Treatment Outcomes of High-Risk Non-Muscle Invasive Bladder Cancer (HR-NMIBC) in Real-World Evidence (RWE) Studies: Systematic Literature Review (SLR)

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Background: To date, there has been limited synthesis of RWE studies in high-risk non-muscle invasive bladder cancer (HR-NMIBC). The objective of this research was to conduct a systematic review of published real-world evidence to better understand the real-world burden and treatment patterns in HR-NMIBC.

Methods: An SLR was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with the scope defined by the Population, Intervention Comparators, Outcomes, and Study design (PICOS) criteria. EMBASE, MEDLINE, and Cochrane databases (Jan 2015–Jul 2020) were searched, and relevant congress abstracts (Jan 2018–Jul 2020) identified. The final analysis only included studies that enrolled ≥100 patients with HR-NMIBC from the US, Europe, Canada, and Australia.

Results: The SLR identified 634 RWE publications in NMIBC, of which 160 studies reported data in HR-NMIBC. The average age of patients in the studies was 71 years, and 79% were males. The rates of BCG intravesical instillations ranged from 3% to 86% (29–95% for induction and 8–83% for maintenance treatment). Five-year outcomes were 17–89% recurrence-free survival (longest survival in patients completing BCG maintenance), 58–89% progression-free survival, 71–96% cancer-specific survival (lowest survival in BCG-unresponsive patients), and 28–90% overall survival (lowest survival in patients who did not receive BCG or instillation therapy).

Conclusion: BCG treatment rates and survival outcomes in patients with HR-NMIBC vary in the real world, with better survival seen in patients completing maintenance BCG, responding to treatment, and not progressing to muscle-invasive disease. There is a need to better understand the factors associated with BCG use and discontinuation and for an effective treatment that improves outcomes in HR-NMIBC. Generalization of these results is limited by variations in data collection, reporting, and methodologies used across RWE studies.

Keywords: real-world outcomes, high-risk NMIBC

Introduction
Bladder cancer is the tenth most common cancer globally.1 In the US, it was the sixth most common type of cancer overall in 2020 and was estimated to account for 4.5% of all new cancer diagnoses, with 81,400 new cases reported in 2020. Bladder cancer is approximately four times more common in men than in women, and the majority of cases are seen in persons aged over 55 years.2 The average 5-year survival rate is approximately 77%, which declines with greater degree of spread, from 95.8% for in situ disease to less than 6% with distant metastases.2
There are four main stages of disease, according to the Tumor, Node, Metastasis Classification (TNM), based on the degree of muscle involvement.\(^3\),\(^4\) TNM classification includes T0 as the first stage of the disease, when there is no evidence of primary tumor. Tumors staged Ta, T1, and/or CIS are considered non-muscle invasive bladder cancer (NMIBC), where the tumor is localized to the inner lining of the bladder without involving deeper muscle layers.\(^3\),\(^5\) NMIBC accounts for over 70% of all bladder cancer cases.\(^6\),\(^7\)

Transurethral resection of the bladder tumor (TURBT) followed by 6-week induction therapy with intravesical Bacillus Calmette-Guerin (BCG) is recommended by guidelines from the European Association of Urology (EAU), and American Urological Association and Society of Urologic Oncology (AUA/SUO) in patients with high-risk NMIBC (HR-NMIBC).\(^3\),\(^4\),\(^8\) There is some variability among guidelines with respect to the length of maintenance BCG therapy in high-risk patients; the NCCN and AUA/SUO recommend maintenance treatment for 3 years,\(^3\),\(^8\) whereas the EAU recommends BCG maintenance for 1–3 years, while noting that 3-year maintenance therapy is more effective than 1 year in high-risk patients.\(^3\),\(^4\),\(^8\) Recommendations also differ slightly across guidelines on the use of repeated resection (re-TURBT). While re-TURBT is recommended across all three organizations within 2–6 weeks following the initial procedure for T1 tumors, it is also recommended in high-risk, high-grade Ta tumors by the AUA/SUO; in high-grade Ta tumors after incomplete resection or if no muscle is present in the specimen by the NCCN; and also after incomplete resection or if no muscle is present in the specimen by the EAU, except for low-grade Ta/G1 or CIS tumors.\(^3\),\(^4\),\(^8\)

Radical cystectomy is a morbid procedure involving complete excision of the bladder, which is reserved for patients at high risk of disease progression and who have not responded to BCG (EAU; AUA/SUO), or in patients with residual high-grade T1 disease (NCCN).\(^3\),\(^4\),\(^8\)

