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Intermediate and high-risk non-muscle-invasive bladder cancer: an overview of epidemiology, burden, and unmet needs

Kristin Grabe-Heyne[1], Christof Henne[1],
Paramananthan Mariappan[2], Götz Geiges[3],
Johannes Pöhlmann[4] and Richard F. Pollock[4]*

[1]Medac GmbH, Wedel, Germany, [2]Edinburgh Bladder Cancer Surgery (EBCS), Department of Urology,
Western General Hospital, Edinburgh, United Kingdom, [3]Praxis Dr. Geiges, Berlin, Germany,
[4]Covalence Research Ltd., Harpenden, United Kingdom

Bladder cancer ranks among the most common cancers globally. At diagnosis, 75% of patients have non-muscle-invasive bladder cancer (NMIBC). Patients with low-risk NMIBC have a good prognosis, but recurrence and progression rates remain high in intermediate- and high-risk NMIBC, despite the decades-long availability of effective treatments for NMIBC such as intravesical Bacillus Calmette-Guérin (BCG). The present review provides an overview of NMIBC, including its burden and treatment options, and then reviews aspects that counteract the successful treatment of NMIBC, referred to as unmet treatment needs. The scale and reasons for each unmet need are described based on a comprehensive review of the literature, including insufficient adherence to treatment guidelines by physicians because of insufficient knowledge, training, or access to certain therapy options. Low rates of lifestyle changes and treatment completion by patients, due to BCG shortages or toxicities and adverse events as well as their impact on social activities, represent additional areas of potential improvement. Highly heterogeneous evidence for the effectiveness and safety of some treatments limits the comparability of results across studies. As a result, efforts are underway to standardize treatment schedules for BCG, but intravesical chemotherapy schedules remain unstandardized. In addition, risk-scoring models often perform unsatisfactorily due to significant differences between derivation and real-world cohorts. Reporting in clinical trials suffers from a lack of consistent outcomes reporting in bladder cancer clinical trials, paired with an under-representation of racial and ethnic minorities in many trials.

1 Introduction

Bladder cancer imposes a substantial burden on patients, healthcare systems, and societies across the globe (1, 2). At diagnosis, approximately 75% of bladder cancer cases are non-muscle-invasive bladder cancer (NMIBC), which is a clinically heterogeneous disease characterized by high recurrence and, in high-risk disease, high progression rates (3–5). Much of the burden of NMIBC persists despite the decade-long availability of effective treatments such as Bacillus Calmette-Guérin (BCG) immunotherapy (6, 7). The NMIBC burden will likely increase due to population aging (2, 8, 9). It is therefore important to investigate the reasons for the current scale of the burden to identify the levers with which clinicians and healthcare decision-makers can improve NMIBC care.

In the present study, we provide a review of bladder cancer and NMIBC, including disease classification, epidemiology, humanistic and economic burden, and treatment options. We focus on patients with intermediate- and high-risk NMIBC (defined below). These patient groups have unmet needs regarding physician adherence to treatment guidelines, as well as lifestyle changes and treatment completion rates. Existing evidence is also often of limited value due to unstandardized treatment schedules and risk stratification systems that perform suboptimally in clinical practice. The paper reviews these unmet treatment and evidence needs and highlights where improvements in treatment use, patient care, and evidence generation could be helpful to achieve better outcomes for patients with intermediate- and high-risk NMIBC.

2 Results

2.1 NMIBC: staging, grading, risk, and outcomes

2.1.1 Staging

Bladder cancer is staged using the American Joint Committee on Cancer and Union for International Cancer Control staging classification, based on tumor size (T), lymph node (N) involvement, and presence of distant metastasis (M) (10). The umbrella term NMIBC includes tumors at stages Ta (confined to the mucosa), T1 (invading the lamina propria), and Tis (carcinoma *in situ*; flat, high-grade tumor confined to the mucosa) (11). This contrasts with bladder cancer which has already invaded the muscle (MIBC) and with metastatic disease.

2.1.2 Grading

Histological grading uses grading systems developed by the World Health Organization (WHO). Until 2004, the WHO 1973 grading system was used, which differentiates papillary urothelial lesions into three grades. In 2004, the classification was revised (with another revision in 2016) to address the problems of the 1973 system. The twice-revised 2004/2016 WHO classification distinguishes papillary urothelial neoplasm of low malignant potential, low-grade, and high-grade tumors (12, 13). The European Association of Urology (EAU) currently recommends using both the three-tier 1973 (G1, G2, G3) and the two-tier 2004/2016 system (low-grade [LG], high-grade [HG]), resulting in a four-tier grading system (LG/G1, LG/G2, HG/G2, and HG/G3) (11, 12). The four-tier system outperforms its constituent systems as it splits the relatively large group of patients with G2 disease into patients with LG and HG disease who have different prognoses (14). Grading is prognostic for disease progression, but not recurrence (11).

2.1.3 Risk stratification

A patient's recurrence and progression risk should inform their treatment. Patient risk is estimated using prognostic models, which allow stratifying patients into risk groups, based on clinical and pathological characteristics (11, 15, 16). Such models and accompanying stratification tables listing the clinical features of each risk group are developed by guideline-issuing organizations such as the EAU and the American Urological Association (AUA) and independent research groups. There are many scoring models and risk stratification tables, which are similar in structure and output but differ in data sources (15–21). In particular, derivation cohorts differ in the type of surgical and intravesical treatment received, which may bias risk estimates and reduce the discriminative ability of models in populations with different treatment experiences (22–28). Clinicians are faced with the challenge of selecting from the many available tools, all of which have specific shortcomings and may not fit their patient population.

An early scoring model was developed on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) (18, 29). The model was developed from individual-level data of 2,596 patients with Ta/T1 bladder cancer enrolled in seven EORTC trials. Recurrence and progression were predicted using tumor number, size, stage, grade, and status (primary or recurrent, including time to recurrence), and presence. In response to perceived shortcomings of the EORTC model, in particular the absence of patients treated with BCG in the derivation cohort, the Spanish Club Urológico Español de Tratamiento Oncológico (CUETO) developed a new risk stratification model (15). The model was designed to account for to account for recurrence and progression following use of BCG and derived from data of 1,062 patients receiving BCG after a transurethral resection of the bladder (TURBT) in four CUETO-sponsored trials. The predictors used were similar to those in the EORTC model and included age, gender (for recurrence prediction), as well as tumor status (primary or recurrence), number, stage, and grade, and presence of carcinoma *in situ* (Cis). Relative to the EORTC model, lower recurrence and, for patients with high-risk tumors, lower progression risks were obtained in the CUETO model (15, 30).

