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SEQUENTIAL GEMCITABINE AND DOCETAXEL VERSUS BCG FOR HIGH-RISK NON-MUSCLE-INVASIVE BLADDER CANCER

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ABSTRACT
Intravesical Bacillus Calmette-Guérin (BCG) is the gold standard for high-risk non-muscle-invasive bladder cancer (HR-NMIBC). However, toxicities and global shortages necessitate alternatives. Sequential gemcitabine and docetaxel (Gem/Doce) is a prominent candidate. To systematically analyze the efficacy, tolerability, and biomarker-driven selection of Gem/Doce versus BCG in BCG-naïve HR-NMIBC. Following PRISMA guidelines, databases (PubMed, Scilit, ScienceDirect, Google Scholar) were searched (2015–2026) for comparative studies in BCG-naïve HR-NMIBC patients. Out of 300 initial records retrieved, 58 duplicates were removed, leaving 242 unique articles for screening. Following title and abstract screening, 229 irrelevant papers were excluded, and 13 full-text manuscripts were assessed for eligibility. Ultimately, 6 high-quality studies met all selection criteria and were included in the qualitative synthesis. Evaluated outcomes included recurrence-free survival (RFS), progression-free survival (PFS), complete response (CR) rates, and adverse events. Risk of bias was assessed using MINORS. Six studies (1,126 patients) were synthesized. In unselected cohorts, Gem/Doce showed comparable or superior 24-month high-grade RFS (HG-RFS: 81% vs. 69%; HR 0.57, p=0.04) and fewer discontinuations due to toxicity (2.9% vs. 9.2%; p=0.02) than BCG. In pure Ta high-grade (TaHG) papillary disease, BCG was superior for RFS (62% vs. 37%, p=0.013) and PFS (97% vs. 83%, p<0.001; HR 13.54). Chronological age did not significantly affect response, though older patients showed stable RFS with Gem/Doce compared to a decline with BCG. AI-powered digital pathology (CHAI) and transcriptomic signatures (ESTIMATE) successfully predicted suboptimal BCG responses (RFS 56% and 63%) but exceptional Gem/Doce responses (RFS 90%). MINORS scores (17–22) indicated low bias. Sequential Gem/Doce is a highly effective, tolerable first-line alternative to BCG, particularly for older patients and those with adverse histologic or immune-score transcriptomic profiles. BCG remains superior for pure TaHG papillary disease.

Keywords: bacillus calmette-guérin; bladder cancer; docetaxel; gemcitabine; sequential chemotherapy; systematic review

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INTRODUCTION

Bladder cancer represents one of the most prevalent and costly malignancies to manage globally, with approximately 75% of newly diagnosed patients presenting with non-muscle-invasive bladder cancer (NMIBC) (Babjuk et al., 2019; Chang et al., 2016; Lindskrog et al., 2021). Among these, patients classified as high-risk non-muscle-invasive bladder cancer (HR-NMIBC)—including those harboring high-grade Ta lesions, invasive T1 tumors, and/or flat carcinoma in situ (CIS)—face a substantial long-term hazard of tumor recurrence (up to 40% at 2 years) and potential progression to muscle-invasive disease (Babjuk et al., 2019; Breyer et al., 2010; Chang et al., 2016; Herr et al., 2007). Since its clinical introduction by Morales et al. in 1976 and subsequent regulatory approvals, intravesical immunotherapy with Bacillus Calmette-Guérin (BCG) has served as the undisputed gold standard adjuvant therapy following complete transurethral resection of bladder tumor

(TURBT) (Gontero et al., 2010; Morales et al., 1976). Multiple large-scale trials and meta-analyses have solidified BCG's superiority over older single-agent chemotherapeutic regimens (such as mitomycin C, epirubicin, and doxorubicin) in delaying recurrence and mitigating the risk of progression (Gontero et al., 2010; Malmström et al., 2009; Shelley et al., 2004).

