90.0% vs. 96.6%; $P = 0.4$), and 3-year metastasis-free survival (96.8% vs. 100.0%; $P = 0.3$) were comparable between the BCG and Gem/Doce maintenance groups, respectively. Multivariable Cox regression analysis confirmed that Gem/Doce versus BCG maintenance was not associated with disease recurrence (hazard ratio 1.04; 95% confidence interval 0.39–2.83; $P > 0.9$). Overall, Gem/Doce maintenance was better tolerated, with fewer patients reporting adverse events (6.7% vs. 28%, $P = 0.02$) and no severe events observed during the maintenance phase. Limitations of the study include its retrospective design and the relatively small sample size of the Gem/Doce cohort.

Conclusion

Sequential Gem/Doce maintenance following BCG induction achieved oncologic outcomes comparable to those with BCG maintenance, with improved tolerability, highlighting its feasibility as an alternative in cases of BCG intolerance or shortage.

Keywords

non-muscle invasive bladder cancer, BCG, gemcitabine, docetaxel, induction, maintenance

Introduction

Non-muscle-invasive bladder cancer (NMIBC) accounts for approximately 75% of all bladder cancer (BC) diagnoses [1]. According to pathological characteristics, NMIBC is classified into low-risk, intermediate-risk (IR), high-risk, and very-high-risk groups for progression to muscle-invasive bladder cancer (MIBC) [2]. Beyond transurethral resection of the bladder tumour (TURBT), patients in the IR, high-

risk, and very-high-risk groups require adjuvant intravesical therapy with close bladder surveillance [2,3]. For the past five decades, Bacillus Calmette–Guérin (BCG) instillations has remained the gold standard for patients with high-risk and very-high-risk disease, with an induction phase, ideally followed by a 3-year maintenance regimen [4]. When properly administered, BCG is highly effective, with 1-year and 2-year recurrence-free survival (RFS) rates of 89% and 85% [5]. However, BCG faces two major limitations:

tolerability issues and recurrent shortages. In fact, only about 50% of patients complete therapy after 1 year because of high rates of adverse events or reduced adherence caused by the large number of sessions and treatment constraints [5]. Prospective studies have attempted dose [6] or schedule reductions [5,6], but these approaches resulted in lower efficacy than the standard protocol. Additionally, recent worldwide shortages have significantly reduced access to BCG [7,8]. These limitations have encouraged the development of alternative therapeutic strategies [9]. In this context, sequential intravesical gemcitabine/docetaxel (Gem/Doce) has emerged as a promising option, not only because of its effectiveness as a bladder-sparing therapy for BCG-unresponsive NMIBC [10] but also because of its accessibility and relatively low cost [11]. Nevertheless, although no prospective trial has yet reported comparative results between BCG and Gem/Doce in BCG-naïve NMIBC, retrospective studies have yielded conflicting findings. Several series have suggested that a single-agent Gem/Doce regimen may be less effective than standard BCG [12–14], whereas others have reported favourable oncological outcomes and even potential superiority of Gem/Doce in selected patient populations [15,16]. Consequently, the place of Gem/Doce within the therapeutic landscape of BCG-naïve NMIBC remains unclear. In this context, a combined approach, including BCG induction followed by Gem/Doce maintenance, has emerged as a potential strategy to address BCG shortages while maintaining high oncological efficacy. We previously reported comparable short-term outcomes with this approach versus standard BCG maintenance [17]. However, this pilot analysis was limited by a small, matched sample size and relatively early outcomes, warranting further validation in a larger cohort with more mature follow-up. Against this backdrop, the present study aimed to evaluate the long-term effectiveness and safety of standard BCG induction and maintenance versus BCG induction followed by sequential Gem/Doce maintenance in patients with treatment-naïve NMIBC.

Patients and Methods

Study Design and Data Collection

This single-centre retrospective cohort study included all consecutive patients with BCG-naïve NMIBC treated with BCG induction followed by BCG or Gem/Doce maintenance at our institution between 2016 and 2026. Patients treated with other intravesical agents, those with incomplete induction, and those receiving a second induction course were excluded. Following approval by the institutional review board (MSH IRB #23–01201), all relevant clinical, pathological, oncological outcomes and treatment tolerance data were retrospectively collected.

Bladder Instillations Protocol

Induction Phase

All patients received a full BCG induction phase, defined as completing five or six weekly intravesical instillations [3]. For each treatment, one vial of BCG (Organon Teknika Co.) was diluted in 50 mL of normal saline and instilled into the bladder. Patients were instructed to retain the solution for 60–90 min before voiding. At 6 weeks after the final induction dose, cystoscopy was performed to assess for bladder recurrence. Only patients with no evidence of disease recurrence proceeded to maintenance therapy.