Subsequently, an EORTC nomogram was developed to predict recurrence and progression in patients treated with standard 1 to 3 years BCG maintenance therapy (versus the much shorter maintenance therapy used in the CUETO model derivation cohort) (31). The derivation cohort comprised 1,812 patients with Ta/T1 NMIBC (not Cis) from two EORTC trials who had received 1 to 3 years of maintenance therapy with BCG. The nomogram included tumor grade and number and prior recurrence. It

showed considerable heterogeneity in time to first recurrence and time to progression among patients receiving BCG maintenance. One of the latest risk models was developed on behalf of the EAU, for predicting time to progression, based on data from patients with Ta/T1 NMIBC treated with TURBT and subsequent intravesical chemotherapy (16). The derivation cohort included 5,145 patients. The model included age, tumor number, stage, and maximum diameter, tumor grade based on either the WHO 1973 or the WHO 2004/2016 grading system, and presence of Cis as predictors. The model introduced the notion of a very high-risk group that should be investigated for prompt treatment.

2.1.4 Clinical outcomes in NMIBC

Clinical outcomes differ across risk groups and countries, as well as by treatment and healthcare system.

A recent systematic review of real-world evidence studies of patients with high-risk NMIBC found 5-year recurrence-free survival (RFS) to vary between 17–89%, while progression-free survival (PFS) varied between 58–89%, cancer-specific survival between 71–96%, and overall survival (OS) between 28–90% (5). In this review, patients who received and completed intravesical therapy with Bacillus Calmette-Guérin (BCG) were found to have longer survival relative to patients not receiving or completing intravesical therapy. Additional data on patients with intermediate- and high-risk NMIBC treated with adequate BCG therapy (32, 33) confirmed excellent survival outcomes over 5 years, with RFS of 86% and 72%, PFS of 100% and 91%, and OS of 79% and 87% in intermediate-risk and high-risk patients, respectively (3). Similarly, following adequate BCG induction treatment, a 10-year PFS of 78% was reported for a US cohort of patients with high-risk NMIBC (34).

More broadly, median survivorship estimates of 5.3 years (95% confidence interval [CI] 5.2 to 5.4 years) and 4.4 years (95% CI 4.3 to 4.6 years), respectively, were reported for US patients between 1988 and 2006 (35). In this US analysis, survivorship differed by age, sex, and race/ethnicity, with non-white and older patients experiencing shorter survival. In Sweden, 59% of patients with intermediate-risk NMIBC experienced a recurrence over a median follow-up of 63 months (36).

2.2 Epidemiology and etiology

2.2.1 Global and regional epidemiology of bladder cancer

Epidemiological data specific to NMIBC are sparse but can be approximated from data for bladder cancer, approximately 75% of which are NMIBC at presentation (37). Western and Southern Europe had the highest age-standardized incidence rates (ASIR) of bladder cancer (and, by extension, NMIBC) in 2020. Central America, West and Middle Africa, and parts of Central and Eastern Europe had the lowest ASIR (38). On a per-country level, the highest ASIR were for European countries, including Greece, the Netherlands, and Italy. Outside Europe, the incidence was highest in Egypt.

Bladder cancer incidence has decreased in many parts of the world. The notable exception, for both sexes, is Europe. Regarding men, five of six countries with statistically significant increases in bladder cancer incidence as per the analysis by Teoh et al. (8) were in Europe (plus Japan). Regarding women, eleven countries saw incidence increases, of which ten were in Europe (plus Japan).

2.2.2 Risk factors

Several factors increase the risk of bladder cancer, of which age is the most important. With a median age at diagnosis of approximately 70 years, bladder cancer is primarily considered a disease of the elderly (2, 39), and its incidence increases with age. Data from California, for example, indicated that age-specific incidence peaked in the 85–95-year age group (40). The link between bladder cancer incidence and age results from longer cumulative environmental exposure to carcinogens and more time available for the development and accumulation of cellular events triggering neoplastic transformations. Higher age might also reduce the ability to empty the bladder completely, so carcinogens excreted in urine remain in longer contact with the bladder. Furthermore, difficult voiding might lead older people to drink less, increasing the concentration of carcinogens in the urine (39).

Sex is another key risk factor for bladder cancer incidence and mortality. Men have a considerably higher risk of developing bladder cancer, which is reflected in men dominating the gender split in most clinical and epidemiological studies (41). This gap persists even if accounting for differential exposure to risk factors and may be attributable to differences in carcinogen metabolism and sex steroid hormones (41, 42). Outcomes are not necessarily worse for men, however, as women present later, with more advanced disease. This may indicate a diagnostic gap, particularly when evaluating hematuria, and treatment that disfavors women (41–43).

A key behavioral risk factor is smoking (44). Population-attributable risks of bladder cancer to cigarette smoking range from 20% in China to 37% in Europe (45). An estimated 37% of global bladder cancer disability-adjusted life-years in 2019 were attributable to smoking (2). Lifetime exposure to second-hand smoke may also elevate the risk of bladder cancer (46). A longer smoking duration and more pack-years are associated with an increased NMIBC recurrence risk, suggesting a dose-dependent link between smoking and recurrence (47).

Diet has also been investigated for its role in bladder cancer. Multiple studies have investigated different aspects of diet, including alcohol consumption, vitamin intake, levels of fluid consumption including coffee and tea, vegetable and fruit consumption, meat consumption and the consumption of a Mediterranean diet (48–50). There is some evidence that a diet rich in red and processed meat is associated with an increased risk of bladder cancer (49, 51, 52) while a Western diet may be associated with higher risks of NMIBC recurrence (50). Mono-unsaturated fatty acids may be associated with reduced NMIBC risk and, in men, there may be a positive association between total cholesterol intake and bladder cancer risk (53). The consumption of sugar-sweetened beverages has also been reported to be associated with overall survival in

NMIBC, as has sodium consumption for bladder cancer-specific survival (54). The overall diet quality, however, was not associated with either overall survival or bladder cancer-specific survival. Overall, the evidence base for many dietary risk factors remains limited as many studies are small, possibly biased, or hard to interpret due to conflicting results between reports (44). Cohorts with bladder cancer have also been shown to be less physically active than the age-matched general population, with reduced physical activity levels associated with higher body mass index (BMI) and increased smoking exposure (55).

Efforts into researching the prognostic and potentially therapeutic role of the microbiome in bladder cancer are also increasing. Based mostly on tissue and urine samples, the abundance of different genera between healthy people and those with bladder cancer or NMIBC are investigated (56, 57). The overall evidence base so far remains limited to small studies, which currently suggests a rather limited role of the microbiome for disease prediction.

