World Journal of Urology (2026) 44:82
https://doi.org/10.1007/s00345-025-06179-y

RESEARCH

Real-world outcomes of bladder-sparing strategies for BCG-unresponsive non-muscle-invasive bladder cancer: a multicenter study

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Received: 21 October 2025 / Accepted: 28 December 2025

Abstract

Introduction Patients with BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC) face a high risk of disease progression. While radical cystectomy (RC) remains the recommended standard of care, many patients are unfit for or unwilling to undergo radical surgery, leading to bladder-sparing strategies spreading in real-world practice. This study aims to describe the oncological outcomes of patients diagnosed with BCG-unresponsive NMIBC treated with gemcitabine/docetaxel (Gem/Doce), electromotive drug administration of mitomycin C (EMDA/MMC), further BCG, or upfront RC.

Methods We included patients diagnosed with BCG-unresponsive NMIBC treated across 21 European centers (2009–2024) with either intravesical Gem/Doce, EMDA/MMC, further BCG, or upfront RC. Cumulative incidence curves were used to estimate the risk of recurrence, high-grade recurrence, progression, cancer-specific and overall mortality. Multivariable Cox regression models were used to assess the association between treatment type and the risk of recurrence and progression.

Results Of the 361 patients, 104 (28%) received Gem/Doce, 58 (16%) EMDA/MMC, 150 (42%) further BCG, and 49 (14%) underwent RC. Overall median follow-up was 73 months. Recurrence and high-grade recurrence rates were comparable between Gem/Doce and EMDA/MMC (adjusted HR: 1.30 and 0.40, respectively; both $p>0.5$). The 2-year risk of progression was 15% with Gem/Doce, 20% with EMDA/MMC, and 30% with further BCG ($p<0.001$). In multivariable analysis, Gem/Doce was associated with a significantly lower risk of progression compared to further BCG (adjusted HR: 0.19, 95% CI 0.09–0.43; $p<0.001$). The 2-year cancer-specific mortality was 0% for both Gem/Doce and EMDA/MMC, 4% for BCG, and 7% for RC, with corresponding other-cause mortality rates of 3%, 8%, 11%, and 8%, respectively.

Conclusions In real-world practice, our study indicates that both Gem/Doce and EMDA/MMC represent viable treatment bladder-sparing options for patients with BCG-unresponsive NMIBC who refuse or are unfit for RC. For patients eligible and consenting to surgery, RC remains the guideline-endorsed standard. Prospective trials are warranted to define the optimal therapeutic algorithm for this challenging patient population.

Keywords Non-muscle invasive bladder cancer · Bacillus Calmette-Guerin · BCG-unresponsive · Oncological outcomes · Survival · Bladder-sparing therapy · Gemcitabine and Docetaxel · EMDA

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Published online: 11 January 2026

Introduction

Bacillus Calmette-Guérin (BCG) is the gold standard intravesical therapy for patients with high-risk non-muscle-invasive bladder cancer (NMIBC) after transurethral resection of the bladder tumor (TURBT) [1]. However, approximately 30–40% of patients will eventually experience disease recurrence or progression despite adequate BCG exposure and are therefore classified as BCG-unresponsive, a definition established by the International Bladder Cancer Group (IBCG) and adopted by regulatory agencies and clinical guidelines [2, 3].

For these patients, radical cystectomy (RC) is widely recognized as the gold standard treatment, offering the best long-term cancer control [1, 4]. In particular, RC is associated with excellent oncological outcomes in appropriately selected patients, especially when performed early in the disease course. Nevertheless, RC is a morbid procedure, and some patients are either medically unfit or unwilling to undergo it [5]. This has led to increasing interest in bladder-sparing alternatives, particularly in the real-world setting, where surgical eligibility and patient preferences play a significant role in clinical decision-making [6].

Despite the recommendation to enroll patients with BCG-unresponsive NMIBC in clinical trials, several intravesical therapies have been adopted off-trial in routine clinical practice. Among these, sequential intravesical administration of gemcitabine and docetaxel (Gem/Doce) has shown promising efficacy and safety in single-center series, with encouraging results in terms of recurrence-free and progression-free survival [7, 8]. Electromotive drug administration of mitomycin C (EMDA/MMC) represents another technique aimed at improving drug delivery and efficacy via enhanced penetration of the bladder wall using electric current [9, 10]. Meanwhile, some patients continue to be treated with additional courses of BCG despite guideline recommendations against this approach, either due to lack of alternatives, physician's decision or patient's ineligibility for RC [11].

Notably, the comparative effectiveness of these diverse bladder-sparing approaches remains poorly investigated. While some retrospective and prospective series have reported favorable outcomes with Gem/Doce or EMDA/MMC, very few studies have directly compared multiple treatment strategies, including RC, in a contemporary, multicenter setting [11]. As such, there is a clear need for real-world evidence to inform clinical decision-making for this challenging population.