Maintenance Phase

Maintenance therapy consisted of either BCG or Gem/Doce, depending on BCG availability and physician or patient preference.

- BCG maintenance: Maintenance regimens were given for 1 year, with three instillations once a week at 3, 6, and 12 months according to the Southwest Oncology Group protocol and American Urological Association guidelines [3], following the same dosing and instillation procedures described above. All patients were planned to receive full-dose maintenance; no dose reduction or split-dose schedule was used.
- Gem/Doce maintenance: Following BCG induction, patients received monthly intravesical instillations for 12 months. Each session consisted of gemcitabine 2 g administered via a 16 Fr catheter and retained for 60 min, immediately followed by docetaxel 37.5 mg in 50 mL saline retained for an additional 60 min.

Follow-Up

After BCG induction, patients underwent an initial surveillance cystoscopy in the office using a white-light cystoscope 6 weeks after the last induction dose. Subsequent bladder surveillance was carried out according to risk stratification and American Urological Association guidelines [3]. If tumour recurrence was detected during follow-up cystoscopy, patients underwent TURBT, urine cytology, and abdominal and pelvic imaging. Histological examination of TURBT specimens was performed to confirm the tumour stage and grade. Random bladder biopsies were taken in cases with negative cystoscopic findings but positive urine cytology.

Outcomes

First, we aimed to report disease recurrence among patients treated with BCG maintenance and those treated with Gem/Doce maintenance. For this analysis, disease recurrence was defined as the documented occurrence of a pathologically

confirmed low-grade or high-grade (HG) bladder tumour after TURBT. Time to recurrence was defined as the interval between the start of the induction therapy and the first documented recurrence.

Second, we aimed to compare HG recurrence-free survival (HG-RFS), progression-free survival (PFS), and metastasis-free survival (MFS) between the two groups. For these analyses, outcomes were defined as follows: HG RFS was defined as the absence of pathologically confirmed HG tumours following induction therapy, progression was defined as a pathologically confirmed increase in tumour stage and/or grade following induction treatment, and metastasis was defined as disease confirmed either pathologically or by imaging.

Finally, overall tolerance during induction and maintenance regimen was also evaluated in both groups, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 classification.

Statistical Analysis

Medians with interquartile ranges (IQRs) were reported for non-normally distributed continuous variables and compared between groups using Student's *t*-test. Categorical variables were presented as frequencies with proportions and compared between groups using the chi-squared test. The Kaplan–Meier method and log-rank test were used to compare oncological outcomes including any RFS, HG RFS, PFS, and MFS according to the maintenance regimens (BCG vs. Gem/Doce). For PFS analyses, both overall PFS and stage-specific PFS were evaluated, including progression to NMIBC (<T2) and progression to MIBC or beyond ($\geq$ T2). Median follow-up time was estimated using the reverse Kaplan–Meier method. Then, univariable Cox regression analyses were conducted to identify covariates associated with disease recurrence, yielding hazard ratios (HRs) and 95% confidence intervals (CIs). Only significant covariates and the maintenance regimen group were included in multivariable Cox regression models to identify the independent predictors of disease recurrence. The data were considered statistically significant at the 95% CI ($P < 0.05$). All statistical analyses were performed using R 4.5.1 software.

Results

Overall, 128 patients with BCG-naïve NMIBC treated with BCG induction, followed by either BCG maintenance ($n = 98$; 76.6%) or Gem/Doce maintenance ($n = 30$; 23.4%), were included in this study. The median age of the cohort was 70 years, and 79% of patients were male. According to the 2024 European Association of Urology risk classification, most patients had high risk disease (64%), 28% had IR, and 7.8% had very high risk disease. Patients treated with Gem/

Doce maintenance were significantly older (73.5 vs. 68.5 years; $P = 0.05$) and had a higher American Society of Anesthesiologists score (>2 : 73% vs. 51%; $P = 0.03$) than those treated with BCG induction and maintenance. Other clinical and pathological characteristics were comparable between the two groups (Table 1).

Oncological Outcomes

After a median follow-up of 75.0 months (IQR 66.7–86.5) in the BCG group and 22.5 months (IQR 14.8–42.9) in the Gem/Doce group ($P < 0.001$), 28 patients (21.9%) experienced disease recurrence, including 21 (16.4%) HG NMIBC, and 15 (11.7%) patients had disease progression. Among patients who experienced disease progression, nine (7%) progressed to muscle-invasive stage or beyond, four (3.1%) progressed from Ta to T1 disease, and two (1.6%) experienced grade progression from low-grade to HG disease. Overall, 11 patients (8.6%) died, including three (2.3%) from bladder cancer.

