

HEALTH-RELATED QUALITY OF LIFE IN NMIBC PATIENTS WITH VARIOUS TREATMENT MODALITIES: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Non-muscle-invasive bladder cancer (NMIBC) is one of the most common urological malignancies, accounting for approximately 75% of newly diagnosed bladder cancer cases. Intravesical instillation therapy is widely utilized as an integral part of NMIBC treatment. **Objective:** This systematic review aims to synthesize current evidence on the impact of various intravesical instillation therapies, including BCG, gemcitabine, and epirubicin, as well as TURBT, on the HRQoL of NMIBC patients. **Material & Methods:** The search was carried out using the Google Scholar and PubMed search engines. Search keywords "Quality of life", "non-muscle-invasive-bladder-cancer", and "intravesical instillation". **Results:** Total of 711 articles were screened by keywords and literature reading. The articles continued screen for the eligibility with exclusion criteria. A total of 8 articles is continued for reading and reviewing process. **Conclusion:** Studies consistently show that gemcitabine/docetaxel regimens can improve QoL with fewer side effects compared to BCG. TURBT combined with intravesical therapies has demonstrated stable or improved QoL over time, reinforcing its role as a preferred treatment. The use of QoL tools, such as the EORTC QLQ-NMIBC24 and CAVICAVENMI, helps to capture patient-reported outcomes and inform the development of tailored interventions.

Keywords: Quality of life, NMIBC, intravesical instillation.

ABSTRAK

Pendahuluan: Inkontinensia urin (UI) merupakan kondisi yang umum terjadi pada perempuan dan dapat menurunkan kualitas hidup. Disfungsi otot dasar panggul berperan dalam terjadinya inkontinensia urin tipe stres dan campuran. Terapi High-Intensity Focused Electromagnetic (HIFEM) merupakan modalitas noninvasif yang menjanjikan untuk meningkatkan fungsi otot dasar panggul. **Tujuan:** Tinjauan sistematis ini bertujuan untuk menyintesis bukti terkini mengenai dampak berbagai terapi instilasi intravesikal termasuk BCG, gemcitabin, dan epirubisin serta TURBT terhadap kualitas hidup terkait kesehatan (HRQoL) pasien NMIBC. **Bahan & Cara:** Pencarian dilakukan menggunakan mesin pencari Google Scholar dan PubMed. Kata kunci pencarian yang digunakan adalah "Quality of life", "non-muscle-invasive-bladder-cancer", dan "intravesical instillation". **Hasil:** Sebanyak 711 artikel disaring berdasarkan kata kunci dan pembacaan literatur. Artikel-artikel tersebut kemudian disaring kembali untuk menentukan kelayakannya menggunakan kriteria eksklusi. Sebanyak 8 artikel dilanjutkan ke tahap pembacaan dan penelaahan. **Simpulan:** Berbagai studi secara konsisten menunjukkan bahwa regimen gemcitabine/docetaxel dapat meningkatkan kualitas hidup dengan efek samping yang lebih sedikit dibandingkan dengan BCG. Prosedur TURBT yang dikombinasikan dengan terapi intravesikal terbukti mampu menjaga stabilitas atau meningkatkan kualitas hidup seiring berjalannya waktu, sehingga memperkuat posisinya sebagai pilihan pengobatan utama. Penggunaan instrumen penilaian kualitas hidup, seperti EORTC QLQ-NMIBC24 dan CAVICAVENMI, membantu dalam memperoleh data mengenai hasil yang dilaporkan oleh pasien serta menjadi acuan bagi pengembangan intervensi yang disesuaikan dengan kebutuhan pasien.

Kata kunci: Kualitas hidup, NMIBC, intravesical instillation.

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INTRODUCTION

Non-muscle invasive bladder cancer (NMIBC) is a type of bladder cancer confined to the mucosal or submucosal layers without invasion into the muscular layer. Although it has a better prognosis

compared to muscle-invasive bladder cancer, NMIBC is associated with a high recurrence rate, necessitating continuous monitoring and repeated treatments.¹ The ongoing management of NMIBC can significantly impact various aspects of a patient's life, including health-related quality of life

(HRQoL). Understanding HRQoL in NMIBC patients is essential to evaluate the overall impact of treatment, including intravesical chemotherapy.²⁻³