Patients with high-risk disease are at an increased risk of disease progression and mortality.\(^9\) Prognostic factors associated with high-risk disease have been proposed by the American Urology Association and Society of Urologic Oncology (AUA/SUA), as well as the European Organization for Research and Treatment of Cancer (EORTC) and the Spanish Club Urológico Español de Tratamiento Oncológico (CUETO).\(^8\),\(^10\),\(^11\) The risk stratification system from the AUA/SUA accounts for prior BCG therapy and classifies high-risk patients as those with high-grade T1 disease, variant histology, prior BCG failure, recurrent Ta disease, high-grade Ta tumor greater than 3 cm in size, and carcinoma in situ (CIS).\(^8\) Furthermore, the 2004 grading system from the World Health Organization/International Society of Urological Pathology (WHO/IUSP) associates high-grade disease with large tumor size, invasion of the lamina propria, >T1 stage, CIS, multiplicity, invasion, and metastasis. The WHO/ISUP states that a higher risk of disease progression, recurrence, and mortality is associated with high-grade versus low-grade disease.\(^9\)

While there are a number of studies that have assessed the real-world effectiveness of therapies in NMIBC, there is a paucity of research that has synthesized this real-world evidence (RWE) in a systematic way. RWE is critical to understanding treatment patterns, and the effectiveness of therapies used in routine clinical practice. A systematic literature review (SLR) was conducted to gain a comprehensive and up-to-date understanding of the real-world use and effectiveness of current therapies used in NMIBC, with a specific focus on patients with HR-NMIBC. Understanding the characteristics of RWE studies (such as by study type, data source, intervention type, and sample size), data sources used, and type and frequency of the main outcomes reported were additional objectives of the SLR.

**Methods**

Searches were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The scope of the SLR was defined in terms of the PICOS criteria (Population, Intervention, Comparators, Outcomes and Study Design) and followed the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions, Centre for Reviews and Dissemination (CRD)’s Guidance for Undertaking Reviews in Health Care, and Methods for the Development of National Institute for Health and Care Excellence (NICE) Public Health Guidance.\(^12\)-\(^15\)

The key biomedical literature databases (Medical Literature Analysis and Retrieval System Online [MEDLINE\(^8\)], Excerpta Medica Database [Embase\(^8\)], and Cochrane database [Collaboration databases], were searched via the Ovid platform between January 1, 2015 and July 2, 2020. The following conferences were searched for relevant abstracts published between 2018 and 2020: American Society of Clinical Oncology
(ASCO), American Society of Clinical Oncology Genitourinary Symposium (ASCO GU), European Society for Medical Oncology (ESMO), and ISPOR.

Given the diverse nature of real-world studies, broad criteria were used to identify relevant publications. “Real-world” evidence encompassed: prospective observational studies, retrospective studies, registry analyses, database analyses, natural history studies, and non-interventional studies. Only studies involving at least 100 patients with NMIBC from the US, Europe, Canada, and Australia were selected due to the large number of hits. Geographic criteria were also added in order to limit the heterogeneity in the reported data. Case reports were excluded regardless of sample size. The patient population included those with NMIBC, early-stage bladder cancer, or stage 0 or 1 bladder cancer. There was no restriction with regards to comparators or outcome measures reported by studies.

Overall, the SLR included all relevant real-world studies in NMIBC. This report focuses on RWE studies that involved patients with HR-NMIBC. As there is no standardized definition for “high-risk” disease in the literature, wide criteria were adopted when assessing risk categories of studies identified in the SLR. Studies were only included if authors defined or specified that patients had high-risk disease. High-risk status was not assumed based on the treatment received, without it being indicated in the publication.

Weighted averages were used to describe patient characteristics, and treatment patterns were categorized by the percent range of reported treatment. A separate category (“100%”) was added for studies that included patients only treated with a certain type of therapy. In contrast, clinical outcomes were reported by individual study rather than using weighted averages or summary statistics due to the heterogeneity across RWE studies in HR-NMIBC.

**Results**

A total of 11,426 publications were identified from searches. Of these, 2879 were selected for title/abstract review, and 376 met the criteria for data extraction. Of these, 160 publications reported HR-NMIBC patient identification or outcomes and were included in this review (Figure 1). In 85 publications, HR-NMIBC comprised the total study population, and 75 publications reported outcomes in HR-NMIBC as a patient subgroup.

One hundred and sixty publications reported outcomes in or identified patients with HR-NMIBC. Regarding the definition of “high-risk” disease, 93 studies used criteria from guidelines to define high-risk. No specific criteria were mentioned in 20 studies and patients were identified by treatment received for high-risk disease (as identified by the publication). In 156 studies, disease category/staging was used to identify high-risk patients (not mutually exclusive; see Tables 1–3 in the Supplementary Appendix).

