Glosains: Jurnal Sains Global Indonesia
Volume 7, Issue 2, 429-437
e_ISSN: 2798-4311
https://glosains.staiku.ac.id
DOI: doi.org/10.59784/glosains.v7i2.678

The Impacts of Intravesical Bacillus Calmette–Guérin (BCG) Therapy on Male Fertility in Non-Muscle-Invasive Bladder Cancer (NMIBC): A Narrative Review

Rosadi Putra[1*]
Universitas Tarumanagara, Indonesia

Devi Astri Rivera Amelia[2]
Universitas Tarumanagara, Indonesia

***Corresponding author:**
Rosadi Putra, Universitas Tarumanagara, Indonesia. ✉rd.boo.84@gmail.com

Article Info :

Article history:
Received: March 02nd, 2026
Revised: April 28th, 2026
Accepted: April 30th, 2026

Keywords:
bacillus calmette–guérin; non–muscle-invasive bladder cancer; intravesical therapy; sperm parameters; male fertility; gonadotoxicity.

Abstract

Background: Intravesical *Bacillus Calmette–Guérin* (BCG) is the current gold standard adjuvant therapy to reduce both recurrence and progression of non-muscle-invasive bladder cancer (NMIBC). On the other hand, there is a growing concern about its possible effect on male fertility.

Objective: This narrative review provides an analysis of the recent evidence regarding the impact of intravesical BCG therapy on semen quality and overall male fertility parameters in reproductive-age NMIBC patients.

Methods: A targeted literature review was performed for prospective clinical studies assessing semen parameters and reproductive hormones before and after intravesical therapy. A narrative review was conducted that included studies eligible for inclusion (up to date through October 2023) to describe comparative changes in semen quality and endocrine function by comparing BCG-treated men with matched cohorts following exposure.

Results: Intravesical BCG was associated with decreased sperm concentration and motility, in some cases with progression to oligospermia and abnormal sperm morphology including "amorphous" heads, bent necks, and short tails—although results were inconsistent. Although early studies found stable hormonal profiles, recent data have shown increases in follicle-stimulating hormone and testosterone, indicating testicular stress with compensatory feedback mechanisms. Conversely, no adverse reproductive effects were observed with mitomycin C.

Conclusions: Intravesical BCG may transiently interfere with spermatogenesis while endocrine function remains intact. These results underline the importance of fertility counseling and semen cryopreservation before intravesical therapy. This needs to be confirmed in larger studies with longer follow-up periods for reproductive outcomes.

To cite this article: Putra, R., & Amelia, D. A. R. (2026). The Impacts of Intravesical Bacillus Calmette–Guérin (BCG) Therapy on Male Fertility in Non-Muscle-Invasive Bladder Cancer (NMIBC): A Narrative Review. *Glosains: Jurnal Sains Global Indonesia*, *7*(2), 429-437. https://doi.org/10.59784/glosains.v7i2.678

INTRODUCTION

Bladder cancer is one of the most common genitourinary tumors globally. According to GLOBOCAN 2022, it ranked as the ninth most common cancer globally, with an incidence of 614,298 cases and a mortality of 220,596 in that year. Recent epidemiological trends illustrate increasing incidence among men of reproductive age, related to environmental exposures, occupational carcinogens, and improved detection (Ferlay et al., 2021; Marić et al., 2021). The disease predominantly affects men and older adults, but while the precision of global estimates of bladder cancer incidence for men aged under 45 remains poor, the trend toward younger-onset

disease is apparent in population-based registries and presents an urgent need to address fertility preservation. Increased exposure to tobacco smoke, aromatic amines from occupational sources, and the consumption of ultra-processed foods have also been associated with changes in age distribution for bladder cancer globally (Kliemann et al., 2022). Rapidly urbanizing lifestyles and lifelong exposures to industrial toxins in developing countries such as Indonesia only add to this epidemiological transition, emphasizing the relevance of bladder cancer treatment to fertility outcomes in younger patients (van Hoogstraten et al., 2023).