Despite its clinical efficacy, standard intravesical BCG therapy is associated with severe localized and systemic toxicities driven by a localized, cell-mediated mycobacterial inflammatory response (Oddens et al., 2013; Sylvester et al., 2003). Common adverse reactions such as severe dysuria, urinary frequency, gross hematuria, and systemic flu-like symptoms lead to early treatment discontinuation in up to 20% of patients, preventing completion of the recommended maintenance schedules (Eraky et al., 2026; Steinberg et al., 2015; Sylvester et al., 2003). Furthermore, continuous, severe global production shortages have severely disrupted the standard urological care pipeline for over a decade, frequently forcing clinicians to ration doses or utilize suboptimal, unproven regimens (Babjuk et al., 2019; Chang et al., 2016). This critical bottleneck has driven an urgent, international search for a highly effective, safe, and readily available first-line alternative.

Sequential intravesical chemotherapy utilizing a doublet of gemcitabine and docetaxel (Gem/Doce) was originally pioneered in 2015 by Steinberg et al. as a salvage protocol, demonstrating impressive durability and survival in patients with multi-recurrent NMIBC who had failed multiple prior rounds of BCG (Steinberg et al., 2015). Biologically, gemcitabine (a nucleoside analog) acts via direct incorporation into tumor cellular DNA, terminating replication and inducing apoptosis, which synergizes with docetaxel (a taxane derivative) that binds microtubule tubulin to prevent mitotic disassembly and tumor cell division (Steinberg et al., 2015; McKiernan et al., 2006). This dual chemotherapy approach exploits non-overlapping cytotoxicity and has recently transitioned into the first-line, treatment-naïve setting during periods of BCG supply failure (McElree et al., 2023; Abou Chakra et al., 2026). While several institutions have adopted Gem/Doce as the preferred first-line alternative, clinical evidence directly comparing these two regimens remains scattered across retrospective cohorts, small prospective pilot trials, and biomarker evaluation platforms. Therefore, this systematic review aims to synthesize and critically analyze all available comparative data regarding the efficacy, tolerability, and predictive biomarker-driven selection of sequential Gem/Doce versus standard BCG in strictly BCG-naïve high-risk NMIBC patients.

METHOD

Search Strategy

Table 1.
Keyword Search Strategy

Database	Keywords / Search Strings Used
PubMed MEDLINE	("Urinary Bladder Neoplasms" OR "bladder cancer" OR "NMIBC" OR "non-muscle-invasive" OR "superficial bladder cancer") AND ("Deoxycytidine/analogs and derivatives" OR "gemcitabine") AND ("Docetaxel" OR "docetaxel") AND ("BCG Vaccine" OR "Bacillus Calmette-Guerin" OR "BCG")
ScienceDirect	("bladder cancer" OR "NMIBC") AND "gemcitabine" AND "docetaxel" AND ("BCG" OR "Bacillus Calmette-Guerin")
Scilit	("bladder cancer" OR "NMIBC" OR "non-muscle-invasive bladder cancer") AND ("gemcitabine") AND ("docetaxel") AND ("BCG" OR "Bacillus Calmette-Guerin")
SpringerLink	("bladder cancer" OR "NMIBC" OR "non-muscle-invasive bladder cancer") AND "gemcitabine" AND "docetaxel" AND "BCG"
Google Scholar	("bladder cancer" OR "NMIBC") "gemcitabine" "docetaxel" ("BCG" OR "Bacillus Calmette-Guerin")

The conduct and reporting of this systematic review adhered strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. To identify relevant studies, a comprehensive and systematic electronic search was executed across major databases, including PubMed/MEDLINE, Scilit, ScienceDirect, and Google Scholar, covering the publication period from 2015 to 2026. The search strings utilized combinations of Boolean

operators and relevant MeSH terms, including: ('non-muscle-invasive bladder cancer' OR 'NMIBC' OR 'high-risk bladder cancer') AND ('Bacillus Calmette-Guérin' OR 'BCG') AND ('gemcitabine and docetaxel' OR 'Gem/Doce' OR 'sequential intravesical chemotherapy') AND ('recurrence-free survival' OR 'tolerability' OR 'adverse events').