In this multicenter collaborative study involving 21 European tertiary referral centers, we sought to compare the oncological outcomes of four different treatment strategies administered to patients with BCG-unresponsive NMIBC between 2009 and 2024: (1) intravesical Gem/Doce, (2) EMDA/MMC, (3) further BCG, and (4) upfront radical cystectomy. By leveraging a large, real-world dataset, this study aims to provide clinically relevant insights into the comparative effectiveness of available therapeutic options for BCG-unresponsive NMIBC in contemporary urologic practice.

Materials and methods

Study design and dataset construction

Following institutional review board approval (GO/URC/ER/mm prot. n. 79/DG), data were retrospectively collected and handled in accordance with anonymization procedures as defined by the General Data Protection Regulation. The Young Academic Urologists Urothelial Carcinoma Working Group served as the central data repository [12].

For this analysis, we included patients with BCG-unresponsive NMIBC, defined according to the criteria established by the Food and Drug Administration (FDA) and the IBCG. Eligible patients were identified from three independent sources: (1) those treated with intravesical GemDoce were drawn from the EuroGemDoce initiative, a multicenter database involving 15 European centers; (2) patients who received additional BCG or underwent RC were selected from a multicenter cohort of BCG-treated patients from 8 European institutions [2, 4]; and (3) patients treated with EMDA/MMC were identified from a dedicated dataset including two hospitals, one in Italy and one in Switzerland [9, 14].

To ensure data consistency and relevance to contemporary practice, we included only patients diagnosed with BCG-unresponsive NMIBC following complete TURBT and BCG intravesical therapy between 2009 and 2024. Patients with missing data for clinically relevant variables were excluded. A detailed overview of the patient selection process is provided in Supplementary Fig. 1.

Treatment protocols

The EMDA/MMC treatment protocol consisted of 30-min intravesical instillations of MMC using the Physion Mini 30N2 device, delivering a current of 20–23 mA. MMC was prepared at a concentration of 40 mg (0.04%) [w/v] in distilled water. Patients underwent an induction course of up to eight weekly EMDA/MMC instillations, followed by a planned maintenance regimen of 12 monthly sessions [9, 14].

The Gem/Doce protocol varied slightly across participating centers. Some institutions administered oral sodium

bicarbonate pre-treatment to optimize urine pH. The dwelling times for both gemcitabine and docetaxel also differed by center. Induction therapy typically consisted of six weekly instillations. In patients without disease recurrence at first follow-up, maintenance therapy was offered, consisting of monthly instillations for either 10 or 24 months, depending on institutional practice [8].

Further BCG instillations were administered at the discretion of the treating physician after the diagnosis of BCG-unresponsive disease, while patients undergoing RC were treated according to international guidelines, with surgery including bilateral pelvic lymph node dissection.

Follow-up protocols followed the international guidelines recommendation [1].

Variables and endpoint definitions

The dataset included demographic and pathological variables such as age, sex, tumor stage, presence of carcinoma in situ (CIS), date of BCG-unresponsiveness, date of progression, date of RC, and dates of cancer-specific and all-cause death. Tumor grading was reported using both the 1973 and 2004/2016 World Health Organization classification systems. Adequate BCG exposure was defined as at least five out of six induction instillations plus at least two out of three maintenance instillations or a second induction course.

BCG-unresponsive NMIBC was defined according to contemporary guideline-recommended criteria and included both BCG-refractory disease and early high-grade recurrences after adequate BCG. BCG-refractory disease included T1 high-grade/G3 tumors at 3 months, persistent Ta/T1 high-grade or CIS at 3–6 months after induction, re-induction, or first maintenance, and the development of any new high-grade tumor during BCG maintenance. In addition, patients with high-grade Ta/T1 recurrence within 6 months of adequate BCG or CIS recurrence within 12 months of adequate BCG exposure were classified as BCG-unresponsive. Patients with prior or concurrent muscle-invasive disease (≥T2) were excluded [1, 13].

Recurrence was defined as any recurrence during follow-up and was assessed only for patients treated with EMDA/MMC or Gem/Doce where recurrence was systematically available. Progression was defined as the first diagnosis of muscle-invasive (≥T2) or metastatic disease. Metastasis was defined as the presence of any distant lymph node, visceral, or bone lesion suspicious for metastatic disease at any imaging. RC during follow-up was recorded to evaluate bladder preservation. Cancer-specific mortality (CSM) was defined as death directly attributable to bladder cancer. Patients were censored at the last known follow-up visit if the event of interest had not occurred.

Statistical analyses

All statistical analyses were conducted in accordance with international reporting guidelines [15].

First, descriptive statistics were used to summarize baseline characteristics. Continuous variables were reported as medians and interquartile ranges (IQR) and compared using the Wilcoxon rank-sum test. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate.

Second, cumulative incidence functions were used to estimate the risk of NMIBC recurrence (limited to EMDA/MMC and Gem/Doce), progression to muscle-invasive disease or metastatic disease, and progression to metastatic disease only. Competing risk cumulative incidence curves were used to plot the cancer-specific and non-cancer related death. Follow-up time was calculated from the date of treatment exposure (e.g. start of treatment or RC for patients receiving RC after BCG-failure).