2.3 Burden of NMIBC

2.3.1 Effect of NMIBC on patient quality of life

Good QoL at the time of NMIBC diagnosis has been reported in multiple studies. In qualitative studies, patients expressed shock and concern, but many quickly adapted to their diagnosis (58, 59). Some patients expressed frustration that their symptoms were initially not taken seriously enough, although few patients suffered from disease symptoms. Most patients were confident about treatment success while finding treatment decision-making demanding and facilitated by open, consistent communication with healthcare professionals (58, 59). These qualitative findings matched those from a quantitative study, which showed that, at diagnosis, QoL in patients with NMIBC was comparable to that of the general population (60).

Treating NMIBC may reduce QoL, at least transiently, but results are inconsistent. Reduced QoL, measured using the Short Form (SF)-36, was observed in patients undergoing TURBT followed by intravesical immunotherapy or chemotherapy at 6 months after TURBT for the SF-36 Physical domain (61). At 12 months post-operation, the physical score had improved to above pre-operative levels, as had the mental health score. In a comparison of BCG, mitomycin-C (MMC), and chemohyperthermia (CHT), all patients had reached baseline QoL at the end of the induction treatment (62). Similarly, no significant changes in QoL over time were observed in a randomized study comparing BCG and gemcitabine for either treatment (63).

Experiences among survivors and adaptation to post-treatment circumstances differ across patients and QoL domains, with most domains improving with time since treatment (59, 64). In general, NMIBC survivors have reduced QoL relative to the general population (65–67). Incontinence and sexual dysfunction affect QoL negatively and limit social and everyday activities (59, 66, 67).

The effect of radical cystectomy on QoL in bladder cancer patients has received particular attention, but findings again are inconsistent. Tsai et al. (68) reported that radical cystectomy was associated with reduced QoL up to 5 years after treatment across the physical, psychological, and social domains of the WHO Quality of Life questionnaire. Health state utility values elicited from the general population, for example by Cooper et al. (69) for the UK, also showed a substantial reduction in QoL following radical cystectomy for BCG-unresponsive NMIBC. In contrast, Clements et al. (70) reported that, within 24 months of radical cystectomy, all QoL domains except sexual function had returned to or surpassed baseline QoL. In an earlier meta-analysis, Yang et al. (71) concluded that QoL may improve after radical cystectomy, but that urinary and sexual dysfunction were persistently worse than in the general population.

Quality of life is reduced by recurrence and progression, but the effect of recurrence requires further investigation. From the United Kingdom (UK) BOXIT trial, statistically significant decrements in QoL were estimated for grade 3 recurrence (but not lower-grade recurrences) and progression to MIBC in high-risk patients (72). Including intermediate-risk patients in the analysis resulted in estimates for recurrence that were no longer statistically significant. A multivariable analysis by Smith et al. (73) also showed no difference in QoL between patients with NMIBC with and without recurrent disease. As in the BOXIT data, progression to MIBC was associated with reductions in the EORTC summary score versus non-recurrent NMIBC, although this relationship was not consistent across all domains.

2.3.2 Economic burden of NMIBC

Assessment of the economic burden of bladder cancer dates back at least to a 2003 health economic review (74). This review of forty-four studies concluded that bladder cancer was associated with the highest per-patient cost of all cancers from diagnosis to death, with, at the time, costs of USD 96,000 to USD 187,000 (2001 values). These costs reflected the long-term survival and associated need for lifelong routine monitoring in patients with bladder cancer. Overall, bladder cancer was the fifth most expensive cancer in the US in terms of total medical expenditure, with direct annual costs of USD 3.7 billion in 2001 values (74). These findings were confirmed in a 2014 review that reviewed costs over the bladder cancer diagnosis, treatment, and surveillance trajectory (75). A sizable portion of the costs associated with bladder cancer management were due to cystoscopic, radiologic, and interventional procedures used to guide treatment decisions, including annual CT scans and routine use of urine cytology. While intravesical therapy was relatively inexpensive, particularly given its ability to prevent costly recurrence, a lack of consensus regarding maintenance therapy at the time meant that BCG maintenance could be improved further to minimize treatment-related toxicity and overall cost-effectiveness. In contrast, radical cystectomy was associated with significant costs, including those of perioperative complications. Surveillance contributed substantially to costs, e.g., cystoscopy performed every 3 months even in patients with low-grade disease (75).

High costs associated with NMIBC specifically were confirmed in a 2020 review (76). Recurrence and progression as well as associated complications of NMIBC were major cost drivers.

Cumulative care costs increase nearly threefold from low-risk to intermediate-risk NMIBC, and increase by a factor of 2.5 again from intermediate-risk to high-risk disease in the US (77). As for bladder cancer generally, surveillance was identified as an important contributor to costs, particularly in patients with high-risk NMIBC. Recent studies, however, have suggested that adaptations to existing surveillance schedules would be possible to reduce costs. In Japan, a surveillance schedule distinguishing high-risk from very high-risk patients and employing period-specific recurrence detection rates to inform the necessity of routine surveillance was shown to reduce 10-year surveillance costs by 40% relative to the standard EAU schedule (78).

Regarding the country-specific economic burden of NMIBC, in the US, 2019 per-patient costs for high-risk NMIBC treated in Department of Veterans Affairs centers were estimated at USD 29,459, USD 55,267, and USD 117,361 at 1, 2, and 5 years, respectively (34). Costs in patients with progression were statistically significantly higher than in patients without progression. Outpatient costs were by far the most important cost category.

For the UK, 3-year average costs per patient with NMIBC, for 2017 from the National Health Service perspective, were estimated at GBP 8,735, with cost increments of GBP 1,217 to GBP 3,957 in case of recurrence and GBP 5,407 in case of progression (72). The 3-year total costs of NMIBC in the UK were estimated at GBP 66 million for the cohort diagnosed in 2015.

For Italy, 2016 cost data were available from a cost-of-illness study, in which 62% of patients had NMIBC (79). The median cost per case with NMIBC was EUR 4,584. The highest costs were due to surgical procedures, radiotherapy, and non-intravesical chemotherapy, while intravesical chemotherapy and BCG were the least significant cost items. Total bladder cancer costs in 2016 for Italy were estimated at EUR 1.2 billion, of which 56% were direct costs.

