Burden and unmet need in non-muscle-invasive bladder: a literature review

Kristin Grabe-Heyne*✉, Christof Henne*, Johannes Pöhlmann‡, Richard F. Pollock‡

*medac GmbH, Wedel, Germany; ‡Covalence Research Ltd, Harpenden, United Kingdom. ✉K.Grabe-Heyne@medac.de

Background

- Bladder cancer (BC) is among the most common cancers, with more than 570,000 incident cases globally in 2020.
- At presentation, between two-thirds and three-quarters have non-muscle-invasive BC (NMIBC).
- NMIBC is a clinically heterogeneous disease commonly classified into low-risk, intermediate-risk (IR), and high-risk (HR) groups. More recently, a very high-risk (VHR) group was introduced in the European Association of Urology (EAU) guidelines [1,2].
- Prognosis for NMIBC is good but recurrence remains a concern in LR and IR groups while progression to muscle-invasive disease (MIBC) remains a concern in HR and VHR disease; a recent review reported 5-year recurrence-free survival (RFS) between 17 to 89%, while progression-free survival (PFS) was 58 to 89%, and overall survival (OS) 28 to 90% [1].
- These findings indicate unmet needs in patients with NMIBC – despite effective treatments, including Bacillus Calmette-Guérin (BCG), having been available for several decades.

Objectives

In consideration of the frequently suboptimal outcomes of patients with NMIBC, the aim of the present review was to:

- Review NMIBC and current treatment options
- Describe the burden of NMIBC
- Characterize unmet needs in patient care and evidence generation for NMIBC, including descriptions of the scale and reasons for each unmet need.

Methods

- A literature search was conducted in January 2022 for studies reporting clinical, cost and resource use, quality of life (QoL), and epidemiological data, treatment guidelines, and unmet needs in NMIBC.
- Searches were run in PubMed (including Medline), Embase, and the Cochrane Library. Searches for epidemiological data were restricted to studies published since 2011.
- An update search using the string "non-muscle-invasive bladder cancer OR NMIBC" was run in August 2022 in PubMed (including MEDLINE) and the Scholarly Works section of Lens.org.

Results: NMIBC definition and risk classification

- "NMIBC" is an umbrella term covering tumours confined to the mucosa (TNM system: Ta), invading the lamina propria (T1), and carcinoma in situ (Tis). It is distinct from BC that has already invaded the muscle [2].
- Treatment should be informed by risk of recurrence and progression. Risk can be estimated with one of the many prognostic models that combine clinical and pathological characteristics, although model users should pay attention to the derivation cohort informing a specific model.

Results: NMIBC epidemiology and aetiology

- Epidemiological data for NMIBC can be approximated from data for BC. The highest age-standardized incidence rates in 2020 were observed in Western and Southern Europe, particularly Greece, the Netherlands, and Italy [3].
- The most important risk factor for developing NMIBC (and BC in general) is age. Sex is another key risk factor, with men much more likely to develop BC than women. Smoking is a major behavioural risk factor, with population-attributable BC risks of 20% (China) to 37% (Europe) [4].

Results: NMIBC treatment options

- Transurethral resection of the bladder tumour (TURBT) is the first step in NMIBC treatment, fulfiling both diagnostic and therapeutic functions [2]. In all but low-risk tumours, the resected specimen should contain detrusor muscle; this is a key quality indicator associated with lower risk of residual disease, early recurrence, and understaging [5].
  - Repeat (second-look) TURBT can be performed 4–6 weeks after incomplete primary TURBT or if no detrusor muscle was resected in T1 high-grade disease and is optional in Ta HG disease. Guidelines recommend repeat TURBT to reduce recurrence risk and improve response to intravesical BCG in HR-NMIBC [2,6].
- After TURBT, a single immediate intravesical post-operative instillation of chemotherapy is recommended (and, for low-risk disease, completes treatment). A single immediate instillation, ideally within 2–6h and at most 24h after TURBT, reduces recurrence risk in all risk groups [7].
- Intravesical BCG is the main adjuvant treatment in IR-/HR-NMIBC. Trials have shown all BCG strains to be safe and effective in reducing recurrence and progression [8,9].
  - Multiple BCG strains exist but are generally considered to have equivalent safety and efficacy [2].
  - Most guidelines recommend BCG administration using the "6+3" (or SWOG) schedule – for IR-NMIBC, this involves a 6-week induction period with one instillation per week, followed by maintenance treatment with three instillations each after 3, 6, and 12 months. For HR-NMIBC, the same induction schedule is used but maintenance extended for up to 3 years [2].
  - In clinical trials, BCG therapy should only be considered "adequate" if at least 5 of 6 initial induction doses plus at least 2 of 3 maintenance doses (or 2 of 6 doses of a second induction course) were given [10].
- Intravesical chemotherapy is an alternative to BCG particularly in IR-NMIBC.
- RC is the preferred option for VHR-NMIBC and an option for some HR-NMIBC cases. Available evidence on immediate RC has generally not differentiated between patients previously treated or not with BCG [2].
- Among novel pharmaceutic agents, only pembrolizumab has received approval to-date, in the US, as a treatment for BCG-unresponsive carcinoma *in situ*. In clinical guidelines, these novel agents do not yet have an established role.