Third, multivariable Cox regression analyses (MVA) were performed to assess the association between treatment type and each outcome of interest, including recurrence, high-grade recurrence, and progression, adjusting for tumor stage, age, sex, year of BCG failure, and Charlson Comorbidity Index (CCI). The models were adapted to the number of events available for each outcome, maintaining a consistent variable inclusion order to avoid overfitting. Proportional hazards assumptions for all Cox models were evaluated using Schoenfeld residuals, and no significant violations were detected.

Finally, a sensitivity analysis restricted to patients in the Gem/Doce group with at least 12 months of follow-up but also including those who experienced an early event (e.g., within 12 months) was performed to validate findings.

Statistical significance was considered at $p < 0.05$. For all statistical analyses, R software environment for statistical computing and graphics was used (version 4.5.1; http://www.r-project.org/).

Results

Descriptive characteristics of patient population

A total of 361 patients with BCG-unresponsive NMIBC treated between 2009 and 2024 were included in the final analysis. Of these, 104 (28%) patients received intravesical Gem/Doce, 58 (16%) were treated with EMDA/MMC, 150 (42%) received further BCG instillations, and 49 (14%) underwent RC.

Baseline clinical and pathological characteristics are summarized in Table 1. The median age was comparable

Table 1 Baseline characteristics of 361 patients diagnosed with BCG-unresponsive NMIBC from 2009 to 2024 treated with either Gemcitabine/Docetaxel, EMDA, further BCG or radical cystectomy

Characteristics	No. of patients (%)				
	Gemcitabine/Docetaxel	EMDA	Further BCG	Radical cystectomy	p value
No. of patients	104 (100)	58 (100)	150 (100)	49 (100)	
Year of treatment					**< 0.001**
2009–2014	0 (0)	26 (45)	21 (14)	15 (31)	
2015–2020	0 (0)	32 (55)	81 (54)	21 (43)	
2021–2024	104 (100)	0 (0)	48 (32)	13 (27)	
Gender					**0.004**
Male	74 (71)	45 (79)	131 (87)	38 (78)	
Age					0.2
Median (IQR)	73 (66–79)	74 (67–82)	74 (66–79)	72 (64–77)	
Charlson Comorbidity Index*					
Median (IQR)	4 (3–5)	6 (5–7)	5 (4–7)	4 (4–6)	**< 0.001**
Smoking					**< 0.001**
Never	23 (22)	0 (0)	38 (25)	10 (20)	
Current	15 (14)	5 (8.6)	0 (0)	0 (0)	
Former	65 (63)	45 (78)	40 (27)	11 (22)	
Unknown	1 (1.0)	8 (14)	72 (48)	28 (57)	
Histology at last positive TURBT before treatment					**< 0.001**
Tis	22 (21)	0 (0)	50 (33)	9 (19)	
TaHG	49 (47)	28 (48)	56 (38)	10 (20)	
T1HG	33 (32)	30 (52)	44 (29)	30 (61)	
Concomitant CIS	9 (8.7)	34 (59)	48 (32)	10 (20)	**< 0.001**
Number of lines after BCG-unresponsive					
1	82 (83)	58 (100)	–	–	
2	13 (13)	0 (0)	–	–	
> 3	4 (4)	0 (0)	–	–	
Unknown	5	–			
Follow-up after BCG unresponsive diagnosis					**< 0.001**
Median (IQR)	12 (8–20)	51 (40–77)	24 (5–46)	34 (15–52)	

Bold values indicate statistically significant p value ($p < 0.05$)

*Computed including bladder cancer diagnosis

BCG Bacillus-Calmette Guérin, *IQR* Interquartile range, *EMDA* Electromotive Drug Administration

across groups, ranging from 72 to 74 years. A higher CCI was observed among patients treated with EMDA/MMC (median 6, IQR 5–7) compared to those who received Gem/Doce (median 4, IQR 3–5), further BCG (median 5, IQR 4–7), or RC (median 4, IQR 4–6) ($p < 0.001$). Patients in the Gem/Doce group were more frequently treated in recent years (100% between 2021–2024), whereas EMDA/MMC was largely administered between 2009–2014 (45%) and 2015–2020 (55%) ($p < 0.001$).

The distribution of histological stage at last TURBT also varied, with a higher proportion of T1 high-grade (HG) disease in the RC group (61%) and EMDA/MMC group (52%) compared to Gem/Doce (32%) and further BCG (29%) ($p < 0.001$). Overall median follow-up was 73 months.

Treatment allocation and decision-making

Table 2 reports the reasons for choosing Gem/Doce or EMDA/MMC. Cystectomy refusal was the most common reason across both groups (55% for Gem/Doce, 58% for EMDA/MMC). A substantial proportion of EMDA/MMC patients were deemed unfit for surgery (42%) compared to the 34% of patients in the Gem/Doce group.