The societal costs of NMIBC survivors over 10 years in Germany were reported as EUR 2,214 for low-risk, EUR 4,758 for intermediate-risk, and EUR 11,325 for high-risk NMIBC in 2020 (80). Patients incurred EUR 606 (low-risk patients), EUR 1,284 (intermediate-risk patients), and EUR 2,931 (high-risk patients) of costs in 2020, with the rest covered by healthcare providers and healthcare insurance. Survivorship costs, highest in the first two years after the first treatment, had increased, with a 65% rise in overall expenditure between 2000 and 2020.

Mortality from bladder cancer also contributes to the economic burden. Productivity losses from premature bladder cancer deaths in Europe were estimated, per premature death, as EUR 117,436 of paid production lost in the employed and as EUR 44,093 and EUR 74,096 of unpaid production lost in the employed and unemployed, respectively (81).

2.4 Treatment options for intermediate- and high-risk NMIBC

An ever-increasing number of guidelines for NMIBC treatment have been issued by national and international societies

(Supplementary Tables S1, S2). The quality of these guidelines varies, particularly regarding stakeholder involvement, the rigor of development, and applicability (82).

2.4.1 TURBT

Following patient assessment and work-up, the first step in managing NMIBC is TURBT (11, 17, 83). During TURBT, all visible tumors should be removed (therapeutic goal) and disease staging performed (diagnostic goal). Fractioned or *en-bloc* techniques can be used, based on tumor size and location, and surgeon experience. The relative merits of each technique remain to be established, but *en-bloc* resection may be associated with reduced hospitalization and catheterization duration, without differences in complication rates (83, 84). A surrogate criterion for resection quality and required part of TURBT in all but Ta G1/LG tumors is the presence of detrusor muscle in the specimen. Its absence is associated with significantly higher risks of residual disease, early recurrence, and tumor understaging (83, 85).

Cystoscopy during TURBT has traditionally been performed using white light. A more recent alternative is blue light cystoscopy, also known as photodynamic diagnosis (PDD), which uses an intravesically administered photosensitizing agent that preferentially accumulates in tumor cells that can subsequently be detected from their fluorescence (86). Relative to white light cystoscopy (WLC), PDD has a higher sensitivity but lower specificity in bladder cancer detection (87), and the use of PDD may affect treatment decisions through improved detection of tumors (88). In guidelines, the use of PDD over WLC is currently a moderate recommendation in the AUA/SUO guideline (17) and a weak recommendation in the EAU guideline (11). Systematic reviews and meta-analyses have suggested that blue light cystoscopy is associated with reduced risks of disease recurrence and possibly disease progression relative to WLC. The benefits of PDD may depend on baseline risk and findings were uncertain given limitations in the available evidence base, including the differential use of adjuvant therapy (89–91).

These reviews did not include the recently published PHOTO RCT, which compared TURBT guided by PDD with standard WLC TURBT in 538 patients with NMIBC across centers in the UK (86). The trial found no evidence for differences in recurrence or progression risk and in overall or bladder cancer-specific survival between PDD-guided and standard WLC TURBT. At 3 years, PDD-guided TURBT was also unlikely to be cost-effective versus WLC TURBT. The authors concluded that PDD-guided TURBT could not be recommended for managing patients with primary intermediate- or high-risk NMIBC (86). The trial has generated some controversy, however, for its inconsistency with the existing literature (92). In particular, the trial has been criticized for excluding a substantial portion of randomly allocated patients from the analysis and for being underpowered to detect differences between PDD and WLC as its power calculations rested on risk reductions considered inadequate and as the planned patient accrual had not concluded by trial end. In addition, adjuvant therapy was not balanced between trial arms as higher rates of patients in the WLC arm received adjuvant therapy,

including BCG. High-risk patients were also considered to be underrepresented in the trial (92). Given the association between (higher) baseline risk and (higher) benefit of PDD, the largely intermediate-risk group studied in PHOTO likely reduced the probability of detecting an effect of PDD (89). Differences in TURBT quality, influenced by surgeon experience, were also suggested as a potential reason why the trial failed to identify differences between PDD and WLC (93). Given these concerns, Stenzl et al. concluded that the PHOTO trial would not invalidate the available evidence in favor of PDD in NMIBC (92).

2.4.2 Repeat TURBT

If the primary TURBT is incomplete or there is no detrusor muscle in the specimen, the second(-look) TURBT should be performed 4–6 weeks after the first resection (11, 17). AUA/ Society of Urologic Oncology (SUO) guidelines recommend considering repeat TURBT also in high-risk Ta HG tumors and T1 tumors, while EAU guidelines consider only T1 tumors for repeat TURBT. Endorsement of re-resection in guidelines reflects consistent findings that second TURBT reduces recurrence risk and improves response to intravesical BCG in patients with high-risk or high-grade NMIBC (94–96). Initial evidence also suggests improved all-cause (but not cancer-specific) mortality associated with a second TURBT in patients with T1 bladder cancer (97). There appears to be no survival difference between re-TURBT performed before or after BCG induction (98).

2.4.3 Single, immediate post-operative instillation of chemotherapy

Adjuvant treatment post-TURBT is recommended to start with a single, immediate instillation of chemotherapy, within 24 hours of surgery, optimally within 2 to 6 hours (11, 17, 99). Such a "single shot", usually of MMC or gemcitabine, has been demonstrated to reduce recurrence risk in patients with NMIBC in all risk groups and regardless of adjuvant BCG therapy (78, 100, 101). The single post-TURBT instillation of chemotherapy is most effective in patients with low-grade Ta cancers (102). For low-risk patients, no treatment beyond this single immediate instillation is needed.

2.4.4 Intravesical BCG

Subsequent adjuvant treatment in patients at intermediate and high risk is intravesical treatment with BCG or chemotherapy (11, 17, 99). Immunotherapy with BCG, a live attenuated strain of *Mycobacterium bovis*, is the mainstay intravesical treatment for NMIBC (7, 103). Clinical trials have shown that BCG is safe and effective in reducing tumor recurrence and progression (104–109). Multiple BCG strains are available, which are considered to have equivalent efficacy and safety (11, 17, 110–112).

Most guidelines recommend that BCG administration follows the so-called "6+3", or SWOG, schedule (11, 17, 104, 113, 114). For high-risk patients, a 6-week induction period (instillations once a week) is followed by maintenance treatment of three instillations (one instillation per week over 3 weeks) at 3 and 6 months and then every 6 months thereafter, up to 36 months from initiation of induction therapy. For intermediate-risk patients, the same induction schedule is used, but maintenance is shortened to 1 year, with three instillations each given at 3, 6, and 12 months (11).

The SWOG protocol is not consistently applied in clinical practice and research, and many interventional studies consider only induction therapy or change the frequency, duration, or doses of BCG (115).