Regarding disease recurrence, Kaplan–Meier curves indicated that 3-year RFS was similar between BCG and Gem/Doce maintenance groups (80.0%, 95% CI 72.1–88.8 vs. 83.8%, 95% CI 67.3–100.0; $P = 0.8$; Fig. 1). Multivariable Cox regression analysis identified multifocality (HR 4.41; 95% CI 2.06–9.44; $P < 0.001$; Table 2) and tumour size ≥ 3 cm (HR 3.22; 95% CI 1.24–8.39; $P = 0.02$; Table 2) as the only independent predictors of disease recurrence. Maintenance regimen was not associated with recurrence (HR 1.04; 95% CI 0.39–2.83; $P > 0.9$; Table 2).

Regarding disease progression, Kaplan–Meier analysis showed similar 3-year overall PFS between the two groups (90.0%, 95% CI 84.1–96.5 vs. 96.6%, 95% CI 90.1–100.0; $P = 0.4$; Fig. 2). The 3-year PFS for NMIBC (<T2) was comparable between the two groups (96.4%, 95% CI 92.6–100.0 vs. 96.6%, 95% CI 90.1–100.0; $P = 0.9$; Fig. S1). Similarly, the 3-year PFS for MIBC or beyond ($\geq$ T2) did not differ significantly between groups (93.5%, 95% CI 88.7–98.7 vs. 100.0%, 95% CI 100.0–100.0; $P = 0.2$; Fig. S2). Other oncological outcomes, including 3-year HG RFS (83.4%, 95% CI 76.1–91.5 vs. 92.2%, 95% CI 82.2–100.0; $P = 0.7$; Fig. 3) and 3-year MFS (96.8%; 95% CI 93.3–100.0 vs. 100.0%, 95% CI 100.0–100.0; $P = 0.3$; Fig. S3) were also similar between BCG and Gem/Doce maintenance.

Adverse Effects

Tolerance in the two groups was assessed during the induction and maintenance phases (Table 3). During induction, 18 patients (18%) in the BCG group and three (10%) in the Gem/Doce group reported AEs ($P = 0.4$). During the maintenance phase, the number of patients

Table 1 Baseline characteristics of patients treated with Bacillus Calmette–Guérin (BCG; induction and maintenance) and those treated with BCG induction followed by gemcitabine/docetaxel (Gem/Doce) maintenance for non-muscle-invasive bladder cancer.

Characteristics	Overall (n = 128; 100%)	BCG maintenance (n = 98; 76.6%)	Gem/Doce maintenance (n = 30; 23.4%)	P-value
Age, year	70.0 (63.0–77.0)	68.5 (62.2–75.8)	73.5 (63.2–80.0)	0.05
Sex				
Male	101 (79)	76 (78)	25 (83)	0.5
Female	27 (21)	22 (22)	5 (17)	
ASA				
≤2	56 (44)	48 (49)	8 (27)	0.03
>2	72 (56)	50 (51)	22 (73)	
BMI, kg/m ²	26.6 (24.3–29.8)	26.6 (24.6–29.9)	26.0 (23.1–28.6)	0.1
Smoking history				
Current	10 (7.8)	8 (8.2)	2 (6.7)	0.9
Former	75 (59)	56 (57)	19 (63)	
Never	43 (34)	34 (35)	9 (30)	
UTUC history				
No	122 (95)	94 (96)	28 (93)	0.6
Yes	6 (4.7)	4 (4.1)	2 (6.7)	
pT stage				
pTa	46 (36)	39 (40)	7 (23)	0.1
pT1	53 (41)	36 (37)	17 (57)	
pTis alone	29 (23)	23 (23)	6 (20)	
Presence of CIS				
No	84 (66)	62 (63)	22 (73)	0.3
Yes	44 (34)	36 (37)	8 (27)	
Grade stage				
Low-grade	7 (5.5)	5 (5.1)	2 (6.7)	0.7
High-grade	121 (95)	93 (95)	28 (93)	
Tumour focality				
Unifocal	90 (70)	70 (71)	20 (67)	0.6
Multifocal	38 (30)	28 (29)	10 (33)	
Tumour size				
<3 cm	111 (87)	88 (90)	23 (77)	0.1
≥3 cm	17 (13)	10 (10)	7 (23)	
Histologic variant				
No	123 (96)	95 (97)	28 (93)	0.3
Yes	5 (3.9)	3 (3.1)	2 (6.7)	
EAU risk classification				
Intermediate	36 (28)	30 (31)	6 (20)	0.5
High	82 (64)	61 (62)	21 (70)	
Very high	10 (7.8)	7 (7.1)	3 (10)	
Complete maintenance				
Yes	95 (74)	74 (76)	21 (70)	0.6
No	33 (26)	24 (24)	9 (30)	
Maintenance instillations	12 (9.75–12)	12 (9.25–12)	12 (10.2–12)	>0.9
Follow-up, months	65.8 (53.8–73.6)	75.0 (66.7–86.5)	22.5 (14.8–42.9)	<0.001

Data are presented as median (interquartile range) or n (%) unless otherwise indicated. Bold values indicate statistically significant p-values.