Oncological outcomes

Risk of recurrence for EMDA/MMC and Gem/Doce

A total of 67 (42%) of patients experienced high-grade recurrence. The 1 and 2-year high-grade recurrence risk was 25% vs. 30%, and 45% vs. 46% for Gem/Doce vs. EMDA/

Table 2 Clinical rationale for treatment selection among patients receiving Gemcitabine/Docetaxel (n = 104) or EMDA-MMC (n = 58)

Reason	No. of patients (%)	
	Gemcitabine/Docetaxel	EMDA
	104 (100)	58 (100)
Declining radical cystectomy	50 (55)	28(58)
Unfit for radical cystectomy due to comorbidities or safety	31(34)	20(42)
Not eligible for clinical trial	3(3.3)	0 (0)
Other	7(7.7)	0 (0)
Unknown	13	10

EMDA Electromotive Drug Administration

MMC (all p > 0.05), respectively. (Supplementary Fig. 2, Supplementary Fig. 3). Gem/Doce was associated with similar recurrence (adjusted hazard ratio (HR): 1.30, 95% CI 0.36–4.62) and high-grade recurrence (HR: 0.40, 95% CI 0.11–1.48) risk profile compared to EMDA/MMC. (Fig. 2).

Progression to muscle-invasive or metastatic disease

A total of 78 patients (25%) experienced disease progression during follow-up. The 2-year progression risk was 15% for Gem/Doce, 20% for EMDA/MMC, and 30% for further BCG (p < 0.001). (Fig. 1A). In MVA, treatment with Gem/Doce was associated with a significantly lower risk of progression compared to further BCG (HR: 0.19, 95% CI 0.09–0.43, p < 0.001). In contrast, EMDA/MMC was not associated with a statistically significant reduction in progression risk compared to further BCG (HR: 0.67, 95% CI 0.34–1.33, p = 0.3) (Fig. 1A, Fig. 2). Progression to metastatic disease alone occurred in 16 patients (5%) who underwent bladder-sparing treatment after BCG-unresponsiveness. At 2 years, the risk of metastasis was 5% for Gem/Doce, 4% for EMDA/MMC, and 3% for further BCG, with no statistically significant differences observed (p > 0.05, Fig. 1C, Supplementary Fig. 2).

Radical cystectomy during follow-up

At 2 years, the rate of subsequent RC was higher among patients initially treated with Gem/Doce (16%) or EMDA/MMC (17%), compared to those receiving further BCG (7%) (Fig. 1B). However, at the 7-year mark, the cumulative RC rate among BCG-treated patients rose to 18%, closely approaching that of the EMDA/MMC group (23%).