Results: Unmet needs

Insufficient adherence to treatment guidelines

- Treatment "failure" is frequently due to treatment not following guideline recommendations, including insufficient quality of the initial TURBT, delay of BCG treatment, or not using BCG maintenance therapy [19,22,23].
- Physician adherence to recommendations was reported as 33% for BCG use in HR-NMIBC, with repeat TURBTs performed in only 43% of high-risk patients [24]. Less than a third of US patients with T1 disease received guideline-based treatment between 2004 and 2014 [19].
- Reasons include insufficient knowledge and training [17,18], lack of access due to BCG shortage and economic barriers [17,18,21], concern about side effects and their suboptimal management [21,25], and misconceptions around the use of BCG [26] (see Table).
- Potential solutions include using quality performance indicators, as pioneered in the Scot BC Quality OPS project [27]. Guidelines could also be made more accessible using modern information technology [28].

Insufficient patient lifestyle change and treatment compliance

- Many patients with NMIBC do not change their lifestyle [29], while treatment is often discontinued even in clinical trials [30].
- Only 14 to 36% of smokers stop smoking [29,31]. The proportion of patients completing maintenance therapy is between 10 and 76%, and decreases with time on maintenance [30,32].
- Reasons include toxicity, which, although mostly transient, may deter patients from continuing therapy. The BCG shortage may prevent patients from starting/continuing BCG [32,33].
- Potential solutions include improvements to management of BCG side effects and to patient-physician communication on the meaning and nature of side effects [34,35]. The BCG shortage requires expanding production capacities, which will take several years to complete [33].

Study	Reasons for/factors influencing non-adherence
Lack of knowledge and/or training	
Balakrishnan et al. [17]	• Treatment in a community cancer centre associated with a higher risk of non-guideline-compliant therapy than treatment in an academic centre.
Choo et al. [18]	• Second TURBT in case of absence of detrusor muscle in first TURBT specimen more likely in academic teaching than in private or non-teaching hospitals and more likely for surgeons with shorter than with longer practice • Single immediate chemotherapy instillation more likely in academic teaching than in private or non-teaching hospitals for T1 and high-grade disease (no statistically significant difference for other indications) • Also reported country-specific differences (between Japan, Korea, and Taiwan) that could not readily be explained
Matulay et al. [19]	• Higher rates of guideline adherence in urologic oncologists versus non-urologic oncologists and in fellowship-trained versus non-fellowship-trained urologists • Higher rates of guideline adherence among physicians based in academic relative to hospital employment and among physicians with shorter relative to longer experience
Tobert et al. [20]	• Guideline adherence is more likely if treated in an academic cancer centre relative to non-academic, non-cancer centres
Lack of access and economic barriers	
Balakrishnan et al. [17]	• Lack of insurance is associated with a higher risk of non-guideline-compliant therapy than being privately or Medicare-insured • Lack of insurance is associated with a higher risk of non-guideline-compliant therapy than being privately or Medicare-insured
Choo et al. [18]	• BCG shortage reported as the main reason for not giving maintenance BCG, particularly in Taiwan (less so in Japan, which has a more stable supply)
Wang et al. [21]	• 75% of deviations from guidelines for BCG due to BCG being inaccessible • 50.4% of indicated second TURBTs, 40.7% of indicated BCG therapies, and 29.2% of indicated radical cystectomies rejected by patients for economic reasons
Fear of complications or patient comorbidities	
Wang et al. [21]	• 37.6% of indicated second TURBTs not performed because urologist concerned about the risk of side effects; in 70.6%, the patient expressed such concerns • 26.0% of indicated BCG therapies not performed because urologist concerned about the risk of side effects; in 62.2%, the patient expressed such concerns • 38.1% of indicated radical cystectomies rejected by patients out of concern for the risk of side effects, while 57.7% rejected by patients out of concern for decreases in QoL

Results: NMIBC burden

Humanistic burden

- At NMIBC diagnosis, QoL is reported as good and comparable to the general population [11]. Following diagnosis and during treatment, QoL is transiently reduced, due to effects of both the disease and treatment [12].
- These findings are currently inconsistent, however, and the impact of specific treatments on QoL remains uncertain, including those for radical cystectomy (RC) and BCG.
- In survivors, most QoL domains improve over time, but QoL is reduced relative to the general population, often due to sexual dysfunction and incontinence that restrict social activities [13].

Economic burden

- Economic data for NMIBC point to a considerable cost burden: Five-year median per-patient costs of HR-NMIBC receiving BCG in the US Veterans Affairs system were USD 117,361 [14].
- In Germany, mean 10-year socioeconomic follow-up costs in 2020 were EUR 4,758 and EUR 11,325 for IR- and HR-NMIBC, respectively [15], while 3-year per-patient costs in the UK in 2017 were GBP 8,375 from the perspective of the National Health Service [16].

Limited usefulness and comparability of the evidence

- Treatment outcomes are difficult to compare across studies given the frequently suboptimal, non-standardized treatment schedules, particularly for intravesical therapy.
- For example, a recent review comparing BCG with mitomycin-C for Ta/T1 bladder cancer included a study with a 6-week induction followed by ten monthly instillations, a study with six weekly instillations followed by monthly mitomycin-C for 3 years, and another study (comparing with mitomycin-C every 2 weeks in the first year and every 4 weeks in the second year) in which BCG was given weekly for 6 weeks then monthly for 4 months [36].
- Study conduct and evidence synthesis would benefit from increased standardization, which is occuring in guidelines and development of definitions of BCG-unresponsive disease and adequate BCG therapy [10].

Conclusions

- The present review has described NMIBC and unmet needs in NMIBC patient care and evidence generation.
- Both care and evidence are limited by a lack of treatment standardization. Efforts to improve standardization are ongoing, which, if implemented alongside guideline recommendations, could lead to better patient outcomes and more robust evidence.

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