Bladder cancer is the fourth most common cancer in men and the 11th most common cancer in woman accounting for 6.6% of all cancer cases. Non-muscle-invasive bladder cancer (NMIBC) is one of the most common urological malignancies, accounting for approximately 75% of newly diagnosed bladder cancer cases.⁴ While NMIBC is less aggressive than muscle-invasive bladder cancer, its high recurrence and progression rates pose significant challenges in long-term management. To address these issues, intravesical instillation therapy is widely utilized as an integral part of NMIBC treatment. This approach involves delivering therapeutic agents directly into the bladder, offering localized effects while minimizing systemic exposure.⁵⁻⁷

The cornerstone of intravesical therapy is *Bacillus Calmette-Guérin* (BCG), which has been shown to reduce recurrence and progression rates significantly, particularly in intermediate- and high-risk NMIBC patients.² However, BCG is often associated with adverse effects, such as urinary symptoms (e.g., frequency, urgency, dysuria) and systemic reactions, which may impact a patient's overall quality of life. In recent years, alternative agents such as gemcitabine and epirubicin have been explored as substitutes or adjuncts to BCG, aiming to provide comparable oncological outcomes with fewer side effects.⁸⁻⁹

Another key component of NMIBC management is transurethral resection of bladder tumors (TURBT), which is the standard initial treatment for diagnosis and removal of visible tumors. TURBT is often combined with intravesical instillation therapy to enhance therapeutic outcomes.¹⁰⁻¹¹ Despite its efficacy, TURBT and subsequent treatments may cause physical discomfort and psychological distress, underscoring the importance of evaluating health-related quality of life (HRQoL) in these patients.

NMIBC patients undergoing intravesical chemotherapy face various challenges, both physical and emotional. Common side effects, such as bladder irritation, painful urination, and haematuria, can interfere with daily activities and overall comfort. Additionally, the anxiety associated with the risk of recurrence and the need for frequent follow-up procedures like cystoscopy further adds to the psychological burden. These factors highlight the importance of HRQoL as a critical measure for

evaluating the treatment impact from the patient's perspective.²

HRQoL in NMIBC patients can be assessed using specific tools, such as the Bladder Cancer Index (BCI) or the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) with bladder cancer-specific modules. These instruments encompass physical, psychological, social, and emotional domains to provide a comprehensive understanding of how treatment affects a patient's life. Such measurements allow healthcare providers to gain deeper insights into patient needs and design more personalized management strategies.^{2,12}

OBJECTIVE

This systematic review aims to synthesize current evidence on the impact of various intravesical instillation therapies, including BCG, gemcitabine, and epirubicin, as well as TURBT, on the HRQoL of NMIBC patients. By comparing outcomes across different treatment modalities, the review seeks to identify patterns, highlight differences in patient-reported experiences, and provide insights into optimizing treatment strategies.

MATERIAL & METHODS

The search was carried out using the Google Scholar, PubMed and ClinicalKey search engines. Search keywords "Quality of life", "non-muscle-invasive-bladder-cancer", "intravesical instillation". Studies were considered eligible if they included NMIBC survivors as study participants, assessed quality of life as an outcome, and were published as clinical trials or original research articles in the English language. Studies were excluded if they were conducted in non-human populations or were deemed irrelevant to the research question and scope of the present systematic review.

Data were extracted using a standardized table that includes the name of the authors, year of publication, study design, and the key findings of each study. After searching and filtering articles based on search keywords, article analysis was done manually by considering the title's and abstract's relevance. Articles that meet the inclusion and exclusion criteria that are unclear will be analyzed further by reading the full text of the article and entering the relevant information in the data extraction table. The results obtained in the included studies will be compared with those of other systematic reviews and literature.

RESULTS

Based on keyword searches, 666 articles were obtained from Google scholar, 43 articles from PubMed and 2 articles from reference reading. 326 and 59 articles were excluded because the articles were review articles and duplicate (Figure 1). A total of 326 articles were continued for title screening. A total of 256 articles were excluded because they did not match the research objectives, therefore 70 articles met the criteria for continued abstract screening. A total of 53 articles were excluded again as the articles not contain the required data and could not be accessed by researchers, for the final process 8 articles were continued to read and reviewed.

The studies primarily involved patients diagnosed with non-muscle-invasive bladder cancer (NMIBC), ranging from low- to high-risk classifications. Sample sizes varied from small cohorts¹³ (42 participants in Rentsch, 2022) to larger trials¹⁴ (359 participants in Van Straten, 2023). Most studies included patients with either newly diagnosed or recurrent NMIBC, with some focusing on specific subgroups, such as BCG-naïve patients¹⁴ (Van Straten, 2023) or those experiencing recurrence after prior BCG therapy¹⁵ (Rentsch, 2022). Treatments were evaluated in randomized controlled trials (RCTs), observational studies, and one descriptive analysis.