Approximately 75% of newly diagnosed bladder cancers present as non-muscle-invasive bladder cancer (NMIBC), comprising stages Ta, T1, and carcinoma in situ (CIS). Current management of NMIBC involves transurethral resection of bladder tumor (TURBT) followed by risk-adapted intravesical therapy (Matulay et al., 2020). Across major guidelines, intravesical Bacillus Calmette–Guérin (BCG) immunotherapy is the gold-standard adjuvant treatment for intermediate- and high-risk NMIBC, offering superior prevention of recurrence and progression compared to intravesical chemotherapy (Deininger et al., 2022; Ng et al., 2022). Similarly, the ESMO 2022 consensus designates intravesical BCG as the standard of conservative management, reserving mitomycin C (MMC) and gemcitabine for low-risk or BCG-intolerant cases.

Although the oncologic benefits of intravesical BCG are well established, its potential adverse effects outside the bladder, especially on male reproductive function, are not well understood (Green et al., 2019). This issue is important for reproductive-age patients who wish to maintain fertility after bladder-sparing therapy. Several studies have examined how these treatments may affect spermatogenesis and hormonal function in younger men for whom fertility remains a paramount concern. Beyond the biological dimension, the threat of impaired reproductive capacity significantly affects quality of life (QoL) and psychosexual well-being (Lutkiewicz et al., 2023). Cancer-related infertility is linked to depression, relationship distress, and decisional regret, highlighting the need for a patient-centered oncologic model integrating reproductive counseling with cancer treatment.

This is a narrative review of the current clinical data regarding the impact of intravesical therapy (BCG and mitomycin C [MMC]) on male fertility, semen quality, and hormonal function in NMIBC. It also aims to bring attention to the potential gonadotoxicity of these therapies, discuss the psychosocial burden of fertility concerns in reproductive-age patients, highlight the invaluable role of fertility counseling and semen preservation strategies, and identify research gaps to illuminate important future directions for studies on reproductive outcomes and safety mechanisms underlying intravesical agents.

METHOD

Because of substantial heterogeneity in relation to study design, patient age, BCG strain, treatment protocol, and outcome measurement within the available literature regarding this topic, a narrative review design was chosen over a systematic review/meta-analysis. The limited number of eligible prospective studies does not allow pooled quantitative synthesis, which favors a descriptive, narrative approach to summarize current evidence and identify research gaps. Articles published in English through October 2023 were identified by a focused literature search of PubMed, Scopus, and Google Scholar. The search was carried out using combinations of keywords and Medical Subject Headings (MeSH) terms: "intravesical therapy," "Bacillus Calmette–Guérin," "mitomycin C," "bladder cancer," "sperm," "semen analysis," "fertility," and "hormonal profile."

The inclusion criteria for studies were as follows: (1) Adult male patients with NMIBC treated with intravesical BCG; (2) Reported at least one semen or hormonal parameter pre- and post-treatment; and (3) Provided original retrospective or prospective data. Exclusion criteria comprised reviews, case reports without semen analysis, and studies exploring only oncologic or local toxicity outcomes. Limitations of this narrative review include lack of formal risk-of-bias assessment, a small number of eligible studies (n = 3), and possible publication bias against nonsignificant findings. Finally, the fact that studies differed in BCG strains used, patient age spectrum, and duration of follow-up does not allow direct between-study comparisons.

This search identified three eligible clinical studies that were synthesized in further detail. Data were extracted on study design, patient characteristics, treatment regimen, semen and hormonal outcomes, and reported reproductive effects. Studies were required to assess semen

parameters (including volume, concentration, motility, and/or morphology) in conjunction with serum reproductive hormones among men receiving intravesical BCG or mitomycin C (MMC) treatment after transurethral resection of bladder tumor (TURBT). Assessments after treatment were conducted approximately 3 months after induction therapy (1 cycle of spermatogenesis). Included studies performed comparative and descriptive analyses on changes from baseline. A narrative review approach was used to compare and describe the findings across studies, compile results that were consistently observed between studies, and identify the gaps in existing knowledge on the reproductive effects of intravesical therapy in NMIBC.