ASA, American Society of Anesthesiologists; BMI, body mass index; CIS, carcinoma in situ; EAU, European Association of Urology; UTUC, upper tract urothelial carcinoma.

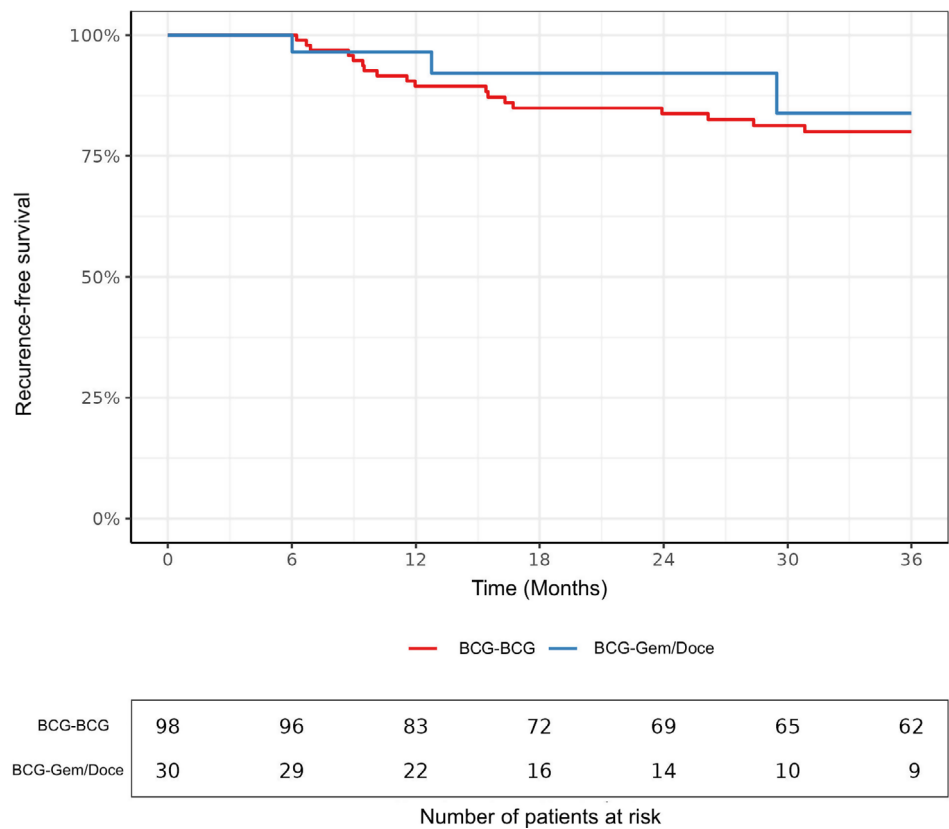
reporting AEs was significantly higher in the BCG group than in the Gem/Doce group (28% vs. 6.7%; $P = 0.02$). Most AEs were grade ≤2 in both groups, with few cases of grade >3. AEs resulted in treatment schedule modifications in seven patients (7.1%) in the BCG group, and no modifications were needed in the Gem/Doce group during maintenance. The most frequent specific events in the BCG group during maintenance included haematuria (8.2%), urinary frequency (6.1%), dysuria (9.2%), and fever or infection (8.2%), whereas in the Gem/Doce group, AEs were mainly limited to haematuria (6.7%) and urinary frequency (6.7%). No severe

events were observed in the Gem/Doce group during maintenance.

Discussion

Given the tolerability and limited adherence associated with BCG instillations, combined with recurrent worldwide shortages, alternative intravesical treatment strategies that maintain comparable oncologic efficacy are urgently needed [18]. These strategies should be feasible, cost effective, and ideally associated with improved tolerability and adherence.

Fig. 1 Kaplan–Meier curves comparing recurrence-free survival in patients treated with Bacillus Calmette–Guérin (BCG; induction and maintenance) and those treated with BCG induction followed by gemcitabine/docetaxel (Gem/Doce) maintenance for non-muscle-invasive bladder cancer.



Moreover, they should allow for a more flexible instillation schedule, ideally reducing patient burden and offering longer bladder rest periods than the recurrent three-weekly BCG maintenance regimen.

