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ROLE OF BACILLUS CALMETTE–GUÉRIN (BCG) IN NON-MUSCLE INVASIVE BLADDER CANCER (NMIBC)

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Abstract

Introduction: Non-muscle invasive bladder cancer (NMIBC) represents approximately 70–75% of newly diagnosed bladder cancers and is associated with high recurrence and progression rates. Intravesical Bacillus Calmette–Guérin (BCG) immunotherapy remains the gold standard adjuvant treatment for intermediate- and high-risk NMIBC due to its significant antitumor efficacy (1,2). Objective: To review the role, mechanism of action, clinical efficacy, indications, and limitations of intravesical BCG therapy in the management of non-muscle invasive bladder cancer. A narrative review of published literature, clinical guidelines, randomized trials, and review articles related to BCG therapy in NMIBC was conducted using indexed medical databases. Relevant studies focusing on immunological mechanisms, treatment protocols, therapeutic outcomes, and adverse effects were included (1–15). Result: BCG therapy exerts its antitumor effect through activation of both innate and adaptive immune responses. Following intravesical instillation, BCG binds to urothelial fibronectin and stimulates cytokine release, inflammatory cell recruitment, and Th1-mediated immune activation (7,8). Clinical studies have demonstrated that BCG significantly reduces tumor recurrence and progression compared with TURBT alone or intravesical chemotherapy (14,15). Maintenance BCG therapy further improves recurrence-free survival in high-risk patients. Despite its effectiveness, treatment-related adverse effects and BCG-unresponsive disease remain important clinical challenges (11,13). Conclusion: Intravesical BCG remains the cornerstone treatment for intermediate- and high-risk NMIBC. Its efficacy is primarily mediated through immune activation leading to durable antitumor responses and bladder preservation. Continued advances in immunotherapy and molecular oncology may improve future management strategies for patients with BCG-resistant disease.

Keywords: Non-muscle invasive bladder cancer; Bacillus Calmette–Guérin; BCG immunotherapy; intravesical therapy; bladder cancer; immune response; urothelial

Introduction

Bladder cancer is one of the most common malignancies of the urinary tract, and nearly 70–75% of newly diagnosed cases are categorized as non-muscle invasive bladder cancer (NMIBC) at presentation (1). NMIBC includes papillary tumors confined to the mucosa (Ta), tumors invading the lamina propria (T1), and carcinoma in situ (CIS) (2). Although these tumors are initially superficial, they are characterized by high recurrence rates and a significant risk of progression into muscle-invasive bladder cancer (MIBC), which carries poorer prognosis and increased mortality (2).