Of the 160 identified publications, 141 specifically reported outcomes or treatment patterns in HR-NMIBC. The majority of real-world studies in HR-NMIBC identified in the SLR were retrospective (84%), and half were single-center studies. Among the selected publications, the majority of studies were conducted in Europe (61%), followed by the US (25%), and other international countries (11%). The number of patients enrolled varied across studies, with 62% including between 100 and 500 patients and 25% including over 1000 patients.

**Patient Characteristics**

Consistent with epidemiologic reports, the majority of patients with HR-NMIBC in real-world studies were males aged over 60 years, with a weighted average age of 71 years (range 65–86 years) and 79% male gender (range 56–100%).

Most patients had Stage 1 and/or high grade (HG) disease, according to the 2004 WHO/ISUP classification criteria (91% and 92%, respectively; Figure 2). A degree of heterogeneity in tumor characteristics was observed across the real-world literature. Multiple tumors were reported in 21–71% patients with HR-NMIBC, multifocality reported in 20–86%, and large tumors (>3cm) reported in 11–76% of the patients across studies. Tumors of variant histology were present in up to 25% of the patients.

**Treatment Patterns**

Sixty-one studies reported the use of BCG in patients with HR-NMIBC. In 43 of these studies (70%), BCG was used in all patients (100% treatment rate). BCG therapy was an inclusion criterion for some of these studies, which contributed to this high rate. In the remaining 18 studies (30%), the reported use of BCG instillations in HR-NMIBC patients ranged from 3% to 86%.

Thirty-five studies reported on the use of BCG induction therapy specifically,
of which 27 (77%) reported the use of BCG induction in all patients (100%). Among the remaining eight studies, rates of BCG induction therapy ranged from 29% to 95%. The use of maintenance BCG in HR-NMIBC was reported in 31 studies, with rates being more variable than those seen with induction therapy. Only 7 studies (23%) reported BCG maintenance being used in all high-risk patients (100%). Among the remaining 24 studies, use of maintenance BCG therapy ranged between 8–83%.

Twelve studies reported the use of mitomycin C in high-risk patients. Treatment rates ranged from 2% to 53% in 9 studies, with few studies reporting its use in all patients (rate of 100% in 3 studies). In 7 of the 11 studies (64%), mitomycin C
Patients completing maintenance BCG, was used in a minority of patients (≤20%).

Adjuvant and intravesical chemotherapy in HR-NMIBC (not including mitomycin C) were rarely used and reported in a small number of studies (4–55,58,66,67 and 8, 23,28,32,33,51,70,74,82 respectively). The proportion of high-risk patients treated with adjuvant chemotherapy in reporting studies ranged from 2% to 19%, and 4% to 34% for intravesical chemotherapy. The use of peri-operative chemotherapy was reported by only three studies and was generally used in less than a third of patients (range of 19–29%).

The use of re-TURBT in patients with HR-NMIBC was reported in 43 studies. Across 27 studies, the use of this procedure varied from 15% to 82%, and in 16 studies, it was used in all patients (100%).

The use of radical cystectomy in HR-NMIBC was reported in 36 studies and rates likewise varied, ranging from 3% to 48% in 31 studies; in the remaining 5 studies, radical cystectomy was used in 100% of the patients. Excluding these studies, ≤20% of the patients were treated with radical cystectomy in the majority (60%) of studies.

Notably, a multicenter retrospective study conducted in Poland showed that following the diagnosis of HR-NMIBC, 48% of the patients undergo restaging TURBT, 14% undergo intravesical BCG, 7% have radical cystectomy, and only 2% undergo intravesical chemotherapy with maintenance treatment, while the remaining 30% are managed under observation.

Another Medicare database study showed a low incidence of aggressive treatment (radical cystectomy, radiotherapy, or systemic chemotherapy), with only 25% of the patients experiencing at least four recurrences undergoing radical cystectomy or radiotherapy within 10 years of diagnosis.

Together, these findings indicate that BCG is a mainstay therapy commonly used in HR-NMIBC in real-world clinical practice settings, with the use of intravesical mitomycin C, chemotherapy, and surgery being more variable and less common.

Clinical Outcomes

The 5-year progression-free survival (PFS), recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) real-world outcomes for patients with HR-NMIBC are presented individually by study in Figure 3. Patients completing maintenance BCG, responding to treatment, and not progressing to muscle-invasive disease have in general better survival.