Based on these considerations, we proposed to evaluate a hybrid intravesical treatment strategy combining BCG induction with Gem/Doce maintenance. In our study, sequential Gem/Doce maintenance following BCG induction achieved oncologic outcomes comparable to those observed with BCG maintenance, supporting Gem/Doce as a feasible and effective alternative in settings of BCG shortage or intolerance. Additionally, we reported significantly fewer AEs in the Gem/Doce maintenance regimen than in the BCG groups (28% vs. 6.7%; $P = 0.02$). Although our study does not aim to test a strategy that entirely excludes BCG, this approach could substantially reduce the total number of BCG instillations per patient to six, thereby decreasing pressure on healthcare resources and potentially improving tolerability and adherence.

Prospective trials have demonstrated the importance of a complete, full-dose BCG regimen in NMIBC. Lamm *et al.* [4] showed that maintenance BCG improved RFS compared with surveillance, with medians of 77 versus 36 months. Grimm

et al. reported higher 1- and 2-year RFS in patients with HG NMIBC receiving the full 1-year BCG regimen (6 induction +9 maintenance) versus a reduced regimen [5]. Oddens *et al.* emphasized the need for 1-year maintenance in IR patients and 3-year maintenance in high-risk patients [6]. Despite these well-established benefits, adherence to prolonged BCG regimens remains low, with fewer than 50% of patients completing 1-year BCG in the Nimbus trial [5] and only 16% completing 3-year maintenance in the study by Lamm *et al.* [4]. These findings highlight the gap between guideline recommendations and real-world feasibility and underscore the need to develop alternative or hybrid treatment strategies, as proposed in our manuscript.

Multiple studies have reported promising oncological efficacy as a bladder-sparing therapy in BCG-unresponsive NMIBC [19]. In BCG-naïve patients, the Gem/Doce strategy has also emerged as a leading alternative to BCG. Between 2022 and 2026, 16 studies evaluated this regimen in the first-line setting, and more than half were published in the past year [12–16,20–30]. In these cohorts, Gem/Doce demonstrated encouraging oncological efficacy: 1-year RFS ranged from approximately 62% to 97%, 1-year HG-RFS from 80% to 100%, 1-year cystectomy-free survival frequently exceeded

Table 2 Univariable and multivariable Cox regression analyses predicting disease recurrence in patients treated with Bacillus Calmette–Guérin (BCG; induction and maintenance) and those treated with BCG induction followed by gemcitabine/docetaxel (Gem/Doce) maintenance for non-muscle-invasive bladder cancer.

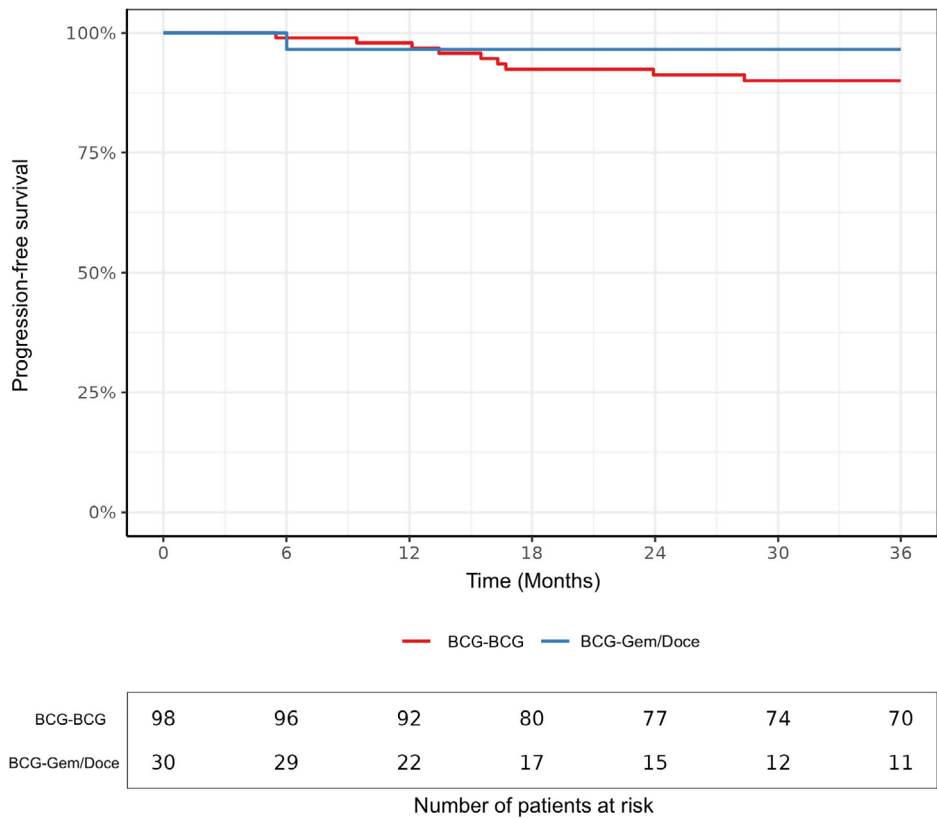
Variables	Univariable analyses		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age				
<70	1 (reference)		–	
≥70	1.22 (0.58–2.58)	0.6	–	–
Sex				
Male	1 (reference)		–	
Female	0.72 (0.27–1.90)	0.5	–	–
ASA				
≤2	1 (reference)		–	
>2	1.79 (0.81–3.96)	0.2	–	–
BMI	0.97 (0.89–1.06)	0.5	–	–
Smoking history				
Never	1 (reference)		–	
Current or former	1.22 (0.55–2.70)	0.6	–	–
pT stage				
pTa	1 (reference)		–	
pT1	1.02 (0.43–2.46)	0.9	–	–
pTis alone	1.13 (0.43–2.98)	0.8	–	–
Presence of CIS				
No	1 (reference)		–	
Yes	0.98 (0.44–2.17)	0.9	–	–
Grade stage				
Low grade	1 (reference)		–	
High grade	1.17 (0.28–4.94)	0.8	–	–
Tumour focality				
Unifocal	1 (reference)		1 (reference)	
Multifocal	4.44 (2.09–9.46)	<0.001	4.41 (2.06–9.44)	<0.001
Tumour size				
<3 cm	1 (reference)		1 (reference)	
≥3 cm	3.32 (1.32–8.39)	0.01	3.22 (1.24–8.39)	0.02
EAU risk classification				
Intermediate	1 (reference)		–	
High	1.40 (0.58–3.35)	0.5	–	–
Very high	1.46 (0.30–7.05)	0.6	–	–
Maintenance regimen				
BCG	1 (reference)		1 (reference)	
Gem/Doce	1.11 (0.42–2.98)	0.8	1.04 (0.39–2.83)	>0.9