Various validated tools were employed to assess quality of life (QoL) and health outcomes. These included the European Organization for Research and Treatment of Cancer (EORTC) questionnaires, such as QLQ-C30, QLQ-BLS24, and QLQ-NMIBC24, which measure general and bladder cancer-specific QoL. The EQ-5D-5L tool was used to evaluate overall health status in multiple studies. Specific tools like the SF-36 Physical and Mental Health scores¹⁵ (Vaioulis, 2021) and the International Prostate Symptom Score (IPSS)¹⁶ (Angulo, 2022) were also employed to gauge mental, physical, and urinary health over time.

Treatments spanned intravesical therapies, including BCG instillations^{13,14} gemcitabine plus docetaxel, and mitomycin C.^{16,17} Surgical approaches included transurethral resection of bladder tumours (TURBT)^{15,18} and radical treatments like cystectomy and radiotherapy.¹⁸ Outcomes varied across treatments. Gemcitabine/docetaxel yielded better QoL than BCG², while radically treated patients reported poorer QoL, particularly regarding body image and sexual function, compared to those undergoing TURBT.¹⁸ QoL generally remained stable or improved over time in studies employing TURBT with adjunctive therapies like BCG or epirubicin¹⁵ (Vaioulis, 2021) and recombinant BCG.¹³

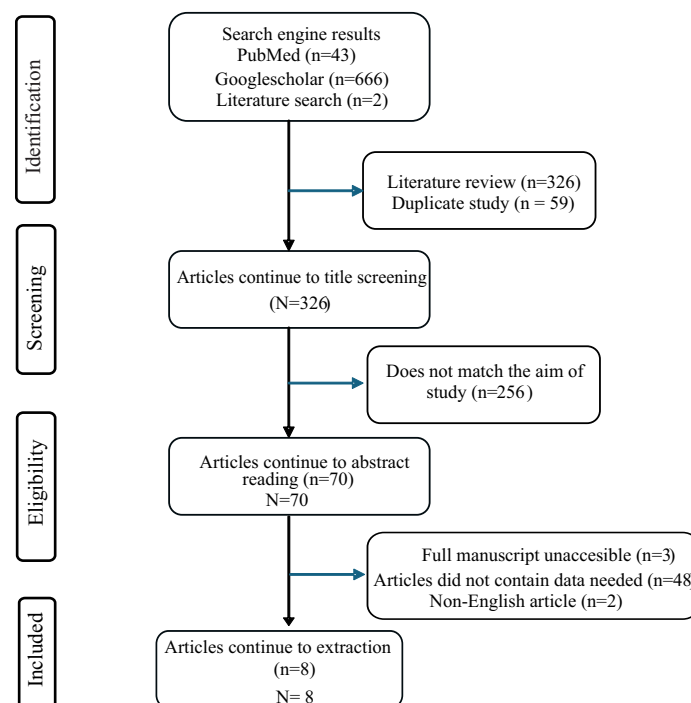


Figure 1. PRISMA flow diagram.

Table 1. Articles extraction and characteristics of the studies.