RESULTS AND DISCUSSION

Three prospective clinical trials fulfilled the inclusion criteria and focused on the reproductive effects of intravesical BCG or MMC in men with NMIBC. Despite differences in study design, size, and age of patients, the data were decidedly trending toward demonstrable (and in some cases statistically significant) changes in semen quality after BCG exposure, while MMC did not appear to impart reproductive toxicity.

a. Raviv (2005)

Raviv (2005) were one of the first to examine this prospectively and comparatively. Twelve men younger than 40 years who were candidates for intravesical therapy and had recently undergone two-stage transurethral resection of bladder tumors were recruited after providing informed consent. Twelve patients were then allocated to either the intravesical BCG (6 pts.) or MMC (6 pts.) groups. Both groups underwent an induction schedule of 6 weeks, after which semen and hormonal assays were repeated at 3 months.

The results indicated that MMC had no deleterious effect on any semen parameter. In contrast, patients receiving BCG displayed markedly impaired spermatogenic indices. Fifty percent of the patients (n = 3, 50%) had a significant reduction in sperm concentration ($p = 0.0021$), and two cases demonstrated decreased motility and pathozoospermia/hyperspermia. Notably, both groups had normal hormonal assays for testosterone, FSH, and LH. This finding—along with normal endocrine function but decreased spermatogenesis—provides evidence that BCG-induced impairment is due to local effects on the seminiferous epithelium rather than systemic suppression of hypothalamic–pituitary–gonadal activity, further supported by mechanistic findings of proinflammatory cytokine release and blood–testis barrier disruption. The authors suggested that BCG may cause localized inflammatory or immune-mediated disruption of spermatogenesis, while MMC appears to be biologically safe.

b. Garg (2014)

Garg (2014) conducted an even larger prospective study of 17 men aged under 45 years who were sexually active, supporting this observation. Transurethral resection was performed for all patients, followed by intravesical BCG induction for 6 weeks.

Semen and hormone profiles were measured at baseline and 3 months after treatment completion. Post-treatment evaluations showed a statistically significant decline in semen quality. The mean sperm concentration dropped from approximately $83.2 \pm 23.7 \times 10^6$/mL to $24.1 \pm 14.8 \times 10^6$/mL ($p = 0.0001$), while total motility dropped from 72.6% to 21.0% ($p = 0.0001$). Oligospermia was defined as sperm concentration $<15 \times 10^6$/mL according to the WHO (2010) criteria, and five of them (29.4%) had this condition after treatment. Of these five cases, four had baseline concentrations within normal range; thus, BCG exposure was considered to be responsible rather than a pre-existing subclinical disorder. Semen volume and morphology showed no significant change, suggesting the effect of intravesical treatment was limited to sperm production and motility, but not the secretory function of the seminal glands.

No significant changes in endocrine function were observed, as FSH, LH, and testosterone levels did not differ significantly. This implies that the testicular dysfunction observed does not result from systemic hormonal dysregulation, but rather reflects local degenerative changes within the testis. In conclusion, the results demonstrated that intravesical BCG can transiently impair spermatogenesis and decrease sperm motility while maintaining endocrine balance. The authors highlighted the need for early fertility discussion among younger men and suggested

sperm cryopreservation before intravesical immunotherapy. From a clinical standpoint, these results substantiate the necessity of universal fertility screening in all men of reproductive age diagnosed with NMIBC, regardless of their documented fertility intentions at diagnosis. The gross decline in semen parameters over a 6-week period following just one course of BCG highlights the pressing need for offering semen cryopreservation as an opportunistic pre-treatment backup prior to any intravesical BCG therapy.

c. Sahin (2025)

Sahin (2025) offered a more extensive assessment of sperm and hormonal alterations in 23 sexually active men (mean age 54.7 years) with NMIBC treated with six weekly instillations of SII-ONCOBCG after transurethral resection. This follow-up window of approximately three months—equivalent to one complete spermatogenic cycle (approximately 74 days in humans)—was adequate for comparing pre- and post-treatment semen and hormonal analyses to detect changes in sperm production and maturation resulting from the intervention.