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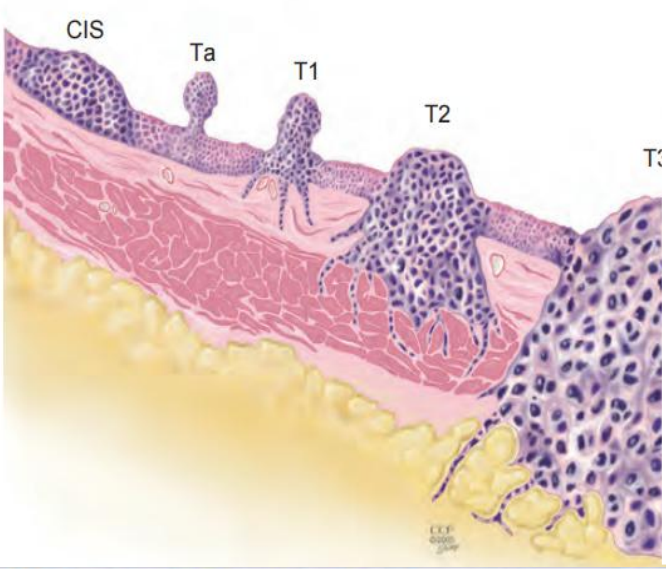
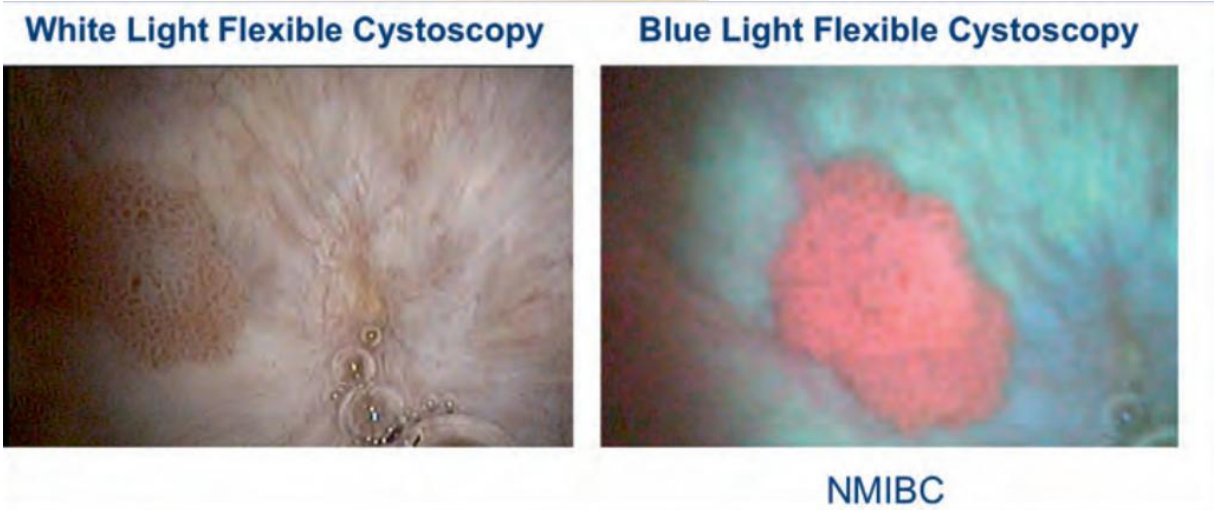


Fig 1; Carcinoma in situ is a high-grade, flat malignancy confined to the urothelium. Papillary tumors confined to the urothelium are Ta, whereas papillary tumors invading lamina propria are T1. The T1 tumor here intertwines with the wispy fibers of the muscularis propria but by definition does not invade the



Fig; White and blue light cystoscopy of non–muscle-invasive bladder cancer (NMIBC) using flexible cystoscopy after administration of hexaminolevulinate.

The standard treatment for NMIBC involves transurethral resection of bladder tumor (TURBT), often followed by intravesical therapy to reduce recurrence and progression (3). Among available intravesical agents, Bacillus Calmette–Guérin (BCG) remains the most effective immunotherapeutic modality for intermediate- and high-risk NMIBC (4). Since its first clinical use by Morales et al. in 1976, intravesical BCG has revolutionized the management of superficial bladder cancer and is currently regarded as the gold standard adjuvant therapy for high-risk NMIBC (5).

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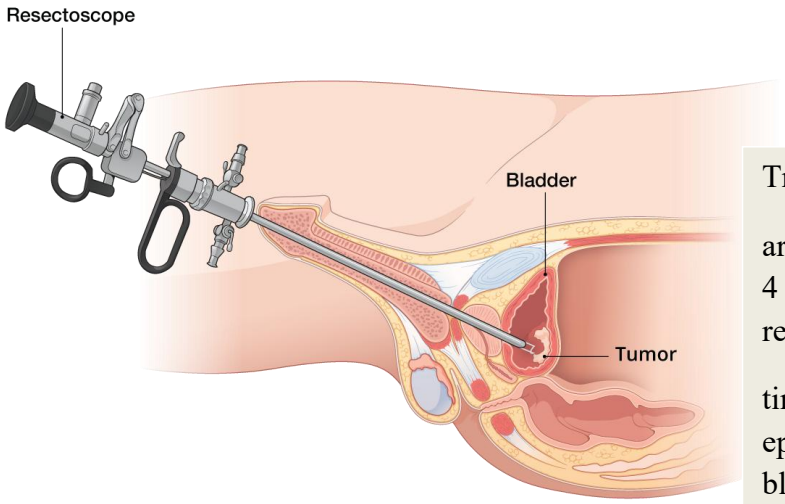