Study Selection

Study selection was strictly structured around the PICO (Population, Intervention, Comparison, Outcome) framework as detailed in Table 2. Eligible study designs were restricted to randomized controlled trials (RCTs), prospective cohort studies, and comparative retrospective observational cohort studies. Single-arm trials, studies incorporating BCG-refractory or pre-treated cohorts, review articles, editorials, and case series were excluded from analysis. Following this rigorous screening protocol, an initial database query successfully retrieved 300 records. Through a structured sequential filtration process consisting of the removal of 58 duplicates, abstract-level screening of 242 unique papers, and a detailed full-text review of 13 potential candidates 7 trials were systematically excluded for failing to satisfy our PICO standards, ultimately yielding 6 premier comparative studies that met all criteria for qualitative and quantitative synthesis. Data extraction from eligible articles was performed independently using a standardized data extraction template, capturing study design, country, patient characteristics, specific dosing protocols, oncologic outcomes (RFS, PFS, and CR rates), and graded adverse events based on the Common Terminology Criteria for Adverse Events (CTCAE).

Table 2.
PICO Framework for Study Eligibility

Criteria	Definition / Study Eligibility Criteria
Population (P)	Adult patients (aged >=18 years) with pathologically confirmed high-risk non-muscle-invasive bladder cancer (HR-NMIBC), including high-grade Ta (TaHG), invasive T1, and/or Carcinoma in situ (CIS), who are strictly BCG-naïve (no prior intravesical immunotherapy).
Intervention (I)	Sequential intravesical chemotherapy utilizing a combination doublet of Gemcitabine (typically 1 g or 2 g) followed sequentially by Docetaxel (typically 37.5 mg or 40 mg).
Comparison (C)	Standard intravesical Bacillus Calmette-Guérin (BCG) therapy (TICE or Danish strain), including at least a 6-week induction course with or without subsequent maintenance therapy.
Outcomes (O)	Primary outcomes: High-grade Recurrence-Free Survival (HG-RFS), Progression-Free Survival (PFS), and Complete Response (CR) rates. Secondary outcomes: Adverse events (AEs) graded via CTCAE and therapy discontinuation rates due to drug intolerance.

Methodological Quality and Risk of Bias Assessment

To satisfy the rigorous quality assessment requirements for international medical journals, the methodological quality of all included studies was systematically evaluated. Given that five of the six included papers represent non-randomized comparative retrospective studies (or sub-cohort analyses) and one represents a prospective non-randomized pilot study with alternative assignment, the Methodological Index for Non-Randomized Studies (MINORS) tool was selected as the most appropriate assessment instrument. The MINORS checklist for comparative studies contains 12 validated items: (1) a clearly stated aim; (2) inclusion of consecutive patients; (3) prospective collection of data; (4) endpoints appropriate to the study aim; (5) unbiased evaluation of endpoints; (6) follow-up period appropriate to the study aim; (7) loss to follow-up <=5%; (8) prospective calculation of study size; (9) an adequate control group; (10) contemporary groups; (11) baseline equivalence of groups; and (12) adequate statistical analyses. Each item was independently scored by two reviewers as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate), yielding a maximum score of 24. A MINORS score of >=17 was prospectively defined as indicating high methodological quality with a low risk of bias.

RESULT

Study Selection and General Characteristics

A total of 300 initial electronic records were retrieved from the databases (PubMed: 7; Scilit: 75; ScienceDirect: 8; SpringerLink: 10; Google Scholar: 200). Following deduplication, 58 duplicate

citations were removed, leaving 242 unique papers for screening based on their titles and abstracts. Of these, 229 irrelevant reports were excluded. The remaining 13 full-text manuscripts were retrieved and thoroughly assessed for PICO eligibility. Ultimately, 7 studies were excluded (2 no relevant data, 1 different outcome, 2 review or editorial, 1 no comparison, 1 not full text), leaving 6 high-quality studies selected for qualitative synthesis. The complete selection process is conceptually illustrated in accordance with standard PRISMA flowcharts (Figure 1).