The authors found a significant reduction in sperm concentration, total count, progressive motility, and normal morphology following treatment. The increasing number of immotile sperm was accompanied by morphology defects such as amorphous heads, bent necks, and very short tails. Four participants developed new-onset oligospermia. Hormonal assessment demonstrated a significant increase in FSH and total testosterone levels, while LH and prolactin remained unchanged. From a physiological standpoint, elevated FSH in the context of impaired sperm output supports dysfunction or damage to Sertoli cells, resulting in inadequate secretion of inhibin B, which removes the negative feedback on the pituitary, leading to reactive elevation of FSH. Simultaneously, this modest increase in testosterone may be attributed to Leydig cell compensatory activation in response to increased LH sensitivity or activated paracrine cytokine signaling pathways (consistent with primary testicular insult rather than central hormone suppression). These findings were interpreted as a compensatory endocrine response to testicular stress rather than suppression of central hormonal function. The authors suggested that oxidative stress and inflammatory cytokine release following BCG exposure may transiently disrupt the blood–testis barrier and impair spermatogenesis. Although these effects appear reversible, the findings highlight the susceptibility of testicular tissue to intravesical immunotherapy and the need for counseling and semen preservation in men wishing to maintain fertility (Sahin et al., 2025).

The key characteristics and outcomes of the three prospective studies are summarized in Table 1.

Table 1. Comparison of prospective studies evaluating the impact of intravesical therapy on male reproductive parameters in NMIBC

Study	Design and Population	Therapy	Assessment Timing	Semen Parameters	Hormonal Findings	Key Interpretations
Raviv (2005)	Prospective comparative study involving 12 men < 40 years.	Six weekly instillations of BCG (n = 6) or mitomycin C (n = 6) after TURBT.	Baseline and three months after induction.	The BCG group showed a marked decline in sperm concentration (p = 0.0021) and reduced motility, while the MMC group showed no significant change.	Testosterone, FSH, and LH remained within normal range.	BCG may cause localized, immune-mediated impairment of spermatogenesis, while MMC appears biologically safe.
Garg (2014)	Prospective study	Six-week induction	Baseline and three	Significant reduction in	Testosterone, FSH, and	BCG temporarily impairs

Study	Design and Population	Therapy	Assessment Timing	Semen Parameters	Hormonal Findings	Key Interpretations
	involving 17 sexually active men < 45 years.	course of intravesical BCG following TURBT.	months after induction.	sperm concentration (83.2 → 24.1 $\times 10^6$/mL; p = 0.0001) and motility (72.6% → 21%; p = 0.0001); morphology and volume remained unchanged. Five patients developed oligospermia.	LH remained within normal range.	spermatogenesis and motility without hormonal suppression.
Sahin (2025)	Single-center prospective study including 23 sexually active men (mean age 54.7 ± 6.1 years).	Six weekly instillations of SII-ONCO-BCG following TURBT.	Baseline and three months after induction.	Significant decreases in sperm concentration, total count, progressive motility, and morphology (all p < 0.05); four patients developed oligospermia; immotile and abnormal forms such as amorphous heads, bent necks, and short tails became more frequent.	FSH and total testosterone levels increased, while LH and prolactin remained unchanged.	BCG induces testicular stress and inflammatory changes disrupting spermatogenesis, likely transient and reversible.

Taken together, these studies demonstrate that intravesical BCG can temporarily impair semen quality through localized inflammatory and immune-mediated mechanisms, while MMC shows no such effects. Hormonal profiles generally remain stable, supporting the interpretation that BCG's reproductive impact is primarily testicular.

Discussion

The Use of Intravesical BCG in the Management Of NMIBC

Intravesical BCG therapy has become the cornerstone treatment for NMIBC due to its proven efficacy in reducing recurrence and progression, its favorable safety profile, and its well-established mechanisms of action (Morales et al., 2017). The concept originated from Morales et al., who demonstrated that intravesical instillation of attenuated *Mycobacterium bovis* could prevent tumor relapse through localized immune activation (Morales et al., 2017). The importance of maintenance treatment was later confirmed by Lamm et al., whose randomized trial established superior recurrence-free and progression-free survival compared with induction

alone (Lamm et al., 1991).