No	Author	Design	Sample size	Populations	Treatment of choice	Outcome
1	Van Straten, 2023 ¹⁴	Randomized controlled trial	359		BCG instillation	There were no significant differences in the means of each QoL scale between the two arms. There were also no significant changes over time in all QoL domains for both arms. However, differences in the incidence of general malaise at T1 (before the last induction instillation), frequency, urgency, and dysuria at T7 (before the last maintenance instillation) were detected in favor of the reduced frequency arm.
2	Pareek, 2022 ²	Observational	60	patients with NMIBC	Gemcitabine+ docetaxel vs BCG	The QOL scores using QLQ -30 and QLQ -BLS-24 showed statistically significant differences with the Gem/ Doce arm showing better outcomes.
3	Rogers,2023 ¹⁸	Observational	233	patients with new bladder cancer diagnoses at 13 NHS Trusts	Transurethral resection, intravesical therapy, radical cystectomy/radiotherapy	Radically treated patients continued to report poorer HRQoL including issues with body image (23.4 vs 12.5, P = 0.007) and male sexual function (75.8 vs 40.4, P < 0.001) compared to those who underwent TURBT. Radically treated patients reported lower EQ-5D utility scores and more problems with usual activities than the general population.
4	Vaioulis,2021 ¹⁵	Observational	108	Patients with NMIBC confirmed histopathologically	Transurethral tumor resection and followed therapy with BCG or Epirubicin instillation	Regarding SF -36 Physical a 6 months decrease was followed by an improvement at 12 months (p = 0.008). Similarly, an increase of the SF-36 Mental health score was identified (p = 0.03). In contrast to STAI -Y2 scores (p = 0.945), a long-term reduction of the state anxiety was identified (p = 0.001) Preoperative SF -36 Physical was inversely correlated with age (p = 0.029), while absence of alcohol was associated with lower mental health (p = 0.003). Overall, patient characteristics, habits and the administered treatment did not affect the postoperative QoL and anxiety.
5	Rogers, 2023	Observational	296	Adults diagnosed with bladder cancer	Various bladder cancer treatments: TURBT intravesical therapy; radical cystectomy or radiotherapy, chemotherapy, other	Assessment Tool: EQ-5D-5L for health status and EORTC QLQ- C30 and QLQ-BLM30 for bladder cancer-specific quality of life
6	Rentsch,2022	Trial	42	Patients with histologically confirmed NMIBC recurrence after at least one prior course of standard BCG therapy and at least one transurethral resection of bladder tumor.	Intravesical instillations of recombinant BCG	Patients reported highlevels of QoL for the functional scales and a low symptomburden at baseline. Some impairment was reported with regard to urinary symptoms, futureworries, and sexual issues. Most of the QoL scales showedstable scores from baseline to the beginning of maintenance therapy
7	Angulo,2022	RCT	202	Patients with primary or recurrent intermediate-risk NMIBC	MMC with different temperature	There was no significant change observed in filling or voiding IPSS
8	Mostafid, 2020	RCT	102	Adults with newly diagnosed, low risk NMIBC confirmed bu TURBT	Chemoablation (intravesical instillation of mitomycin C) vs surgical management	Assessment Tools: ○ EORTC QLQ-C30: A general cancer -specific quality of life questionnaire. ○ EORTC QLQ-NMIBC24: A bladder cancer -specific quality of life module. The two treatment groupsexhibited similar HRQoL throughout follow-up, both inglobal quality of life and other key subscales of interest. The study was not powered for formal statistical comparisons of HRQoL between groups.

DISCUSSION

The studies consistently highlight the role of intravesical therapies, such as BCG instillations and gemcitabine/docetaxel, in managing NMIBC while preserving QoL. For instance, Pareek (2022) demonstrated that gemcitabine/docetaxel provided a statistically significant improvement in QoL compared to BCG. This is consistent with previous

meta-analyses, such as those by Na Zeng et al. (2023), which found gemcitabine-based regimens to be effective in reducing recurrence rates with fewer adverse events compared to BCG.¹⁹Survivors of non-muscle-invasive bladder cancer experience reduced physical, psychological, and social quality of life compared to the general population. It is crucial to assess and understand the symptom burden and quality of life of NMIBC survivors to identify

which symptoms are most challenging at different stages—from diagnosis and treatment to survivorship. This understanding is essential for developing effective intervention strategies.²⁰

Rogers (2023) highlighted the negative impact of radical treatments (e.g., cystectomy and radiotherapy) on QoL, particularly in body image and sexual function, compared to TURBT. This aligns with findings from systematic reviews such as Mitra et al. (2020), which showed that radical cystectomy is associated with poorer health-related QoL (HRQoL) outcomes compared to less invasive treatments. However, TURBT combined with intravesical therapies, as studied by Vaioulis (2021), demonstrated stable or improved QoL over time, reinforcing its role as a preferred first-line treatment for NMIBC. These findings are consistent with meta-analyses that support TURBT with adjuvant therapies as the gold standard for reducing recurrence and progression rates in NMIBC while maintaining better QoL. Radical cystectomy (RC) is currently the standard treatment for NMIBC that does not respond to BCG. However, RC is a complex procedure with significant perioperative morbidity influenced by patient factors, disease characteristics, and surgical variables, and it has a substantial impact on quality of life. As a result, there is a critical need for alternative bladder-preserving treatments for patients who either prefer to retain their bladder or are too frail to undergo major surgery.^{9,21}

New intravesical treatments, such as chemotherapeutic agents, immune checkpoint inhibitors, monoclonal antibodies, and gene therapies, have shown varying levels of effectiveness in managing NMIBC. However, most available evidence for these therapies comes from single-arm trials involving patients with recurrent NMIBC. Additionally, innovative drug delivery methods have been explored, with promising early findings supporting the intravesical use of hyperthermic mitomycin C (MMC) and MMC hydrogel formulations.²² Intravesical therapy with *Bacillus Calmette–Guérin* (BCG) or certain chemotherapeutic agents increases symptom burden and reduces functional performance during the initial induction phase, though improvements are observed over the course of maintenance treatment and beyond. Hyperthermia has shown potential in improving the quality of life (QoL) of patients undergoing intravesical chemotherapy, but further research is needed.¹