Table 3.
Characteristics of Included Studies Comparing BCG and Sequential Gem/Doce

Study & Design	Cohort & Size (N)	Primary Findings / Parameters	Key Clinical Conclusions
McElree et al. (2023) Retrospective cohort	BCG: n=174 Gem/Doce: n=138 Total: 312	24-mo HG-RFS: 81% for Gem/Doce vs. 69% for BCG (HR 0.57, p=0.04). Induction discontinuation: 2.9% vs. 9.2% (p=0.02).	Gem/Doce yields superior RFS and better tolerability compared to standard BCG in unselected high-risk NMIBC.
Pareek et al. (2022) Prospective comparative	BCG: n=30 Gem/Doce: n=30 Total: 60	Significant improvement in QLQ-C30 & QLQ-BLS-24 scores for Gem/Doce (p<0.05). Zero progressions; equal RFS at short-term 6-mo.	Gem/Doce sequential therapy is a highly safe, effective alternative that preserves patient-reported quality of life.
Eraky et al. (2026) Retrospective cohort	BCG: n=99 Gem/Doce: n=74 Total: 173	In pure TaHG: 2-year any-grade RFS was 62% for BCG vs. 37% for Gem/Doce (p=0.013). 2-year PFS was 97% vs. 83% (p<0.001).	BCG remains superior for exophytic, papillary Ta high-grade tumors. Caution should be used with Gem/Doce in this subset.
Abou Chakra et al. (2026) Retrospective cohort	BCG: n=192 Gem/Doce: n=209 Total: 401	Age not statistically associated with RFS in either cohort (p>0.05). BCG showed descriptive RFS decline in elderly; Gem/Doce stable.	Chronological age should not exclude patients from therapy. Gem/Doce shows stable efficacy in elderly cohorts.
Packiam et al. (2025a) Multicenter validation	BCG: n=159 Gem/Doce: n=94 Total: 253	Presence of CHAI biomarker: 24-mo HG-RFS of 56% with BCG vs. 90% with Gem/Doce (HR 5.4, p=0.007). Interaction p=0.029.	The AI-based CHAI biomarker successfully predicts poor BCG response. Gem/Doce is highly effective for CHAI-positive tumors.
Packiam et al. (2025b) Transcriptomic model	BCG: n=92 Gem/Doce: n=51 Total: 143	High ESTIMATE immune score: 24-mo HG-RFS of 90% with Gem/Doce vs. 63% with BCG (HR 0.25, p=0.02).	High baseline immune infiltration is associated with poor BCG response but exceptional sequential Gem/Doce response.

As detailed in Table 3 above, among the 6 selected papers, McElree et al. (2023) represented the benchmark, large-scale comparative retrospective cohort study conducted at a high-volume tertiary urological center, assessing 312 patients with a median follow-up of 23–49 months. Pareek et al. (2022) conducted a prospective comparative pilot trial evaluating 60 patients, which represents the first clinical trial evaluating patient-reported quality of life (QOL) between these two cohorts. Eraky et al. (2026) isolated a cohort of 173 patients presenting strictly with Ta high-grade (TaHG) papillary tumors. Abou Chakra et al. (2026) conducted the largest comparative cohort analysis to date (401 patients) specifically designed to evaluate the impact of chronological age on therapeutic response. The remaining two studies by Packiam et al. focused on cutting-edge predictive biomarkers of response, evaluating artificial intelligence-powered digital pathology (CHAI biomarker, 253 patients) (Packiam et al., 2025a) and transcriptomic gene expression signatures of local immune infiltration (ESTIMATE score, 143 patients) (Packiam et al., 2025b).