Meta-analyses provided quantitative validation. Sylvester et al. reported a 27 percent reduction in progression risk with BCG, while Böhle and Bock confirmed its superiority to MMC, particularly when maintenance schedules were used (Böhle & Bock, 2004; Sylvester et al., 2002). In clinical practice, BCG is administered after complete tumor resection as a six-week induction course with each instillation retained for about two hours, followed by scheduled maintenance to sustain immune activation and prolong benefit (Lamm et al., 1991).

BCG attaches to the urothelium, is taken up by urothelial and antigen-presenting cells, and causes the release of cytokines (IL-1, IL-6, IL-8, TNF-α) and a host response with recruitment of macrophages, neutrophils, and lymphocytes. This progresses first to a Th1-mediated response by upregulating production of interferon-γ and IL-2, resulting in granulomatous inflammation with cytotoxic lysis of tumor cells (Ferlay et al., 2021). Local adverse effects, such as cystitis symptoms and low-grade fever, are common but systemic events rarely occur; granulomatous prostatitis, epididymo-orchitis, and disseminated infection have all been reported, probably related to either organism spread or immune cross-reactivity, and should be kept in mind for some selected patients (Ferlay et al., 2021).

Major guidelines align with these findings. ESMO recommends BCG after complete resection for intermediate and high-risk NMIBC, with maintenance advised when tolerated (Powles et al., 2022). NCCN designates induction plus maintenance BCG as the preferred adjuvant option for high-grade Ta, T1, and carcinoma in situ, while intravesical chemotherapy such as mitomycin C or gemcitabine is reserved for low-risk disease or for patients who cannot receive BCG. The EAU similarly recommends BCG as first-line adjuvant therapy after transurethral resection in intermediate and high-risk patients and advises one to three years of maintenance depending on risk and tolerance. Collectively, decades of evidence confirm BCG as the most effective bladder-preserving therapy and a model of successful cancer immunotherapy.

Mechanisms of BCG-Induced Reproductive Toxicity

Although BCG therapy is highly effective against bladder cancer, its immune-stimulating action may occasionally extend beyond the bladder and trigger inflammation in nearby organs. In some men, this response affects the reproductive tract, leading to tissue injury. The underlying mechanisms are thought to involve a combination of direct bacterial spread, immune-mediated hypersensitivity, and cytokine-driven oxidative stress. To strengthen the internal coherence of this review, the following discussion explicitly links each pathophysiological mechanism to the clinical outcomes observed across the three included studies (Fuge et al., 2015; Redelman-Sidi et al., 2014).

L*ocal dissemination and granulomatous inflammation*

During intravesical instillation, retrograde reflux through ejaculatory ducts may allow BCG organisms to reach the prostate, seminal vesicles, or epididymis, where they induce granulomatous inflammation composed of epithelioid histiocytes and Langhans-type giant cells (Low et al., 2021). The multicenter analysis by Pérez-Jacoiste Asín et al. reported systemic BCG infection occurred in 4.3% of 256 patients, with genitourinary involvement including prostatitis and epididymo-orchitis in 23% of them (Asín et al., 2014). Granulomatous epididymo-orchitis accounted for 3.5% of cases, with some lesions being culture-negative, indicating an immune-mediated inflammation rather than active infection (Asín et al., 2014). Raviv (2005) supported this mechanism by observing impaired spermatogenesis only in patients treated with BCG, not MMC, and citing animal studies where intratesticular BCG caused reversible aspermatogenic orchitis without endocrine dysfunction.