Bold values indicate statistically significant p-values. ASA, American Society of Anesthesiologists; BMI, Body mass index; CI, confidence interval; CIS, carcinoma in situ; EAU, European Association of Urology; HR, hazard ratio.

90%, and 1-year PFS ranged from approximately 94% to 100%. Regarding the direct comparison between BCG and Gem/Doce instillations, 12 studies have directly evaluated both regimens [12–16,20,21,24,26–28,30]. Among these, five found no statistically significant differences in oncological outcomes between the two approaches [20,21,24,28,30]. In contrast, three studies reported improved oncological outcomes with Gem/Doce, particularly in terms of any RFS in high-risk and very-high-risk populations, with absolute gains of approximately 20% at 1 year [16] and 15% at 2 years [15]. Conversely, four studies demonstrated a significant advantage for BCG [12–14,26], particularly in HG tumours [13]. Taken together, these data remain contradictory and preclude definitive conclusions, but more robust oncological evidence is expected from the ongoing phase III BRIDGE trial (NCT05538663) and the COBRA trial (NCT06781879).

When interpreting both the published literature and our own findings, several methodological considerations deserve attention. First, substantial heterogeneity exists across Gem/Doce protocols. In our cohort, gemcitabine maintenance was administered at a dose of 2 g, whereas most published protocols have used 1 g [15,16,21–30]. Similarly, maintenance duration varies considerably among studies: several groups have administered maintenance for up to 2 years [15,16,21–24,27–29] compared with the 1-year schedule used in our institution. Such differences in dose intensity and treatment duration may contribute to variability in reported oncological outcomes and should be considered when comparing studies. Second, treatment efficacy is strongly influenced by baseline disease risk. In our cohort, patients receiving BCG maintenance and those receiving Gem/Doce maintenance were well balanced according to the 2024

Fig. 2 Kaplan–Meier curves comparing progression-free survival in patients treated with Bacillus Calmette–Guérin (BCG; induction and maintenance) and those treated with BCG induction followed by gemcitabine/docetaxel (Gem/Doce) maintenance for non-muscle-invasive bladder cancer.



European Association of Urology risk classification ($P = 0.5$). Although alternative classification systems could have been applied, the distribution of high-risk disease remained comparable between groups, supporting the validity of our comparisons.

Beyond efficacy comparisons, an important unanswered question concerns the optimal sequencing of intravesical therapies. Although our results support the feasibility of BCG induction followed by Gem/Doce maintenance, it remains unclear how this strategy may influence subsequent treatment options in the event of recurrence. Specifically, prior exposure to Gem/Doce maintenance could theoretically reduce the rationale for administering a complete Gem/Doce induction course as salvage therapy. In our series, five (16.7%) patients treated with Gem/Doce maintenance developed recurrence, including two low-grade and three HG recurrences. Notably, all HG recurrences were successfully managed with a second BCG induction course, and none progressed to MIBC. Although these observations are based on a limited number of patients, they suggest that BCG rechallenge may remain a viable salvage option after failure of the hybrid strategy. Larger studies with longer follow-up are required to better define optimal sequencing algorithms and long-term oncological safety.