Treatments

are typically started 2 to 4 weeks after tumor resection, allowing

time for re-epithelialization of the bladder after TURBT

Bacillus Calmette–Guérin (BCG)

BCG is a live attenuated strain of Mycobacterium bovis, originally developed as a vaccine against tuberculosis (6). The antitumor properties of BCG were discovered when experimental studies demonstrated immune stimulation and tumor regression after administration into the bladder (5). Unlike conventional chemotherapeutic agents that directly destroy tumor cells, BCG acts primarily by stimulating a strong local immune response against malignant urothelial cells (7).Intravesical BCG therapy involves the instillation of BCG directly into the bladder through a urethral catheter. This localized administration allows direct interaction between BCG and bladder mucosa while minimizing systemic toxicity (4).

Mechanism of Action of BCG in NMIBC

The exact mechanism of BCG therapy is complex and multifactorial. Its efficacy depends on interactions between BCG, urothelial cells, tumor cells, and host immune responses involving both innate and adaptive immunity (7,8).

1. Attachment of BCG to Urothelial Cells

Following intravesical instillation, BCG comes into contact with the bladder urothelium. The organism binds to fibronectin, an extracellular matrix glycoprotein present on urothelial cells, through fibronectin attachment proteins (FAPs) expressed by BCG organisms (7). This attachment is essential because it facilitates internalization of BCG into urothelial and bladder cancer cells. Internalized BCG acts as an immunogenic stimulus that initiates inflammatory and immune-mediated reactions within the bladder wall (8).

2. Activation of Innate Immune Response

The innate immune response represents the earliest phase of BCG-induced antitumor activity. Once internalized, BCG stimulates urothelial cells, macrophages, dendritic cells, and neutrophils to release numerous pro-inflammatory cytokines and chemokines (7). Important cytokines released include: Interleukin-1 (IL-1) ,Interleukin-2 (IL-2), Interleukin-6 (IL-6) , Interleukin-8 (IL-8) , Interleukin-12 (IL-12) , Tumor necrosis factor-alpha (TNF-α) , Interferon-gamma (IFN-γ) . These cytokines promote recruitment of inflammatory cells into the bladder wall and create a highly cytotoxic tumor microenvironment (8). Neutrophils are among the earliest cells recruited after BCG instillation and are believed to play a major role in initiating antitumor immunity (9). Macrophages activated by BCG can directly destroy tumor cells through the production of nitric oxide, reactive oxygen species, and tumor necrosis factors (10).

3. Activation of Adaptive Immune Response

The adaptive immune response is critical for long-term tumor control. BCG therapy predominantly induces a T helper-1 (Th1) mediated immune response, which is associated with effective antitumor activity (7).Antigen-presenting cells process BCG antigens and present them to CD4+ T lymphocytes, resulting in activation of cytotoxic CD8+ T cells and natural killer (NK) cells (11). Activated T lymphocytes produce IFN-γ and IL-2, which enhance cellular immunity

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against bladder cancer cells (8). Patients with stronger Th1 cytokine responses generally demonstrate better clinical outcomes and lower recurrence rates following BCG therapy (11).

4. Direct Cytotoxic Effects on Tumor Cells

Besides immune activation, BCG may exert direct cytotoxic effects on bladder tumor cells. Activated immune cells release perforins, granzymes, reactive oxygen species, and TRAIL (tumor necrosis factor-related apoptosis-inducing ligand), leading to apoptosis and necrosis of malignant urothelial cells (10). Additionally, BCG may alter tumor cell signaling pathways and increase expression of major histocompatibility complex (MHC) molecules, thereby improving immune recognition of cancer cells (7).