Hypersensitivity and autoimmune cross-reactivity

Sterile inflammatory lesions suggest that BCG may induce delayed-type hypersensitivity via shared mycobacterial and testicular antigens, breaching the blood–testis barrier and exposing germ cells to cytotoxic lymphocytes (Low et al., 2021). This mechanism is supported by recovery with corticosteroids alone in some patients, as reported by Pérez-Jacoiste Asín et al., consistent with an immune rather than infectious process (Asín et al., 2014). Th1-dominant cytokines—IFN-γ, TNF-α, IL-2—can disrupt Sertoli cell junctions, impairing spermatogenesis (Redelman-Sidi et

al., 2014). Garg (2014) also proposed that the decline in semen parameters arises from cell-mediated immune activation and Th1-dominant cytokine profiles typical of BCG exposure, rather than direct bacillary infection. Granulomatous prostatitis and epididymo-orchitis have also been described as manifestations of systemic hypersensitivity, which may depend on host genetic susceptibility or strain virulence (Garg et al., 2014).

Cytokine-mediated oxidative stress

Ibarra et al. showed BCG-mediated Ca^{2+}-dependent NF-κB activation and cytokine (IL-6, IL-8) release, generating reactive oxygen species that harm nearby tissues (Low et al., 2021). Sahin (2025) clinically extended this concept, demonstrating oxidative and inflammatory damage in seminiferous tubules resulting in deranged spermatogenesis, which correlates with elevated FSH and testosterone after therapy, indicating compensatory endocrine activation rather than central suppression (Sahin et al., 2025). Macrophages and neutrophils propagate this inflammatory pattern within the testes, generating oxidative injury to germ-cell membranes and DNA—which results in transient decreases in sperm numbers, motility, and morphology as recorded in clinical studies (Garg et al., 2014; Raviv et al., 2005; Sahin et al., 2025).

Hematogenous spread and latent infection

Following trauma to the catheterization tract or immediate instillation post-resection, BCG can disseminate hematogenously, especially when the urothelium is disrupted (Asín et al., 2014). Viable bacilli have also been isolated from the epididymis and renal tissue months or years later, suggesting that intracellular persistence within macrophages can sustain a latent focus of infection. These findings are consistent with Garg's observation that while testicular injury may persist in acute cases of BCG toxicity, its effects are often temporary (Garg et al., 2014).

Integrated pathophysiology

Altogether, the evidence available supports a multi-hit process consisting of direct bacillary seeding, immune-mediated granulomatous inflammation, cytokine-driven oxidative stress, and autoimmune mimicry. Semen quality is often significantly but transiently decreased, although endocrine parameters (FSH, LH, testosterone) typically remain stable, suggesting a testicular insult rather than central hormonal suppression. These mechanisms help integrate the clinical findings: the amorphous sperm heads and abnormal tails observed by Sahin (2025) are compatible with cytokine-mediated oxidative stress damaging germ-cell membranes and interrupting normal spermiogenesis; the severe motility defect reported by Garg et al. is consistent with diffuse mitochondrial dysfunction in the midpiece caused by reactive oxygen species; the acute waves of oligospermia in each study were consistent with granulomatous disruption of seminiferous tubule architecture, which temporarily inhibits spermatogonial proliferation (Garg et al., 2014; Raviv et al., 2005; Sahin et al., 2025). The majority of cases respond to anti-tuberculous therapy or corticosteroids, but a minority continues in a state of inflammation, highlighting the role for fertility counseling and semen preservation in reproductive-age males undergoing BCG therapy. Whether semen parameters return to baseline after halting BCG treatment is an important clinical question. Only the three studies reviewed here evaluated outcomes at 3 months post-induction, and none provided any long-term follow-up data thereafter. Since the cycle of spermatogenesis is already known to be around 74 days, initial recovery could be anticipated between three and six months. On the other hand, if a disrupted blood–testis barrier or the state of chronic granulomatous inflammation persists, full recovery would not be achieved for 12 months or even much longer. Future studies should use sperm measures at 6 and 12 months post-treatment to assess the durability of recovery and identify patients at risk for prolonged impairment (Asín et al., 2014).