Finally, our results highlight the current heterogeneity of treatment strategies for patients with NMIBC, with the emergence of multiple approaches driven by treatment shortages, as well as by patient history and preferences. In addition, encouraging data from combination strategies associating BCG with systemic immunotherapy or alternative intravesical regimens currently under investigation [31] are expected to further expand the therapeutic landscape for these patients. This underscores, on the one hand, the need to adapt definitions of treatment response and resistance to more contemporary therapeutic modalities, rather than relying solely on BCG-based strategies. On the other hand, given the dynamic emergence of novel treatments, these considerations support the development of adaptive, *STAMPEDE-like* clinical trial designs, incorporating a standard BCG arm (induction plus maintenance) with the flexibility to introduce new comparator arms dynamically, in line with evolving contemporary strategies, including non-BCG-based or hybrid approaches.

Although our study is the first to evaluate a combined BCG induction and Gem/Doce maintenance regimen in BCG-naïve NMIBC, several limitations should be acknowledged. First, the retrospective design inherently introduces potential biases. Although we attempted to mitigate these using a

Fig. 3 Kaplan–Meier curves comparing high-grade recurrence-free survival in patients treated with Bacillus Calmette–Guérin (BCG; induction and maintenance) and those treated with BCG induction followed by gemcitabine/docetaxel (Gem/Doce) maintenance for non-muscle-invasive bladder cancer.

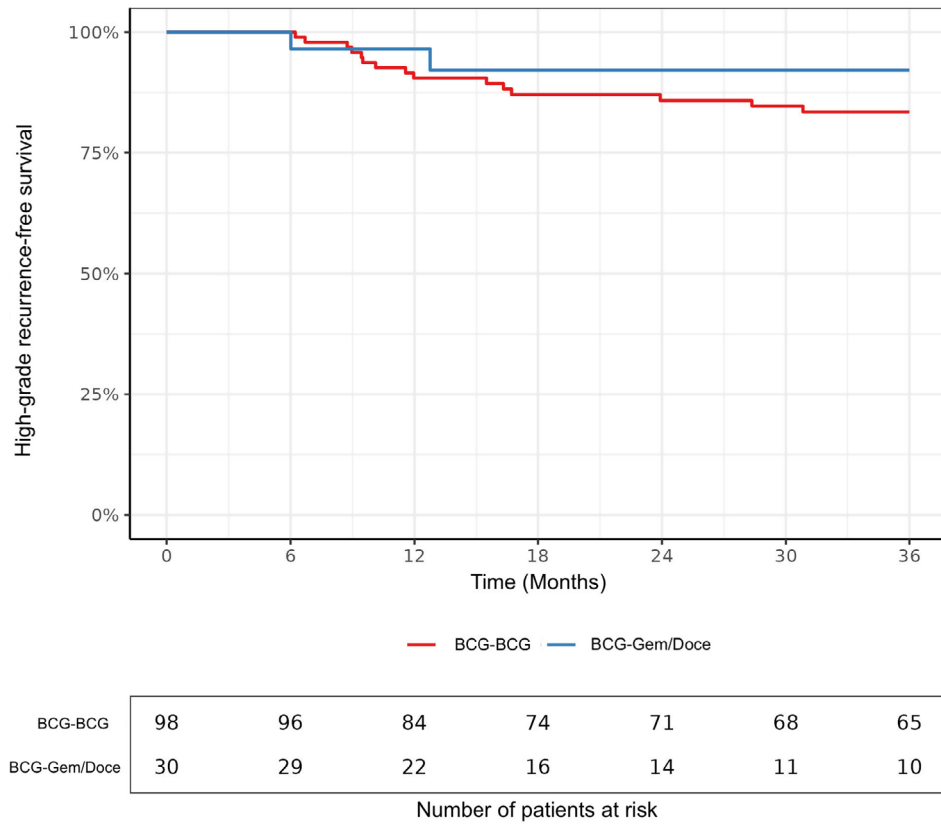


Table 3 Patient-reported adverse events (AEs) after Bacillus Calmette–Guérin (BCG) induction and BCG maintenance (group BCG maintenance) and BCG induction and gemcitabine and docetaxel (Gem/Doce) maintenance (group Gem/Doce maintenance).