In particular, data on the benefit of maintenance therapy are inconsistent and often underpowered, and drawing definitive conclusions is therefore challenging (116). In the CUETO 98013 study, a maintenance schedule of one instillation every 3 months for 3 years was not associated with decreased recurrence or progression relative to induction-only therapy in high-risk patients (117). Palou et al. (118) found no recurrence or progression benefit of maintenance therapy given as six instillations every 6 months for 2 years relative to no maintenance therapy. In contrast, the SWOG 8507 study in high-risk patients showed clear benefits in RFS and worsening-free survival (defined as no evidence of progression) for the maintenance regimen now known as the SWOG schedule, compared to no maintenance therapy. The NIMBUS trial in high-grade NMIBC confirmed that a reduced BCG schedule is associated with increased recurrence risk versus the standard schedule (119). Similar results were reported in observational studies, although benefits for progression were not always shown (120, 121). Reduced recurrence and progression risks with maintenance BCG were shown in several systematic reviews and meta-analyses, regardless of patient risk group (122, 123); in turn, the superiority of BCG over MMC was found only if maintenance therapy was given (106, 107, 109).

On balance, maintenance therapy is likely beneficial, as stipulated by guidelines and consensus documents (11, 17, 99, 113). It appears plausible that between-study differences were influenced in part by different, regularly inadequate maintenance schedules. Inadequate dosing may also have contributed. While BCG doses are difficult to compare between studies as they are often reported by weight instead of colony-forming units, not all studies used the full doses recommended for treatment. In a randomized trial of intermediate- and high-risk patients, receiving one-third of a standard BCG dose was associated with shorter disease-free survival relative to a full dose, with no differences in toxicity (124). In high-risk patients, 3-year maintenance therapy decreased the recurrence risk with full, but not with reduced doses.

2.4.5 Intravesical chemotherapy

Intravesical chemotherapy is an alternative to BCG in intermediate-risk NMIBC, in particular for recurrent low-grade disease. In high-risk patients, while BGC should be the preferred treatment option, chemohypothermia with mitomycin-C (MMC) is an alternative to BCG where BCG is unavailable or not tolerated (125–127). Pre-operative/neoadjuvant use of intravesical chemotherapy with MMC (also referred to as "chemoresection") has also been suggested to help reduce the number of invasive procedures (TURBT) in patients with recurrent intermediate-risk NMIBC (128). In addition to MMC, other available chemotherapeutic agents include epirubicin, gemcitabine and

docetaxel (129). Given the BCG shortage, sequential gemcitabine-docetaxel has been investigated as an alternative or salvage therapy in NMIBC. This sequential instillation treatment was found to be effective and well-tolerated in retrospective studies of high-risk patients who were BCG-naïve or had failed BCG (130, 131). A comparative retrospective study reported improved outcomes and reduced treatment discontinuation in treatment-naïve high-risk patients for gemcitabine-docetaxel relative to BCG (132). However, the comparison of contemporary gemcitabine-docetaxel patients with a historic BCG cohort, with different follow-up periods and the use of a non-standard reduced-dose BCG-IFN-2α combination treatment as comparator, limit the interpretation of these results. A recent systematic review of sequential gemcitabine-docetaxel therapy concluded that the therapy was promising, but that additional large studies of good quality that compare gemcitabine-docetaxel with BCG are necessary (133).

BCG shortages have forced urologists to investigate strategies to improve the efficacy of chemotherapy delivery. The concept of device-assisted intravesical therapy, particularly chemohyperthermia (hyperthermic intravesical chemotherapy [HIVEC] or radiofrequency-induced thermo-chemotherapy effect [RITE]), to improve the penetration of MMC and other chemotherapeutic agents into the bladder wall appears promising as enhanced antitumor effects have been evident. However, despite accumulating data in the BCG-naïve (134–137) and BCG-unresponsive settings (138, 139), intravesical device-assisted chemotherapy is not broadly available for NMIBC patients (134–136, 140–145). Electromotive Drug Administration (EMDA) improves penetration of chemotherapy agents by electroosmosis, iontophoresis, and electroporation (140) but as with chemohyperthermia, is not yet recommended in treatment guidelines due to insufficient evidence (140, 146).

2.4.6 Radical cystectomy

Radical cystectomy is the gold standard treatment for MIBC, and early radical cystectomy is the preferred treatment in patients with very high-risk NMIBC, although recent evidence also suggests a clinical benefit of intravesical BCG in these patients (11, 125, 147). Early radical cystectomy is also recommended for BCG-unresponsive disease (11). While the high-risk characteristics prompting eligibility for radical cystectomy differ between guidelines (Supplementary Tables S1, S2), studies evaluating the benefits of early radical cystectomy have not differentiated BCG-naïve patients from those who have failed BCG. The benefit of early radical cystectomy in BCG-naïve patients, therefore, remains unclear. The BRAVO-Feasibility study demonstrated that patients with high-grade NMIBC treated with early radical cystectomy experience acceptable outcomes, but the feasibility of recruiting into a larger trial was considered doubtful, particularly as the majority of patients preferred bladder preservation (148).

2.4.7 Novel pharmaceutical agents

Novel pharmaceutical agents as well as improvements to existing intravesical therapy for second-line treatment of NMIBC are under investigation (149, 150). Agents under investigation span multiple modalities and therapeutic classes, including chemohyperthermia with MMC, recombinant viruses (IFNα2b-encoding nadofaragene firadenovec), oncolytic viruses (GM-CSF-encoding adenovirus CG0070), immune checkpoint inhibitors (ICIs; PD-1 and PD-L1 inhibitors such as pembrolizumab, cetrelimab, atezolizumab, durvalumab and sasanlimab), immunomodulatory agents (IL-15 superagonist nogapendekin alfa inbakicept [NAI] or N-803), photodynamic therapy (PDT; ruthenium-based photosensitizer TLD1433), a Nectin-4-directed antibody and microtubule inhibitor conjugate (enfortumab vedotin), and a pan-FGFR tyrosine kinase inhibitor (erdafitinib). Furthermore, many of these agents are currently being investigated in combination, including N-803 in combination with BCG, ICIs in combination with BCG, CG0070 in combination with pembrolizumab, and cetrelimab in combination with gemcitabine (151). New agents that are available as intravesical formulations are generally favored by urologists.