5. Trained Immunity and Immunologic Memory

Recent evidence suggests that BCG induces "trained immunity," a process involving epigenetic and metabolic reprogramming of innate immune cells such as monocytes and macrophages (12). Unlike classical immunologic memory associated with adaptive immunity, trained immunity enhances the responsiveness of innate immune cells to subsequent tumor-related stimuli.This mechanism may explain the prolonged protective effect of BCG therapy and its ability to reduce tumor recurrence over time (12).

Clinical Role of BCG in NMIBC

Indications for BCG Therapy BCG therapy is mainly indicated in:

- High-grade Ta tumors
- T1 tumors
- Carcinoma in situ (CIS)
- Intermediate-risk recurrent tumors (2)

Current European Association of Urology (EAU) and American Urological Association (AUA) guidelines recommend BCG as first-line adjuvant therapy for high-risk NMIBC because of its superior efficacy compared with intravesical chemotherapy (2,13).

BCG Treatment Protocol

Induction Therapy

The standard induction course consists of weekly intravesical instillation of BCG for six consecutive weeks (4). Treatment usually begins 2–3 weeks after TURBT to allow healing of the urothelial mucosa and reduce systemic absorption (13).

Maintenance Therapy

Maintenance BCG therapy significantly improves recurrence-free survival and progression-free survival compared with induction therapy alone (14). The Southwest Oncology Group (SWOG) regimen is the most widely used protocol and involves: Three weekly instillations at: 3 months , 6 months , Every 6 months thereafter up to 3 years Long-term maintenance is particularly beneficial in high-risk NMIBC (14).

Efficacy of BCG Therapy

Numerous clinical trials and meta-analyses have demonstrated the superiority of BCG over TURBT alone and intravesical chemotherapy (4).

Benefits include:Reduction in tumor recurrence , Delayed progression to muscle-invasive disease , Improved disease-specific survival , Effective treatment for carcinoma in situ , Preservation of the urinary bladder (2,4)

Sylvester et al. reported that BCG therapy with maintenance reduced progression risk by approximately 27% compared with controls (15).

Adverse Effects of BCG Therapy

Although effective, BCG therapy is associated with local and systemic adverse effects resulting from immune activation (11).

Local Side Effects; Common local adverse effects include: Dysuria , Frequency, Urgency , Hematuria , Suprapubic pain These symptoms are usually self-limiting and indicate local immune activation (11).

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Systemic Side Effects; Fever , Malaise , Arthralgia , Fatigue . Rare but serious complications include: Granulomatous prostatitis , Pneumonitis , Hepatitis, Osteomyelitis, Disseminated BCG infection (BCG sepsis) ,BCG sepsis is rare but potentially life-threatening and requires prompt antitubercular therapy (13).

BCG Failure and BCG-Unresponsive Disease

Despite its success, approximately 30–40% of patients eventually experience BCG failure (10). BCG-unresponsive disease includes persistent or recurrent high-grade tumors despite adequate BCG therapy.Management options for BCG-unresponsive NMIBC include:

- Radical cystectomy
- Intravesical chemotherapy
- Immune checkpoint inhibitors
- Novel immunotherapeutic agents (13)

Pembrolizumab, an anti-PD-1 monoclonal antibody, has shown promising results in selected patients with BCG-unresponsive carcinoma in situ (13).

Conclusion

Intravesical BCG remains the cornerstone treatment for intermediate- and high-risk NMIBC. Its efficacy is mediated through a complex interaction between BCG organisms, urothelial cells, and host immune responses involving both innate and adaptive immunity. BCG significantly reduces recurrence and progression while preserving bladder function. Although adverse effects, treatment resistance, and global shortages remain important challenges, BCG continues to represent one of the most successful examples of cancer immunotherapy in modern urology.

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