Adverse events	Group BCG maintenance (n = 98; 76.6%)		Group Gem/Doce maintenance (n = 30; 23.4%)		P-value	
	Induction	Maintenance	Induction	Maintenance	Induction	Maintenance
Patients reporting AEs	18 (18)	27 (28)	3 (10)	2 (6.7)	0.4	0.02
Grade AEs						
Grade ≤2	17 (17.3)	24 (24.5)	2 (6.7)	2 (6.7)	0.3	1
Grade >3	1 (1)	3 (3.1)	1 (3.3)	0 (0)		
AE affecting treatment schedule	1 (1)	7 (7.1)	1 (3.3)	0 (0)	0.4	0.2
Specific events						
Haematuria	9 (9.2)	8 (8.2)	2 (6.7)	0 (0)	1	0.2
Frequency	4 (4.1)	6 (6.1)	1 (3.3)	2 (6.7)	1	1
Retention	2 (2)	1 (1)	0 (0)	0 (0)	1	1
Urgency	2 (2)	5 (5.1)	1 (3.3)	0 (0)	0.6	0.6
Dysuria	5 (5.1)	9 (9.2)	1 (3.3)	0 (0)	1	0.1
Incontinence	1 (1)	1 (1)	0 (0)	0 (0)	1	1
Nausea/vomiting	2 (2)	1 (1)	0 (0)	0 (0)	1	1
Fever/infection	2 (2)	8 (8.2)	0 (0)	0 (0)	1	0.2
Malaise	2 (2)	0 (0)	0 (0)	0 (0)	1	1
Pelvic discomfort	3 (3.1)	4 (4.1)	0 (0)	0 (0)	1	0.6

Data are presented as n (%). Bold values indicate statistically significant p-values.

multivariable Cox model, residual confounding cannot be entirely excluded. Second, the cohort receiving the combined regimen remains relatively small, limiting the generalizability of our findings. Third, the BCG and Gem/Doce maintenance duration limited to 1 year in our cohort may have reduced treatment efficacy, which also represents a potential bias to consider. Finally, systematic biopsies at first surveillance cystoscopy were not mandated, and biopsies were performed only in cases of suspicious lesions or positive urinary cytology. Consequently, early recurrences may have been under-detected, potentially leading to an overestimation of short-term oncological outcomes. Nonetheless, our results provide valuable preliminary evidence highlighting the emergence of new hybrid therapies and supporting the feasibility and potential efficacy of this strategy, underscoring the need for larger prospective studies.

Conclusion

In patients who completed BCG induction, sequential maintenance with Gem/Doce showed oncologic outcomes comparable to those with maintenance BCG, with better overall tolerability, suggesting that Gem/Doce could be an effective and feasible alternative therapy in the context of BCG shortage or intolerance.

Author Contributions

Pierre-Etienne Gabriel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Pierre-Etienne Gabriel, Alec Zhu, Peter Wiklund, and John P Sfakianos. Acquisition of data: Pierre-Etienne Gabriel, Alec Zhu, Christopher G. Karim, Ahmed Eraky, Raghav Gupta, and Reuben Ben-David. Analysis and interpretation of data: Pierre-Etienne Gabriel, Alec Zhu, Christopher G. Karim, Ahmed Eraky, Raghav Gupta, Reuben Ben-David, Reza Mehrazin, Peter Wiklund, and John P Sfakianos. Drafting of the manuscript: Pierre-Etienne Gabriel, Alec Zhu, Christopher G. Karim, Peter Wiklund, and John P Sfakianos. Critical revision of the manuscript for important intellectual content: Ahmed Eraky, Raghav Gupta, Reuben Ben-David, Reza Mehrazin, Peter Wiklund, and John P Sfakianos. Statistical analysis: Pierre-Etienne Gabriel, Alec Zhu, and John P Sfakianos. Obtaining funding: None. Administrative, technical, or material support: Pierre-Etienne Gabriel, Alec Zhu, Christopher G. Karim, Ahmed Eraky, Raghav Gupta, Reuben Ben-David, Reza Mehrazin, Peter Wiklund, and John P Sfakianos. Supervision: Reza Mehrazin, Peter Wiklund, and John P Sfakianos.

Disclosure of Interest

Pierre-Etienne Gabriel certifies that all authors have no conflicts of interest, including specific financial interests and

relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending).

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Kaplan–Meier curves comparing progression-free survival (stage <T2) in patients treated with Bacillus Calmette–Guérin (BCG; induction and maintenance) and those treated with BCG induction followed by gemcitabine/docetaxel (Gem/Doce) maintenance for non-muscle-invasive bladder cancer.

Fig. S2. Kaplan–Meier curves comparing progression-free survival (stage ≥T2) in patients treated with Bacillus Calmette–Guérin (BCG; induction and maintenance) and those treated with BCG induction followed by gemcitabine/docetaxel (Gem/Doce) maintenance for non-muscle-invasive bladder cancer.

Fig. S3. Kaplan–Meier curves comparing metastasis-free survival in patients treated with Bacillus Calmette–Guérin (BCG; induction and maintenance) and those treated with BCG induction followed by gemcitabine/docetaxel (Gem/Doce) maintenance for non-muscle-invasive bladder cancer.