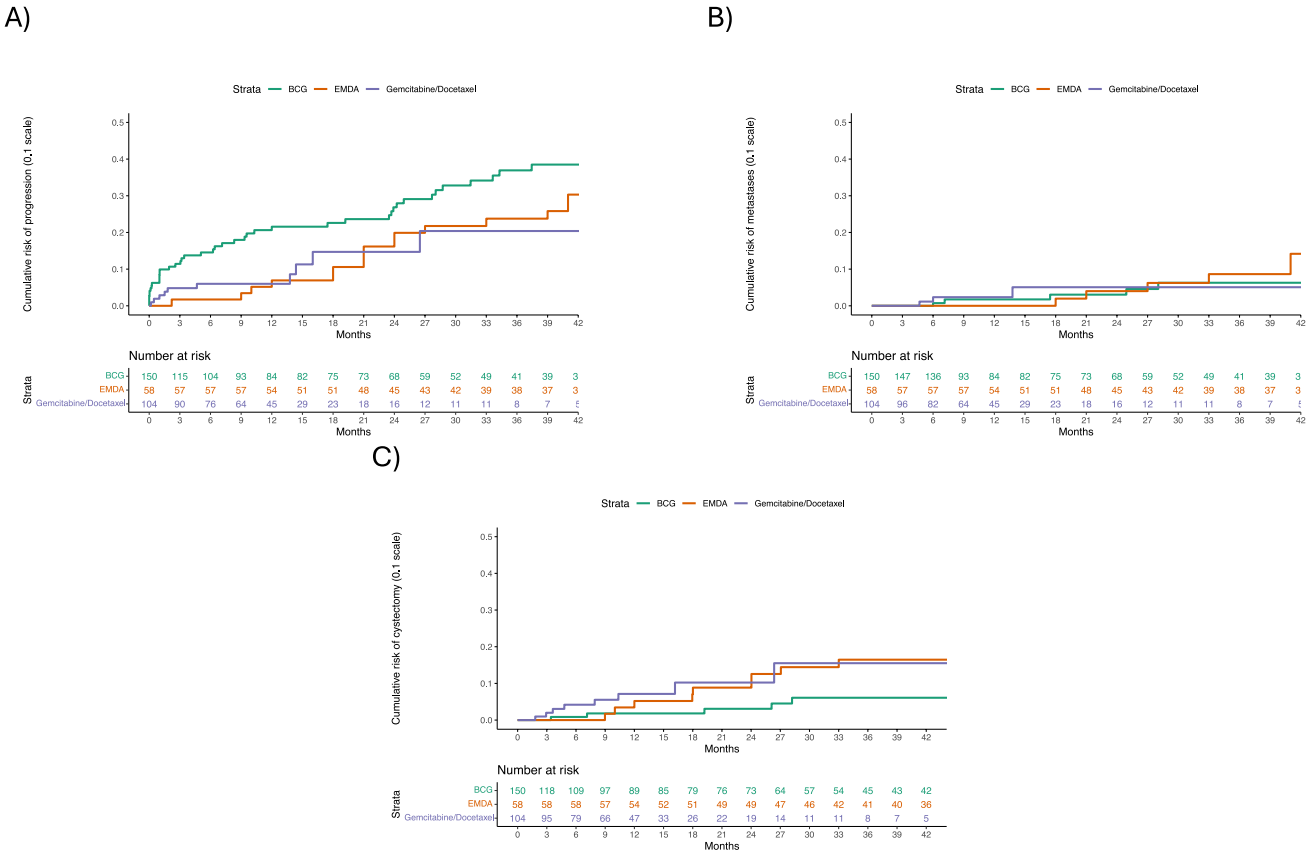

Fig. 1 Risk of **A** progression; **B** metastases; **C** radical cystectomy according to type of management in patients treated with either gemcitabine/docetaxel, EMDA/MMC or further BCG for BCG-unresponsive NMIBC

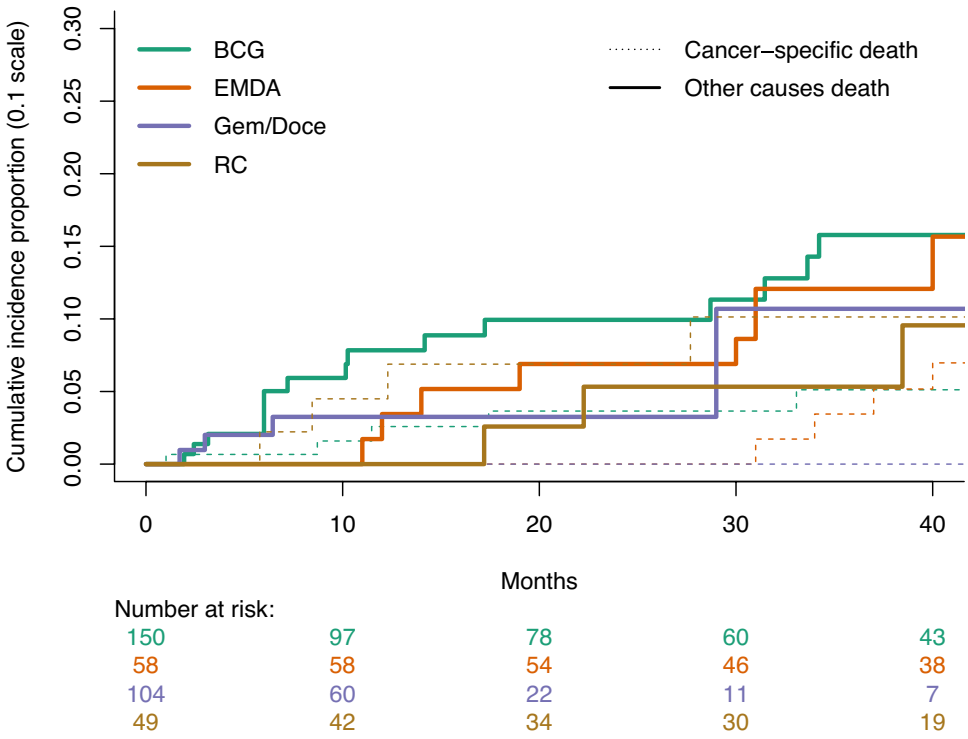

Fig. 2 Competing cumulative risk cumulative of cancer and other causes death

Treatment strategies following disease progression or high-grade recurrence were available for 57 out of 128 patients (45%). Notably, chemoradiotherapy was administered in 17% (n = 7) of patients in the EMDA/MMC group compared to 8.3% (n = 3) in the Gem/Doce group. Among patients treated with BCG, 11 (38%) received other adjuvant intravesical therapies, while 9 (15%) were managed with observation alone (e.g. TURBT and further surveillance) due to comorbidities, despite being candidates for RC (Fig. 3, Supplementary Table 1).

Cancer-specific mortality and other cause mortality

By the end of follow-up, a total of 84 (23%) patients had died. The 2-year competing risk of death from bladder cancer was 0% for Gem/Doce, 0% for EMDA/MMC, 4% for BCG, and 7% for RC. The corresponding 2-year risk of death from other causes was 3%, 8%, 11%, and 8%, respectively (Fig. 4).

Sensitivity analysis

In sensitivity analyses, restricted to patients in the Gem/Doce group with at least 12 months of follow-up but also including those who experienced an early event within 12 months (n = 56, median follow-up 17 months (IQR: 13-28), the results were largely consistent with the main findings (Supplementary Figs. 4 and 5).