Methodological quality evaluation using the MINORS scale demonstrated exceptionally strong and consistent clinical-scientific evidence. The prospective pilot clinical trial by Pareek et al. (2022) achieved a score of 22 out of 24, reflecting the highest methodological rigour, characterized by

explicit study power calculations and zero loss to follow-up. The remaining retrospective comparative studies and retrospective molecular validation cohort analyses scored 17 or 18 out of 24. Points in these retrospective trials were primarily deducted due to the non-prospective nature of data collection and the absence of prospective study size power calculations. Nonetheless, all six included studies demonstrated an acceptable low risk of bias (MINORS >= 17), ensuring outstanding internal and external validity for our qualitative synthesis. The detailed itemized and cumulative scores for each paper are reported in table 4.

Table 4.
Methodological Quality Assessment of Included Studies using the Comparative MINORS Instrument

Study	I1	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12	Total
McElree et al. (2023)	2	2	0	2	1	2	1	0	2	2	1	2	17 / 24
Pareek et al. (2022)	2	2	2	2	1	1	2	2	2	2	2	2	22 / 24
Eraky et al. (2026)	2	2	0	2	1	2	1	0	2	2	1	2	17 / 24
Abou Chakra et al. (2026)	2	2	0	2	1	2	1	0	2	2	1	2	17 / 24
Packiam et al. (2025a)	2	2	0	2	2	2	1	0	2	2	1	2	18 / 24
Packiam et al. (2025b)	2	2	0	2	2	2	1	0	2	2	1	2	18 / 24

**I1=Clearly stated aim; I2=Consecutive patient inclusion; I3=Prospective data collection; I4=Appropriate endpoints; I5=Unbiased evaluation of endpoints; I6=Appropriate follow-up period; I7=Loss to follow-up <=5%; I8=Prospective calculation of study size; I9=Adequate control group; I10=Contemporary groups; I11=Baseline equivalence of groups; I12=Adequate statistical analyses. Total scores >=17 indicate low risk of bias.*

Oncological Efficacy: Recurrence and Progression

Synthesized data from unselected high-risk NMIBC cohorts demonstrate excellent and durable therapeutic efficacy for sequential Gem/Doce, matching or exceeding BCG outcomes (McElree et al., 2023; Abou Chakra et al., 2026). In the benchmark study by McElree et al. (2023), the 24-month high-grade recurrence-free survival (HG-RFS) was 81% for Gem/Doce versus 69% for the BCG group. On multivariable Cox regression controlling for age, sex, and concomitant CIS, Gem/Doce was associated with a statistically significant 43% reduction in the risk of high-grade recurrence (HR 0.57, 95% CI 0.33–0.97, p=0.04) and a 44% reduction in overall recurrence (HR 0.56, 95% CI 0.34–0.92, p=0.02) compared to standard BCG (McElree et al., 2023). Furthermore, progression-free survival (PFS) was comparable between the two cohorts at 24 months, with 97% in the Gem/Doce group versus 92% in the BCG group (McElree et al., 2023; Abou Chakra et al., 2026).

However, this superior efficacy profile experiences a critical reversal in the subpopulation of patients with pure Ta high-grade (TaHG) papillary tumors, as isolated by Eraky et al. (2026)[3]. In this retrospective study of 173 patients, standard intravesical BCG demonstrated a highly significant therapeutic advantage over Gem/Doce[3]. At 24 months, the any-grade RFS was 62% for BCG versus 37% for Gem/Doce (p=0.013). More critically, the 2-year PFS was 97% in the BCG group compared to 83% in the Gem/Doce group (p<0.001)[3]. On multivariate Cox analysis, treatment with sequential Gem/Doce was associated with an extreme risk increase for disease progression (HR 13.54, 95% CI 1.63–112.18, p<0.001) and any-grade recurrence (HR 1.91, p=0.008) in this specific papillary cohort[3]. This indicates a striking contrast in efficacy depending on baseline tumor morphology and infiltration.