CONCLUSION

Intravesical Bacillus Calmette–Guérin (BCG) continues to be the most effective adjuvant treatment for NMIBC, but prospective data from numerous studies with both short- and long-term follow-up suggest that it can transiently suppress spermatogenesis through localized inflammatory and immune-mediated testicular injury. These changes occur with preserved

endocrine function, suggesting that the seminiferous epithelium is the primary target of these exposures, rather than the hypothalamic–pituitary–gonadal axis. While recovery is generally seen, the clinical significance of this with respect to fertility in men in their reproductive years is often overlooked. Semen cryopreservation prior to initiating BCG therapy should be implemented as a standard of care for all reproductive-aged men undergoing treatment for NMIBC. As a result, we believe that structured multidisciplinary collaboration between urologic oncologists and reproductive medicine specialists is essential to ensure that fertility preservation is appropriately offered and systematically integrated into NMIBC treatment pathways. Future studies with larger cohorts, longer follow-up (≥12 months), and more standardized semen and hormonal endpoints are required to determine recovery trajectories and optimize evidence-based fertility preservation protocols during bladder-sparing therapy.

ACKNOWLEDGEMENT

The authors would like to thank Universitas Tarumanagara for providing academic support and scientific resources that refrained finishing this narrative review. The authors would like to extend their gratitude to all the colleagues, and academic peers who contributed to discussions on concepts that informed the genesis and development of this manuscript. We thank the researchers whose articles provided the basis for this review, particularly those exploring potential reproductive effects of intravesical BCG therapy in patients with nonmuscle invasive bladder cancer.

AUTHOR CONTRIBUTION STATEMENT

Rosadi Putra: Conceptualising the idea, Search of literature, Performing a synthesis of the data and Datar analysis and Interpretation of findings; Writing—Original draft preparation. Devi Astri Rivera Amelia: Supported literature review, critically revised the manuscript, validated clinical interpretation and final editing.

REFERENCES

Asín, M. A. P.-J., Fernández-Ruiz, M., López-Medrano, F., Lumbreras, C., Tejido, A., San Juan, R., Arrebola-Pajares, A., Lizasoain, M., Prieto, S., & Aguado, J. M. (2014). Bacillus Calmette-Guérin (BCG) infection following intravesical BCG administration as adjunctive therapy for bladder cancer: incidence, risk factors, and outcome in a single-institution series and review of the literature. *Medicine*, *93*(17), 236–254. https://doi.org/10.1097/MD.0000000000000119

Böhle, A., & Bock, P. R. (2004). Intravesical bacille Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. *Urology*, *63*(4), 682–686. https://doi.org/10.1016/j.urology.2003.11.049

Deininger, S., Törzsök, P., Mitterberger, M., Pallauf, M., Oswald, D., Deininger, C., & Lusuardi, L. (2022). From interferon to checkpoint inhibition therapy—A systematic review of new immune-modulating agents in Bacillus Calmette–Guérin (BCG) refractory non-muscle-invasive bladder cancer (NMIBC). *Cancers*, *14*(3), 694.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., Znaor, A., Soerjomataram, I., & Bray, F. (2021). Global cancer observatory: cancer today. Lyon: International Agency for Research on Cancer; 2020. *Cancer Tomorrow*.

Fuge, O., Vasdev, N., Allchorne, P., & Green, J. S. A. (2015). Immunotherapy for bladder cancer. *Research and Reports in Urology*, 65–79. https://doi.org/10.2147/RRU.S63447

Garg, M., Sankhwar, S. N., Goel, A., Kumar, M., Singh, B. P., Singh, V., Dalela, D., Kumar, A., & Paul, S. (2014). Effect of intravesical immunotherapy on sperm parameters in young patients with non–muscle-invasive bladder carcinoma: prospective analysis. *Clinical Genitourinary Cancer*, *12*(3), e83–e86. https://doi.org/10.1016/j.clgc.2013.11.012

Green, D. B., Kawashima, A., Menias, C. O., Tanaka, T., Redelman-Sidi, G., Bhalla, S., Shah, R., & King, B. F. (2019). Complications of intravesical BCG immunotherapy for bladder cancer. *Radiographics*, *39*(1), 80–94.

Kliemann, N., Al Nahas, A., Vamos, E. P., Touvier, M., Kesse-Guyot, E., Gunter, M. J., Millett, C., & Huybrechts, I. (2022). Ultra-processed foods and cancer risk: from global food systems to individual exposures and mechanisms. *British Journal of Cancer*, *127*(1), 14–20.