Among immunotherapies, pembrolizumab has been approved by the US Food and Drug Administration (FDA) for the treatment of BCG-unresponsive, high-risk NMIBC with Cis with or without papillary tumors. In December 2022, the FDA also approved nadofaragene firadenovec, a gene therapy using a recombinant adenovirus as its vector, for the same indication, but this option is not yet clinically available. As of writing, pembrolizumab and nadofaragene firadenovec have not been approved for the treatment of NMIBC by the European Medicines Agency (EMA). An FDA decision on the use of N-803 in combination with BCG is due in May 2023.

3 Discussion

Despite the approval of novel and the effectiveness of already available treatments, recurrence and, in high-risk disease, progression rates remain high. In many instances, treatment failure can be attributed to non-adherence to guideline recommendations across the treatment pathway, from TURBT to intravesical therapy and early radical cystectomy. Although guidelines differ to some extent and vary in quality (82, 125), recommendations for the treatment of high-risk NMIBC are sufficiently aligned and based on evidence of sufficient quality to warrant familiarity and consistent use of guidelines.

Examples of guideline non-adherence include not administering repeat TURBT in high-grade T1 NMIBC and possibly high-grade Ta NMIBC if the initial TURBT failed to retrieve detrusor muscle, not using single immediate instillations of chemotherapy following TURBT, delaying BCG therapy, and not administering BCG maintenance therapy or full BCG doses to achieve the best possible outcomes (3, 5, 85, 119, 124, 152–155). In a systematic review, Mori et al. (156) evaluated compliance rates for most steps in a typical NMIBC treatment pathway. They reported overall compliance rates between 33%, for the administration of BCG in high-risk NMIBC, to 82% for follow-up cystoscopy. Repeat TURBT was performed in fewer than half of high-risk patients (43%), and only about a third (37%) of intermediate-risk patients received intravesical therapy. Studies

published since then continue to show treatment to be underused, in particular single, immediate chemotherapy instillations, second TURBT, and BCG maintenance (Supplementary Table S3) – fewer than a third of US patients with T1 disease received guideline-based treatment between 2004–2014 (157, 158).

The reasons for this unmet need can be categorized as lack of knowledge and training [or adherence to "myths and mysteries" concerning BCG (114)], lack of access, economic barriers, fear of side effects, and patient comorbidities (Supplementary Table S4). Adequate training and knowledge are important determinants of guideline-compliant treatment, e.g., for use of single, immediate instillations of chemotherapy (159). Second TURBT and intravesical therapy were more likely if treatment was performed in academic institutions and by a specialist (157, 158, 160, 161). Urologists with less time in practice were more likely to treat in compliance with guidelines than those with more experience, potentially because younger physicians were more willing to consult guidelines to compensate for their (perceived) lack of experience (157, 160).

Economic barriers have also been reported, for instance for uninsured patients in the US and for Chinese patients who refused indicated surgeries and treatment due to financial concerns (158, 162). The shortage of BCG (discussed below), is another reason why treatment, in particular BCG maintenance therapy, may not be performed in compliance with guidelines (160, 162). Concerns about side effects and patient comorbidities represent further causes of non-guideline-compliant treatment. Between 20–60% of patients do not receive second TURBT or intravesical therapy due to their general health (161). Such concerns may be voiced by treating physicians, but also by patients worrying about potential side effects and reduced QoL (162).

Guideline-based treatment has become more common (142, 148), but additional efforts are needed to make it the default. Suggestions discussed in the literature include, firstly, improvements to risk stratification models. More reliable models would help to facilitate targeted and personalized treatment decisions, including early identification of patients unlikely to benefit from specific treatments such as BCG (163–165). Secondly, guideline adherence could be made more prominent in clinical practice by defining quality performance indicators (QPI) that include key guideline recommendations. Perhaps the best-known example of such an approach and its success is the Scottish QPI Programme, which developed and implemented bladder cancer-related QPIs in Scotland from 2012 onwards, with clinical outcomes being evaluated through the Scot BC Quality OPS clinical project (166). The project has resulted in improved TURBT quality (including using single, immediate instillations of chemotherapy) with subsequent long-term recurrence benefits (152, 154). These indicators, if audited and reviewed with clinical staff, have increased motivation not to underperform compared to peers. Modern instillation technology and relatively simple changes such as including reminders in surgical documentation also contributed to improved care quality (159). Thirdly, guidelines and their contents as well as QPIs could be made more accessible using modern information technology. Beardo et al. (167) have presented initial results from using a computer application that combines

clinicopathological information with treatment suggestions derived from guidelines. Initial results were promising, with reduced rates of recurrence in cases where the app- and urologist-proposed treatments agree, relative to cases without agreement. Further validation work is needed, but such an application may aid physicians in treatment decision-making. Fourthly, for the very heterogenous group of intermediate-risk NMIBC, further efforts into improved risk substratification, research into the relative benefits of chemotherapy versus immunotherapy, and optimized intravesical chemotherapy schedules, and treatment harmonization are required, such as recent work by the International Bladder Cancer Group (137).

Apart from suboptimal treatment, the outcomes of NMIBC are negatively affected by insufficient patient lifestyle changes, including smoking cessation (63, 168–171). Adherence to lifestyle recommendations is associated with reduced recurrence risk and improved QoL in patients with NMIBC (172, 173), but several surveys have shown low rates of lifestyle changes following NMIBC diagnosis (Table 1). Among Dutch patients, only 36% of smokers had stopped smoking 3 months after the diagnosis (171). A recent analysis of UroLife data confirmed largely unchanged lifestyles following NMIBC diagnosis – only minor to moderate changes were found for most lifestyle categories, most smokers continued to smoke, and BMI remained unchanged in the first 15 months since diagnosis (168). For the UK, an even lower smoking cessation rate of 14% was reported over 4.2 years after diagnosis (169). In Turkish patients, a higher cessation rate (58%) was reported (170). This lack of adherence to lifestyle recommendations likely results from patients being insufficiently aware of risk factors and detrimental lifestyle. Among Dutch patients, most (89%) identified smoking as a cancer risk factor but only between 29% and 67% were knowledgeable about other risk factors such as insufficient consumption of vegetables and fruit or being overweight (171).

Patients may not receive enough counseling and assistance from healthcare providers. Only 29% of current smokers that had been advised to quit smoking had received an offer of help to stop smoking in the Netherlands, and only 21% of all patients reported advice from their physician on at least one lifestyle behavior (171). In Turkey, only 4.1% of current or ex-smokers have been referred to a smoking cessation program (170). Further evidence on the effectiveness and practicality of lifestyle recommendations would also be required to increase awareness of and confidence in such recommendations (172).