Tolerability and Therapy Discontinuation Profiles

The tolerability profiles of both regimens represent a crucial factor in clinical compliance. Graded adverse events (AEs) show distinct pathophysiological patterns based on the mechanism of action (McElree et al., 2023; Pareek et al., 2022; Sylvester et al., 2003). Patients receiving sequential Gem/Doce are significantly more likely to experience transient localized mechanical side effects such as severe bladder spasms (21.0% vs. 5.2%, p<0.001) and nausea (3.6% vs. 0.6%, p=0.09),

which are primarily attributed to the cumulative catheter dwell time (up to 180 minutes) required for consecutive chemotherapy instillations (McElree et al., 2023; Pareek et al., 2022). Conversely, patients treated with BCG are significantly more likely to suffer from localized inflammatory and systemic immunological toxicities, including severe dysuria (12.6% vs. 5.1%, p=0.03), hematuria (10.9% vs. 5.8%, p=0.16), severe systemic fatigue/flu-like symptoms (6.9% vs. 5.1%), and arthralgias (4.0% vs. 0%, p=0.02) (McElree et al., 2023). Critically, this localized and systemic immunological burden translated into a significantly higher rate of induction therapy discontinuation due to intolerance in the BCG group compared to the sequential Gem/Doce doublet (9.2% vs. 2.9%, p=0.02) (McElree et al., 2023; Abou Chakra et al., 2026).

Table 5.
Comparative Adverse Events and Treatment Discontinuation Rates between Intravesical BCG and Sequential Gem/Doce

Adverse Event (AE) / Parameter	BCG Cohort (N = 174)	Gem/Doce Cohort (N = 138)	p-value
Induction Discontinuation due to Intolerance	16 (9.2%)	4 (2.9%)	0.02
Bladder Spasms (Grade 1-2)	9 (5.2%)	29 (21.0%)	<0.001
Dysuria (Grade 1-2)	22 (12.6%)	7 (5.1%)	0.03
Hematuria (Grade 1-2)	19 (10.9%)	8 (5.8%)	0.16
Arthralgias (Grade 1-2 / Systemic)	7 (4.0%)	0 (0.0%)	0.02
Fatigue and Flu-like Symptoms	12 (6.9%)	7 (5.1%)	0.64

Impact of Age and Precision Biomarkers

In terms of age stratification, Abou Chakra et al. (2026) demonstrated that chronological age is not a statistically significant predictor of RFS or HG-RFS following either intravesical BCG or Gem/Doce therapy. However, descriptive Kaplan-Meier trends revealed a progressive and steady decline in 12- and 24-month RFS with advancing age specifically in the BCG group (24-month RFS of 64% in patients <60 years versus 58% in those aged 70–79 years and 59% in those >=80 years), matching historical concerns of immunosenescence (Abou Chakra et al., 2026; Solana et al., 2006). Conversely, older patients treated with sequential Gem/Doce exhibited highly stable, robust outcomes over time (24-month RFS: 73% for <60 years vs. 80% for 70–79 years and 76% for >=80 years) (Abou Chakra et al., 2026). Most importantly, precision medicine advances were identified in the two Packiam et al. (2025) studies (Packiam et al., 2025a; Packiam et al., 2025b). The presence of the AI-powered H&E slide-based CHAI biomarker predicted a poor response to BCG (24-month HG-RFS of 56%) but an outstanding response to sequential Gem/Doce (HG-RFS of 90%; HR 5.4, p=0.007) (Packiam et al., 2025a). Similarly, the transcriptomic ESTIMATE model revealed that patients harboring high immune score signatures had particularly suboptimal responses to standard BCG (2-year HG-RFS of 63%) but achieved an exceptional response to sequential Gem/Doce (2-year HG-RFS of 90%; HR 0.25, 95% CI 0.07–0.85, p=0.02) (Packiam et al., 2025b). These findings represent the first validated tools for guiding individualised, personalized intravesical therapy selection.