Previous review suggests that gemcitabine may offer better recurrence and progression-free survival compared to saline and mitomycin; however, there is uncertainty regarding how it compares in terms of major adverse events. Similarly, when comparing gemcitabine to BCG in high-risk patients who have previously failed BCG treatment, the outcomes remain unclear.²³

The use of validated QoL tools, such as the EORTC QLQ-C30 and SF-36, enabled nuanced assessments of physical, emotional, and social well-being in these studies. Two quality-of-life (QoL) scales are available for patients with non-muscle invasive bladder cancer (NMIBC): the EORTC QLQ-NMIBC24 and CAVICAVENMI. The EORTC QLQ-NMIBC24 originated as the EORTC QLQ-BLS24 in 1996, comprising 24 questions on urinary symptoms, chemotherapy tolerance, sexual and bowel functions, and clinical aspects, designed as a supplement to the EORTC QLQ-C30. In 2014, it was revised and renamed following validation, improving its reliability and suitability for intermediate- and high-risk bladder cancer patients, though its applicability across different regions remains limited. CAVICAVENMI, developed in 2016 by a Spanish research team, features 21 items addressing disease state, emotional and work status, self-evaluation, and sexual life. It is shorter and simpler than the EORTC tools and includes questions on mesentery treatment and mitomycin use. However, it is currently only available in Spanish and lacks validation in other languages or regions. Both scales have strengths but differ in scope, complexity, and global applicability.²⁴

Previous systematic reviews have emphasized the importance of these tools in capturing patient-reported outcomes, which are often underreported in clinical trials. The findings from Vaioulis (2021) and Rentsch (2022) on long-term stability or improvement in QoL after TURBT and intravesical therapies align with prior reviews showing that most NMIBC patients regain baseline QoL after the initial postoperative period. This highlights the need for tailored interventions that minimize symptom burden during the early treatment phase.^{13,15}

Previous systematic reviews have underscored the oncological superiority of BCG over other intravesical agents in reducing recurrence, the present studies provide additional context on QoL outcomes, suggesting that

alternative regimens like gemcitabine/docetaxel may offer comparable efficacy with fewer side effects.^{8,25} Additionally, the observed poorer QoL outcomes with radical treatments echo findings from 2021, which emphasized the trade-off between survival benefits and QoL deterioration in patients undergoing radical cystectomy or radiotherapy. Previous study in Korea identified 18% of NMIBC survivors fall into the "QOL-low" group which tend to experience more frequent NMIBC recurrences, perceive a higher risk and severity of cancer recurrence, and report depressive symptoms. These findings highlight the need for targeted intervention programs to enhance the quality of life (QOL) of NMIBC survivors, particularly those with characteristics similar to those in the "QOL-low" group identified in this study.²⁶

LIMITATIONS AND FUTURE DIRECTIONS

While the results align well with existing evidence, some gaps remain. Most studies lacked long-term follow-up beyond 12 months, limiting the understanding of QoL trajectories over extended periods. Additionally, variability in study designs and QoL tools complicates direct comparisons across studies. Future research should focus on head-to-head comparisons of alternative intravesical therapies and longer-term assessments of QoL in NMIBC patients to inform clinical decision-making.

CONCLUSION

In conclusion, this review underscores the importance of intravesical therapies, such as BCG, gemcitabine, and docetaxel, in managing NMIBC while preserving quality of life (QoL). Studies consistently show that gemcitabine/docetaxel regimens can improve QoL with fewer side effects compared to BCG, which is supported by meta-analyses and other trials. Additionally, TURBT combined with intravesical therapies has demonstrated stable or improved QoL over time, reinforcing its role as a preferred treatment. While radical treatments like cystectomy and radiotherapy show better oncological outcomes, they come with significant QoL burdens, particularly in body image and sexual function.

This highlights the ongoing need for bladder-preserving alternatives, particularly for patients unable to undergo major surgery. Emerging treatments, including novel chemotherapeutic agents, immune therapies, and innovative drug

delivery methods, offer promising results, but further research is required to fully understand their effectiveness and impact on QoL.

The use of QoL tools, such as the EORTC QLQ-NMIBC24 and CAVICAVENMI, helps to capture patient-reported outcomes and inform the development of tailored interventions. Lastly, understanding the symptom burden and QoL challenges faced by NMIBC survivors, particularly those in the "QOL-low" group, is essential for designing targeted strategies to improve their long-term well-being.

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