Patients may not only find it difficult to adhere to lifestyle recommendations – their compliance with surveillance and treatment regimens is also often suboptimal, leading to frequent treatment discontinuation and less favorable clinical outcomes (5, 124, 161, 174–179).

NMIBC care is beset by high rates of treatment discontinuation, particularly for intravesical therapy (Supplementary Table S5). Compliance with cystoscopic surveillance protocols has been reported at below 20% (174, 179). For intravesical BCG, completion of induction therapy is 80–90%, but completion of maintenance therapy varies between 10–76% – depending in particular on the proposed maintenance duration since longer therapy was less likely to be completed (19, 124, 161, 175–177).

TABLE 1 Lifestyle changes in patients with NMIBC.

Study, study design	Findings on patient lifestyle changes
Beeren et al. (168), survey of Dutch patients from the UroLife study (n=966: smoking, n=961: physical activity, n=960: BMI, n=949: diet, n=935: overall WCRF/AICR recommendation score)	Small to moderate albeit statistically significant effect sizes for lifestyle change (for all domains except BMI), baseline → 15 months: • Overall WCRF/AICR: 3.3 → 3.3 • BMI: 26.8 → 26.9 kg/m^2 • Physical activity: 750 → 665 min/week • Red and processed meat: 704 → 608 g/week • Smoking: 23.2 → 15.0%
Van Osch et al. (169), semi-structured face-to-face interviews and questionnaires in 722 UK patients with NMIBC at risk of recurrence	• Of 174 patients smoking at diagnosis, 25 (14%) quit over a median of 4.21 years of follow-up • No statistically significant effect of smoking cessation on 5-year recurrence risk but too few cessation events for firm conclusions

Westhoff et al. (171), survey of 969 Dutch patients with NMIBC from the UroLife cohort	• Patients receiving lifestyle advice from a physician on:
	  o Smoking cessation (in smokers): 70%
	  o Weight loss (in patients with BMI >25 kg/m^2): 6% (34% considered that weight loss advice did not apply to them)
	    o Healthy diet: 9%
	    o Physical activity: 15%
	• Smoking cessation at 3 months after diagnosis: 36%

Yuruk et al. (170), survey of 187 Turkish patients with NMIBC enrolled under cystoscopic surveillance	• At diagnosis, 61% of patients were active smokers, of whom 76% received advice to quit smoking and of whom 58% quit smoking • 4.1% of current or ex-smokers had been referred to smoking cessation programs

AICR, American Institute for Cancer Research; NMIBC, Non-Muscle-Invasive Bladder Cancer; UK, United Kingdom; WCRF, World Cancer Research Fund.

Side effects of BCG therapy, particularly in the first year of treatment, may contribute to treatment discontinuation, with proportions of patients stopping BCG treatment in trials reported between 8% and 20% (177, 178, 180, 181). Not complying with treatment and surveillance protocols was associated with increased rates of clinical events, including recurrence, progression, and mortality, of which patients may not be sufficiently aware when deciding to discontinue treatment (174, 175, 179) or surveillance (179).

Toxicities and adverse events are important reasons why patients discontinue or do not start treatment, particularly for BCG and radical cystectomy (19, 176, 178). Although BCG is generally safe, and most associated toxicities and adverse events are transient, patients may be deterred from continuing with therapy, especially if activities of daily living and social activities are impaired (176, 178, 182). The BCG shortage is another reason for not starting or continuing (maintenance) therapy (175, 176). The shortage was triggered by the closure of a BCG-producing facility and subsequent struggles by other manufacturers to meet the production shortfall. The BCG shortage has negatively affected timely treatment and patient outcomes, and has increased treatment costs in some settings (76, 183–186). A more recent interruption to treatment for many patients was the COVID-19 pandemic. In studies from Italy, Turkey, and the US, delays to second resection, lower rates of maintenance therapy, and increased risks of missed treatments were reported (187, 188). In the Netherlands, bladder cancer diagnoses decreased during the first wave of the pandemic, but care was less affected than for other cancers and in other countries (189).

Potential solutions to high treatment discontinuation rates will likely have to include further enhancements to BCG tolerability,

with improved prevention and management of BCG side effects (190). Communication between physicians and patients on side effects, including risk, severity, and meaning (e.g., inflammation as a painful but promising sign in line with BCG's expected mechanism), might improve compliance and would likely be met with interest from patients (190, 191). Similarly, physicians should not assume patient awareness of risk factors or beneficial lifestyle changes. Instead, healthcare staff should aim, within the acknowledged constraints of a busy schedule, to inform and advise patients on the disease and how patients could adapt their lifestyles (171). It should be noted, however, that not all patients appreciate lifestyle advice – among Dutch patients, 80% thought lifestyle advice was beneficial and 70% agreed that physicians had a duty to provide advice, but 15% perceived advice as intrusive and superfluous (171).

The BCG shortage is more difficult to address. Manufacturers have announced production increases, but given the complexity of BCG manufacturing, supply increases will take time (192). Until BCG supply meets demand, alternative treatments and modified BCG treatment approaches could be explored and available resources more carefully used, although treatment schedules and doses should remain guideline-based as far as possible (11, 193). While future developments of the COVID-19 pandemic remain uncertain, the first waves can be considered a chance to improve bladder cancer and NMIBC care, by highlighting areas worthy of (re-)prioritization. This may include avoidance of overtreatment and excessive surveillance in patients at low risk (166, 194) and an increased focus on timely diagnosis, TURBT, and adjuvant therapy initiation (195, 196).

The unmet needs discussed so far are mostly a consequence of physician and patient behavior. They are accompanied by evidence

gaps that make informed treatment decisions challenging. In particular, a corollary of suboptimal, non-guideline-compliant treatment and different treatment schedules is the limited ability to compare outcomes across studies and draw conclusions about relative effectiveness and safety, including on the optimal management of side effects of BCG (197–200). Differences in BCG administration schedules and dosing have made it challenging to compare efficacy and safety outcomes between studies (201). It remains difficult to establish if BCG therapy failure is a genuine failure of BCG or reflects inadequate treatment. The challenge of having to combine estimates from studies using different intravesical schedules affects several systematic reviews and meta-analyses. As an example, a review comparing BCG with MMC for Ta and T1 bladder cancer included, among others, a study using 6-week induction of MMC (two arms with the same dose but different instillation times) and BCG, followed by ten once-monthly instillations (if no recurrence) or second induction for 6 weeks (if recurrence); a study using six weekly instillations for BCG and MCC and with one arm of monthly MMC for another 3 years after induction; a study comparing MMC given every 2 weeks in the first and then every 4 weeks in the second year with BCG given weekly over 6 weeks and then once a month for 4 months (127). Other reviews face similar challenges with heterogeneous data (109, 126).