Discussion

In this multicenter, real-world cohort of patients with BCG-unresponsive NMIBC, Gem/Doce and EMDA/MMC were associated with low short-term rates of progression and metastasis, with cystectomy rates in the range expected for bladder-preserving strategies. These findings support their use for carefully selected, well-informed patients who are ineligible for or decline RC. [16] Importantly, our comparisons should be interpreted in the context of confounding by indication, patients undergoing RC in this cohort harbored more adverse baseline disease, and era effects, as EMDA/MMC was implemented earlier under different TURBT, surveillance, and referral standards. Accordingly, these data are not intended to demonstrate non-inferiority to RC; rather, they provide realistic outcome estimates to guide counseling when RC is not pursued. This study offers several key insights.

First, despite their distinct mechanisms of action, both EMDA/MMC and Gem/Doce demonstrated similar efficacy in reducing the risk of recurrence, including high-grade disease. EMDA/MMC enhances intravesical drug delivery through electric current–induced iontophoresis, promoting deeper drug penetration compared to passive diffusion [17, 18]. In contrast, the combination of gemcitabine and docetaxel leverages synergistic cytotoxicity, with preclinical and early clinical studies supporting improved efficacy over either agent alone [19]. Our results are consistent with previous reports, including a 2-year recurrence-free survival

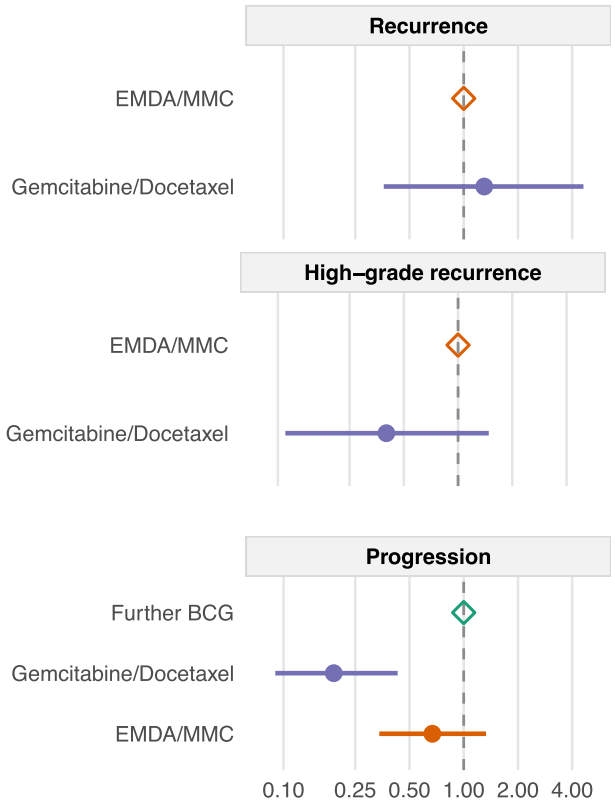

Fig. 3 Forest plots depicting the HRs and 95% confidence intervals derived from multivariable models assessing the association between type of treatment and recurrence, high-grade recurrence, progression to muscle invasive or metastatic disease. All multivariable models were adjusted for [tumor stage, age, sex, year of failure, smoke, Charlson Comorbidity Index] based on the number of levels to avoid of overfitting

of 46%-58% with Gem/Doce [7, 11], and 62% with EMDA/MMC in BCG-unresponsive patients [10]. While differences in patient selection and protocols limit direct comparison, both approaches appear to provide meaningful real-world benefit in this setting.

Second, both EMDA/MMC and Gem/Doce were associated with significantly lower risks of disease progression compared to further BCG, which is normally not recommended by major international guidelines [1, 20, 21] for BCG-unresponsive NMIBC. These findings are reinforced by data from Taylor et al., who reported a 2.6-fold increased risk of progression in patients receiving additional BCG following a BCG-unresponsive diagnosis [11] and underscores the limited efficacy of re-challenging with BCG once resistance is established supporting the adoption of EMDA/MMC and Gem/Doce as more effective bladder-sparing options [2]. In addition, the observed lower progression rates in both groups suggest that, in carefully selected patients, bladder preservation remains a viable goal [6].

Third, differences in mortality patterns should be interpreted with caution, given the design of the study. The EMDA/MMC cohort, with follow-up extending back to 2009, inherently accumulated a greater number of non-cancer-related deaths, a phenomenon often observed in cohorts with prolonged surveillance. Moreover, nearly 40% of this cohort were deemed unfit for RC and had higher CCI scores, reflecting both a less favorable baseline profile and selection criteria that differ from contemporary practice. Patients undergoing RC presented with more aggressive disease at baseline, with over 60% harboring T1 high-grade tumors at the time of BCG-unresponsive diagnosis yet exhibited a lower incidence of non-cancer-related mortality compared to the BCG and EMDA/MMC groups. This finding likely reflects selection bias, with RC candidates being younger and having lower CCI scores. As expected, however, the risk of CSM was marginally higher in the RC group compared to other treatment groups, consistent with the more advanced disease burden at the time of treatment selection.