DISCUSSION

The findings of this systematic review provide robust, practice-changing insights into first-line adjuvant therapy for BCG-naïve high-risk NMIBC, demonstrating that the therapeutic superiority of sequential Gem/Doce or standard BCG is heavily dictated by baseline clinical, morphological, and molecular features (McElree et al., 2023; Eraky et al., 2026; Packiam et al., 2025a). In unselected cohorts of high-risk patients, sequential Gem/Doce achieves superior high-grade RFS (81% vs. 69% at 24 months) and significantly lower discontinuation rates than standard BCG, presenting a highly viable, cost-effective generic first-line alternative, particularly during periods of severe global BCG shortages (McElree et al., 2023; Pareek et al., 2022; McKiernan et al., 2006). The clinical superiority of Gem/Doce in unselected cohorts is further reinforced by prospective quality of life data from Pareek et al. (2022), showing that patients receiving the chemotherapy doublet experience significantly less urinary irritation and better role, physical, and emotional functioning scores compared to those undergoing BCG instillation (Pareek et al., 2022; Tavelli et al., 2025).

However, a critical clinical paradox arises in patients with pure Ta high-grade (TaHG) papillary disease. As reported by Eraky et al. (2026), standard BCG demonstrates a clear and substantial advantage in preventing any-grade recurrence and stage progression over Gem/Doce in this specific cohort. The biological mechanism explaining this divergence is rooted in the distinct physical and cellular features of exophytic papillary lesions (Eraky et al., 2026; Shariat et al., 2009). Papillary TaHG tumors are exophytic, remaining entirely above the epithelial basement membrane, making them highly amenable to the localized, Th1-mediated localized cellular immune response triggered by BCG (Eraky et al., 2026; Gontero et al., 2010; Morales et al., 1976). This intense immune cascade—which involves mycobacterial internalization by urothelial cells, antigen presentation via MHC class II, and massive release of proinflammatory Th1 cytokines—clears superficial microscopic cells more effectively than passive chemotherapeutic cytotoxicity (Eraky et al., 2026; Morales et al., 1976). Conversely, infiltrative (T1) or flat (CIS) tumors may possess distinct microenvironmental features that are resistant to BCG-mediated clearance but highly susceptible to direct, rapid tissue absorption and cytotoxicity of consecutive gemcitabine and docetaxel (McElree et al., 2023; Steinberg et al., 2015). This highlights that tumor stage and baseline architecture represent essential clinical parameters for therapy selection.

The age-stratified data from Abou Chakra et al. (2026) also provide a key biological piece of the puzzle. Older patients are historically known to experience suboptimal responses and higher recurrence rates following cancer immunotherapies due to systemic immunosenescence—the age-associated exhaustion of naive T-cell populations, progressive atrophy of the lymphoid microenvironment, and a compromised capacity to mount a productive, sustained Th1-mediated localized inflammatory response to BCG (Abou Chakra et al., 2026; Solana et al., 2006). This is descriptively highlighted by the progressive decline in BCG efficacy among patients aged 70–79 years (58% RFS) and >=80 years (59% RFS) compared to younger patients (64% RFS) (Abou Chakra et al., 2026). In contrast, because sequential Gem/Doce relies entirely on direct, non-immune-dependent chemotherapeutic cytotoxicity (inducing mitotic arrest and direct DNA chain termination), its high efficacy is fully preserved in the elderly, achieving stable, superior 24-month RFS rates (80% for 70–79 years and 76% for >=80 years) independent of host immune status (Abou Chakra et al., 2026; Steinberg et al., 2015). This suggests that chronological age represents a strong clinical indicator favoring Gem/Doce over BCG.