These concerns have led to the definition of "adequate BCG therapy" when defining "BCG-unresponsive" disease. For clinical trials, adequate therapy has been defined as ≥5 of six induction and ≥2 of three maintenance doses or as ≥5 of six induction and ≥2 of six second induction courses (32, 33). Defining adequate BCG therapy provides some standardization of BCG schedules that improve between-study comparability, and the definition has already seen use in published studies (3, 202). The definition also allows for defining BCG-unresponsive disease, i.e., distinguishing insufficient BCG administration from cases of BCG failure, in clinical trial design (11). Outside clinical trials, up to 21% of patients have been reported as BCG-unresponsive based on data collected mainly in the 2010s, and unresponsive patients have significantly reduced overall and cancer-specific survival relative to responsive patients (203). More recent data have pointed to improved outcomes with adequate BCG in high-risk patients (119, 204), in patients with Cis (3, 202), and even in patients with very high risk disease (22, 204, 205).

If these definitions and concepts are consistently applied in clinical practice, they should help facilitate study conduct and evidence synthesis in the future. The increasing availability of high-quality evidence, e.g., from clinical trials instead of observational studies (119), should also contribute to the accuracy and robustness of evidence synthesis. For intermediate-risk NMIBC, further work is required on identifying optimal therapies, including the benefits of immune- versus chemotherapy and of maintenance therapy as recurrence rates in this patient group remain unsatisfactorily high (5, 126, 136, 137, 206–210). In high-risk patients, data on the time to initiation of BCG and on the effects of delays in BCG initiation remain sparse, and further data would be welcome (155).

The quality of clinical trials in patients with NMIBC also suffers from inconsistent outcome reporting and under-representation of certain patient groups. In a review of fifty-seven randomized controlled trials, Veskimae et al. (211) found that, while recurrence, progression, treatment response, and adverse events were reported in most studies. Overall and cancer-specific survival, treatment discontinuation, QoL, and economic outcomes were less frequently or rarely reported. The review further found substantial variation in how recurrence and progression were labeled and defined; for example, progression was defined as progression to MIBC, with or without including metastases, or as patients moving from Ta to T1 and from T1 to MIBC.

Trial populations also often do not represent real-world patient collectives. A review of phase 1–3 studies from the US and Canada on BCG-unresponsive disease found that only 41% of trials reported data on race/ethnicity. Trials that reported race/ethnicity mostly included white participants (94%), which did not reflect the burden of bladder cancer in racial/ethnic minorities (212). These findings were mirrored when comparing cancer incidence proportions with trial population proportions in US studies, which showed Black and Hispanic patients to be underrepresented in bladder cancer trials relative to non-Hispanic white patients (213). The proportion of Black patients enrolled in trials remained unchanged between 2000 and 2019.

More stringent definitions of treatment schedules and ideally a core outcome set as well as design guidelines for bladder cancer trials should be able to reduce this unmet evidence need (32, 33, 211, 214). Increased patient involvement in trial design could increase the likelihood that patient-relevant outcomes are considered (73). An increased commitment to diversity and inclusivity among trial sponsors and investigators to combat under-representations is required (215).

Not only the available clinical data, but also the available scoring models and risk stratification tables are often limited in their usefulness, which increases the difficulty of selecting the right treatment for patients. Validation studies are available for several prominent models (Supplementary Table S6). For all, validation exercises show reduced discriminative ability and differences in estimated risks if applied to different populations, although it must be acknowledged that not all cohorts used for validation work reflect the current standard of care and improved treatment (29, 92). In a recent validation study of the new EAU 2021 model, for example, the model's discriminative ability was found to be reduced, and progression risks were overestimated, when used in US patients treated with BCG (22). Risk stratification and subsequent treatment selection are especially challenging for patients with intermediate-risk NMIBC, given the clinically heterogeneous makeup of this patient group (137).

These issues should be addressed by continuous validation of existing models in different populations, including in non-European and non-US cohorts, should be performed to further assess which model is suitable in which populations. In addition, model developers should clearly communicate potential model shortcomings. Models can likely be further improved by applying novel statistical and computational tools and by considering additional predictors as well as using ever larger datasets (216,

217). There is also likely untapped potential in biomarkers as predictors of recurrence and progression risk (20, 164, 192, 218).

4 Conclusion

This study presented an overview of NMIBC, including its burden and treatment options, and summarized current unmet needs in NMIBC care and evidence generation. There are many aspects of treatment that are not standardized, including the quality of TURBT, repeat TURBT and intravesical therapy with BCG or chemotherapy. Standardization efforts, like the definition of BCG-unresponsive disease and "adequate" BCG therapy, are new, and guideline recommendations are often not followed in clinical practice and interventional studies. This not only needlessly risks suboptimal patient outcomes in a disease for which effective and safe treatments have been available for decades, but also limits study comparability and evidence synthesis. Addressing these unmet needs should be a priority in clinical practice and research. The present review offered some suggestions as to how these needs could be addressed, including increasing treatment guideline awareness among physicians through improved training, technological advances, and the use of QPIs; strengthening the focus on optimal prevention and management of side effects of intravesical treatment; and changing the mindset about the biology of bladder cancer as a disease of "field cancerization" requiring field rather than local treatment.

Author contributions

KG-H formulated the idea for the present review. Literature searches were performed by RP and JP. The first draft of the manuscript was written by JP. KG-H, CH, PM, GG, and RP commented on and revised earlier versions of the manuscript. KG-H, CH, PM, GG, RP, and JP contributed to the study's design and/or data analysis and interpretation. KG-H, CH, PM, GG, RP, and JP read and approved the final manuscript. JP, RP, and CH prepared responses to peer review comments. All authors contributed to the article and approved the submitted version.

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Conflict of interest

KG-H and CH are employees of medac GmbH, Wedel, Germany, which manufacturers treatments for non-muscle-invasive bladder cancer, including a Bacillus Calmette-Guérin strain and mitomycin C. PM reports honoraria from Photocure for European Faculty meetings, travel, registration, and accommodation support by Photocure for attending the EAU 2022 congress, honoraria from medac for speaking at their satellite symposium on NMIBC at BAUS 2022 (June 2022), and support from medac, Photocure, and Storz for running an endoscopic bladder cancer surgery workshop in Edinburgh (August 2022). JP is an employee and RP is a director at Covalence Research Ltd, Harpenden, United Kingdom, which received consultancy fees from medac to perform the literature searches and develop this article.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1170124/full#supplementary-material

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