Notably, patients treated with Gem/Doce demonstrated the highest overall survival in our cohort, a finding that likely reflects both favorable patient selection and the relatively shorter follow-up inherent to this group. Indeed, Taylor et al. reported comparable survival outcomes with longer follow-up, even when comparing Gem/Doce to additional BCG in the BCG-unresponsive setting [11]. Moreover, emerging multicenter evidence suggests no significant difference in overall survival between patients managed with RC versus bladder-sparing approaches [22], further supporting the role of conservative management in appropriately selected patients in the real-world setting.

We observed a lower rate of subsequent RC among patients receiving additional BCG, likely reflecting their earlier placement within the treatment algorithm compared to those in the Gem/Doce and EMDA/MMC groups. Supporting this, the RC rate in the BCG cohort rose from 7% at 3 years to 23% at 7 years, suggesting that many of these patients received further intravesical therapies before proceeding to RC. Among those who failed additional BCG, 38% underwent further intravesical treatment, compared to just 3% in the Gem/Doce group and none in the EMDA/MMC group. While the decision to proceed with RC is multifactorial, shaped by clinician judgment, institutional experience, and regional practice norms, these findings highlight the individualized and stepwise nature of treatment selection in this setting. Notably, the 2-year risk of metastatic progression remained low across all bladder-sparing approaches, with rates consistently below 5%. Unfortunately, our dataset did not allow for comparable assessment of post-RC metastatic progression. Nevertheless, by reporting progression, metastatic events, and subsequent RC rates, we provide decision-relevant outcomes for clinicians and patients

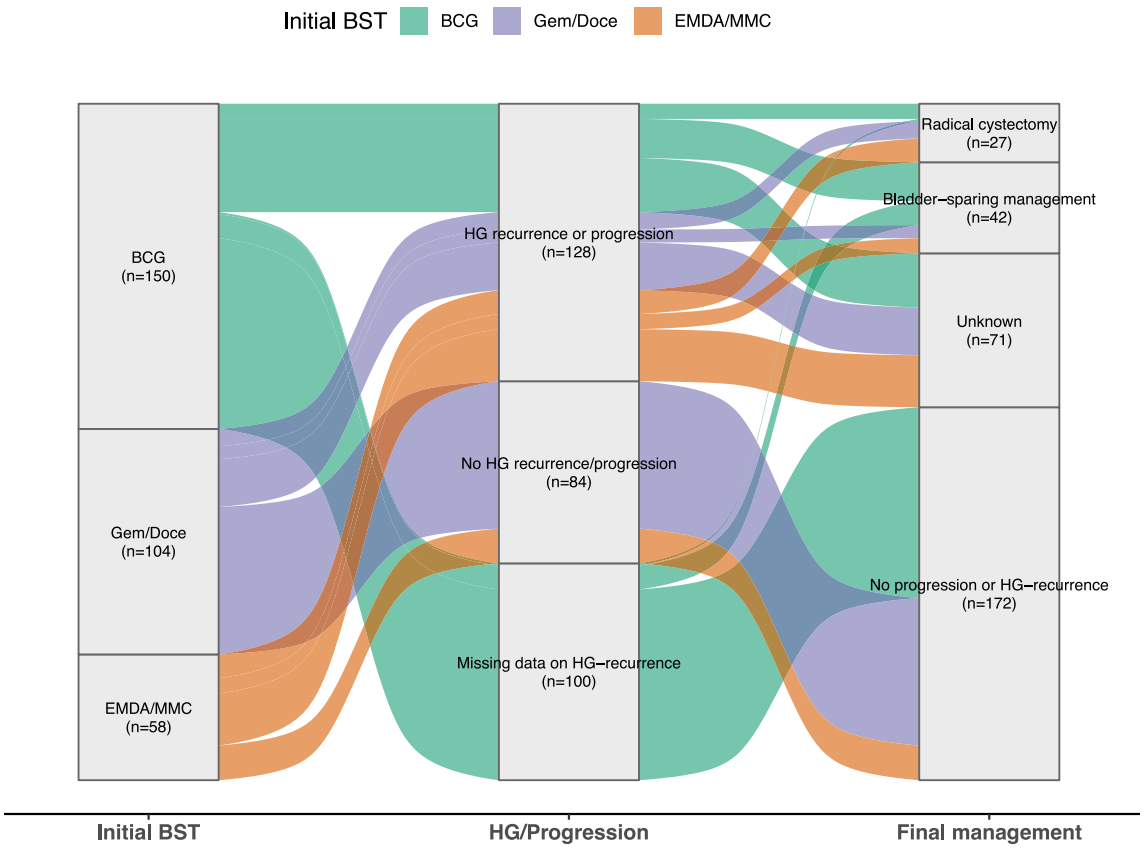

Fig. 4 Sankey diagram of patients with BCG-unresponsive NMIBC showing flow from the initial bladder-sparing strategy (BCG, Gem/Doce, EMDA/MMC) to disease status (recurrence or progression) and onward to final management (radical cystectomy or bladder-sparing management). Flow widths are proportional to the number of patients. Node labels report counts for each stratum

weighing bladder preservation against early cystectomy. Importantly, RC rates across groups should be interpreted in the context of treatment sequencing, institutional practice norms, and patient characteristics; they do not imply treatment superiority or inferiority but rather reflect complex, multifactorial decision-making in real-world management of BCG-unresponsive NMIBC.