Finally, the landmark studies by Packiam et al. (2025) transition HR-NMIBC management from empirical treatment to a precision-medicine paradigm (Packiam et al., 2025; Packiam et al, 2025). The Computational Histologic Artificial Intelligence (CHAI) biomarker is the first H&E-based predictive tool showing that patients with CHAI-positive tumors experience poor response to BCG (56% RFS) but highly superior responses to sequential Gem/Doce (90% RFS) (Packiam et al., 2025). Biologically matching this finding, transcriptomic molecular profiling utilizing ESTIMATE immune scores revealed that patients harboring high immune signatures had an extremely poor response to standard BCG (63% RFS) but an outstanding response to Gem/Doce (90% RFS) (Packiam et al., 2025). This biological paradox—where high baseline immune infiltration predicts poor response to a localized immunotherapy—is explained by the presence of a 'pre-exhausted' microenvironment (Packiam et al., 2025; Morales et al., 1976). High immune scores in high-grade urothelial specimens are frequently characterized by dense infiltration of regulatory T-cells (Tregs) and marked upregulation of immune checkpoint molecules (such as PD-1/PD-L1), which actively suppress the active, productive inflammatory response required for BCG efficacy (Packiam et al., 2025; Morales et al., 1976). However, this hyper-vascularized and cellularly dense microenvironment facilitates rapid uptake, retention, and localized tissue concentration of sequentially instilled gemcitabine and docetaxel, leading to profound cytotoxic tumor clearance (Packiam et al., 2025; Steinberg et al., 2015). Combining clinical histopathology, patient age, and

these novel predictive assays represents the future gold standard for HR-NMIBC treatment selection.

Study Limitation and Clinical Confounders

To ensure a balanced and scientific appraisal, several limitations and clinical confounders inherent in the current literature must be discussed. First, the majority of the clinical comparative evidence currently available is derived from retrospective cohort studies (McElree et al., 2023; Eraky et al., 2026; Abou Chakra et al., 2026), which carry an inherent vulnerability to patient selection biases and residual confounding factors. Second, although the prospective pilot trial by Pareek et al. (2022) provides invaluable, patient-reported quality of life (QOL) data, its overall cohort size was small (N = 60), restricting its statistical power to detect subtle differences in long-term progression rates. Third, clinical practice variations represent a substantial source of clinical heterogeneity; for instance, the BCG cohort in McElree et al. (2023) and Abou Chakra et al. (2026) frequently received combination immunotherapy with Interferon-alpha-2b (IFN-a2b) and tailored, reduced one-third dosing during periods of limited BCG supply, mirroring real-world clinical compromises rather than standardized academic protocols. Furthermore, a critical methodological confounder is the overlap of patient populations among the sub-analyses. The transcriptomic study (Packiam et al., 2025) and the AI-histologic CHAI study (Packiam et al., 2025) evaluate subsets of the primary cohort detailed in McElree et al. (2023) and Abou Chakra et al. (2026) (predominantly from the University of Iowa tertiary care center). Consequently, these molecular and sub-group findings must be interpreted as specialized characterizations of a shared parent population rather than completely independent validation cohorts. Finally, the retrospective median follow-up times were highly imbalanced, ranging from up to 84 months for BCG but limited to 20-23 months for the newly adopted Gem/Doce regimen (McElree et al., 2023; Abou Chakra et al., 2026). While this represents the longest follow-up for Gem/Doce currently published, longer, multi-institutional, prospectively randomized trials (such as the ongoing phase III BRIDGE clinical trial (Kates et al., 2023) are strictly necessary to fully validate the long-term durability of sequential Gem/Doce as a gold-standard first-line alternative.

CONCLUSION

This systematic review demonstrates that sequential intravesical Gem/Doce represents a highly effective, safe, and well-tolerated first-line alternative to standard BCG for BCG-naïve high-risk NMIBC, providing superior tolerability and significantly lower therapy discontinuation rates. Adjuvant therapy selection should be highly personalized: standard BCG remains the optimal choice for patients presenting with pure exophytic Ta high-grade papillary tumors, while sequential Gem/Doce should be highly prioritized for older, immunosenescent cohorts, and patients harboring adverse H&E histologic (CHAI biomarker-positive) or high immune-signature transcriptomic profiles.

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