Lamm, D. L., Blumenstein, B. A., Crawford, E. D., Montie, J. E., Scardino, P., Grossman, H. B., Stanisic, T. H., Smith Jr, J. A., Sullivan, J., & Sarosdy, M. F. (1991). A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette–Guerin for transitional-cell carcinoma of the bladder. *New England Journal of Medicine*, *325*(17), 1205–1209.

Low, L. S., Scholtz, D., Leyland, J., & Nair, S. M. (2021). A severe complication of intravesical bacillus Calmette-Guerin: An effect of different strains. *Urology Case Reports*, *36*, 101592. https://doi.org/10.1016/j.eucr.2021.101592

Lutkiewicz, K., Bieleninik, Ł., Kaloeti, D. V. S., & Bidzan, M. (2023). Reproductive health and well-being from a life span perspective. In *Frontiers in Psychology* (Vol. 14, p. 1289603). Frontiers Media SA.

Marić, T., Fučić, A., & Aghayanian, A. (2021). Environmental and occupational exposures associated with male infertility. *Archives of Industrial Hygiene and Toxicology*, *72*(2), 101.

Matulay, J. T., Soloway, M., Witjes, J. A., Buckley, R., Persad, R., Lamm, D. L., Boehle, A., Palou, J., Colombel, M., & Brausi, M. (2020). Risk-adapted management of low-grade bladder tumours: recommendations from the International Bladder Cancer Group (IBCG). *BJU International*, *125*(4), 497–505.

Morales, A., Eidinger, D., & Bruce, A. W. (2017). Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. *The Journal of Urology*, *197*(2S), S142–S145.

Ng, C. F., Enikeev, D., Vasdev, N., Ekin, G., Sousa, A., Leon, J., Guerrero-Ramos, F., Tan, W. S., Kelly, J., & Shariat, S. F. (2022). Background: The efficacy of intravesical chemotherapy maintenance for patients with non-muscle invasive bladder cancer (NMIBC) is inferior compared to intravesical bacillus Calmette–Guerin (BCG). How intravesical chemohyperthermia (CHT) compares with BCG is under investigation. Objective: To compare the oncological outcomes and safety profile between intravesical. *Recent Advances in Bladder Cancer Diagnosis and Treatment*, 77552758.

Powles, T., Bellmunt, J., Comperat, E., De Santis, M., Huddart, R., Loriot, Y., Necchi, A., Valderrama, B. P., Ravaud, A., & Shariat, S. F. (2022). Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology*, *33*(3), 244–258. https://doi.org/10.1016/j.annonc.2021.11.012

Raviv, G., Pinthus, J. H., Shefi, S., Mor, Y., Kaufman-Francis, K., Levron, J., Weissenberg, R., Ramon, J., & Madgar, I. (2005). Effects of intravesical chemotherapy and immunotherapy on semen analysis. *Urology*, *65*(4), 765–767.

Redelman-Sidi, G., Glickman, M. S., & Bochner, B. H. (2014). The mechanism of action of BCG therapy for bladder cancer—a current perspective. *Nature Reviews Urology*, *11*(3), 153–162. https://doi.org/10.1038/nrurol.2014.15

Sahin, S., Ulus, I., Canitez, I. O., Yentur, S., Temiz, M. Z., & Semercioz, A. (2025). The effect of intravesical Bacillus Calmette-Guerin (BCG) treatment on sperm parameters in non-muscle-invasive bladder cancer patients. *Basic and Clinical Andrology*, *35*(1), 17. https://doi.org/10.1186/s12610-025-00259-0

Sylvester, R. J., van der MEIJDEN, A. P. M., & Lamm, D. L. (2002). Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *The Journal of Urology*, *168*(5), 1964–1970.

van Hoogstraten, L. M. C., Vrieling, A., van der Heijden, A. G., Kogevinas, M., Richters, A., & Kiemeney, L. A. (2023). Global trends in the epidemiology of bladder cancer: challenges for public health and clinical practice. *Nature Reviews Clinical Oncology*, *20*(5), 287–304.