Taken together, our findings provide real-world estimates of available day-to-day bladder-preserving strategies for BCG-unresponsive NMIBC. RC remains the gold-standard and most definitive oncologic treatment, offering the highest likelihood of durable disease control. However, it is not universally applicable or acceptable in routine practice; in our cohort, nearly half of those eligible for RC and managed with EMDA/MMC or Gem/Doce declined surgery. Meanwhile, the therapeutic landscape is rapidly evolving, KEYNOTE-057 (pembrolizumab), IL-15 plus BCG combinations, gene therapy (e.g., nadofaragene firadenovec), and TAR-200 all underscore momentum toward nonsurgical options [23–26]. In this context, intravesical Gem/Doce and EMDA/MMC remain pragmatic options, particularly in settings where newer agents are not yet approved or reimbursed in Europe [27, 28], but they should be viewed as complementary strategies rather than replacements for RC in appropriately selected patients.

This study is not devoid of limitations. Follow-up in the Gem/Doce cohort was shorter, which may have led to an underestimation of long-term recurrence risk. To address this, we performed a sensitivity analysis restricted to patients with ≥12 months of follow-up, including those experiencing early events, and the results remained consistent. Data completeness and the rigor of data collection varied across cohorts. The Gem/Doce dataset benefited from contemporary, standardized multicenter collection (2021–2024), whereas the further BCG and RC cohorts were extracted from a broader historical BCG database that was not originally designed to capture granular recurrence or metastatic outcomes. This explains the absence of recurrence data after BCG rechallenge, the lack of metastatic information following RC, and the treatment contamination observed in the further BCG group (38%). As such, readers should be aware that the comparator cohorts contain greater amounts of missing information, which may introduce information bias. Moreover, information on the specific BCG strains and protocols used across centers and on potential dose reductions during periods of global shortages was not available.

Although the vast majority of patients were treated with full-dose BCG according to local practice, the absence of detailed data on strain type and dosing heterogeneity represents an additional limitation. Outcome definitions were standardized across centers, and follow-up adhered to international NMIBC guidelines; however, TURBT quality parameters and pathological review were not centrally standardized due to the multicenter retrospective design. These elements introduce potential variability in staging accuracy and pathological interpretation, which should be considered when interpreting comparative outcomes. Treatments were administered over different time periods, which could have influenced patient selection and outcome ascertainment, given the dynamic changes in guidelines recommendations over the years; however, we attempted to reduce these limitations by adjusting multivariable models for the year of BCG failure, and by using a uniform definition of BCG-unresponsive disease across all cohorts. The retrospective nature of the study precludes causal inference and carries risks of selection bias and unmeasured confounding. Additionally, although all participating centers were high-volume academic institutions, generalizability to other settings may be limited.

Conclusion

Our findings indicate that Gem/Doce and EMDA/MMC represent reasonable bladder-preserving alternatives for well-selected, well-informed patients with BCG-unresponsive NMIBC who are unfit for or decline radical cystectomy. Both approaches were associated with a lower risk of progression compared with further BCG, offering meaningful options for patients seeking nonsurgical management. Nevertheless, radical cystectomy remains the guideline-endorsed definitive treatment for eligible candidates, and prospective comparative trials are needed to define the optimal therapeutic algorithm for this complex population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00345-025-06179-y.

Author contributions Conceptualization: Scilipoti, Zaurito, Moschini. Data curation: Scilipoti, Zaurito, Longoni, Tremolada, Cosenza, Ślusarczyk, Dutto, Katzendorn, Krajewski, Laukhtina, Oberneder, Rodríguez Elena, Aranda, Lafuente Puentedura, Subiela, Fernández, Szostek, Mastroianni, Simone, Pichler, Álvarez-Maestro, Aguilera Bazán, Klatte, Massiet du Biest, Ferrando, Buisan, Villares López, Zazzara, Carando. Formal analysis: Scilipoti, Zaurito, Moschini. Funding acquisition: no funding. Investigation: Scilipoti, Zaurito, Moschini. Methodology: Scilipoti, Zaurito, Moschini. Project administration, Resources, Software, Supervision: Moschini. Validation: Moschini, Visualization, Writing—original draft: Scilipoti, Zaurito, Moschini. Writing—review & editing: Ślusarczyk, Krajewski, Aranda, Caño Velasco, Contieri, Hurle, Subiela, Fernández, Marcq, Simone, Pichler, Álvarez-Maestro, Aguilera Bazán, Klatte, Massiet du Biest, Ferrando, Buisan, Villares López, Zazzara, Ludovico, Carando, Radziszewski, Soria, Pradere, D'Andrea, Shariat, Montorsi, Salonia, Briganti, Gontero, Xylinas.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability All data supporting the findings of this study are available within the paper and its material.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval This study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

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