Five-Year Outcomes

Five-year RFS rates were reported by 12 studies in the high-risk NMIBC population and ranged from 17% to 89%. The highest RFS rate was seen in a single-center study conducted in Spain in patients who completed BCG maintenance. Lower rates were seen in patients with high rates of disease recurrence and in those with a high disease burden, as based on the
Figure 3 Five-year survival outcomes. Five-year survival outcomes for (A) recurrence-free survival (RFS), (B) progression-free survival (PFS), (C) cancer-specific survival (CSS), and (D) overall survival (OS).

Notes: These results for RFS, PFS, CSS, and OS reflect the outcomes for high-grade disease as opposed to high-risk as few studies reported HR-NMIBC specifically, except for two studies that reported median OS results. Rates are presented as reported by individual study, they do not reflect weighted averages.

Abbreviations: BCG, Bacillus Calmette-Guerin; DOC, docetaxel; G2, grade 2; G3, grade 3; GEM, gemcitabine; HG, high-grade; HR, high-risk; IR, intermediate-risk; LG, low-grade; maint, maintenance therapy; NMIBC, non-muscle invasive bladder cancer; RC, radical cystectomy; TURB, transurethral resection of bladder tumor.
need to undergo repeated TURBT or radical cystectomy.27,46,54 The Spanish single-center study assessed outcomes among patients treated with different BCG strains due to a supply shortage of Connaught BCG at their clinic (Immucyst®). Three treatment groups were evaluated: 1) Connaught group, 2) Tice (Ontice®) group, and 3) induction Connaught followed by maintenance Tice group. Across the three groups, time to recurrence (TTR) ranged between 13 and 28 months and time to progression (TTP) between 16 and 46 months (no significant difference between groups).34 Patients with a history of NMIBC had significantly lower median TTR compared with those with primary NMIBC (11.9 vs 21.2 months) in a retrospective review of HR-NMIBC patients.78 Heavily pretreated patients receiving salvage therapy with gemcitabine and docetaxel after BCG failure, demonstrated a low median TTR of 6.8 months in a retrospective multicenter review.97 It is interesting to note that a study in HR-NMIBC patients with residual T1 high-grade G3 (HG/G3) disease treated with re-TURBT and BCG maintenance reported the lowest 5-year RFS (17%) of the 12 studies.27

Five-year PFS rates were reported by 11 studies among the HR/IR NMIBC population, ranging from 58% to 89%.27,36,37,41,42,46,54,81,88,98,104 Among the 11 studies, the lowest PFS rate of 58% was reported in the same population of patients with the lowest RFS rate (Ferro et al 2018), ie, those with residual T1 HG/G3 disease at re-TURBT.27 The study reporting the highest PFS rate was in a population of patients with pT1 G2 disease treated with re-TURBT and adjuvant BCG (89%).54

Five-year CSS rates in HR-NMIBC patients were reported by 12 studies and ranged between 71% and 96%.27,37,41,42,46,73,76,88,94,98,102,104 The study reporting the lowest rate was in patients who did not respond to intravesical BCG.76 Two studies reported 10-year CSS, which was achieved in the majority of patients (85% and 92%).32,73

Five-year OS rates were reported by 10 studies and ranged widely from 28% to 90%.27,37,41,46,50,67,72,73,88,104 Among the 10 studies, the lowest OS rate was reported in a study of patients with T1 HG disease who did not receive BCG or instillation therapy (28%).50 Significantly lower 5-year OS was reported in one study in patients with T1 HG undergoing initial local treatment compared with those receiving early radical cystectomy (52.4% vs 71.1%; p<0.001).67 T1 HG disease at re-TURBT was also associated with lower survival compared with other NMIBC types of recurrence in the study by Ferro et al (74% vs 90%).27

Ten-year OS was reported in only 2 studies and was 49% in HR-NMIBC patients (Ta/T1 HG, majority treated with at least 6 doses of BCG) and 59% in T1 HG patients treated with complete induction and at least one dose of maintenance BCG.32,73

Event-free survival (EFS) is related to recurrence, disease progression, and survival. EFS was only reported by one study (with two publications) of patients with primary NMIBC or MIBC who underwent TURBT or radical cystectomy.105,106 In these patients, EFS was 68% and 32%, respectively.

Time to Event Outcomes
Median RFS/TTR was reported by 13 studies and ranged from 5.1 to 28.0 months (7 studies reported two or more values by subgroup).17,31,34,36,41,43,46,58,68,72,78,97,108 Six studies reported median PFS/TTP, which ranged widely from 9.2 to 45.8 months (1 study reported PFS by three subgroups based on BCG type).17,34,36,58,68,87 Median CSS of 47.1 months was reported in only one study in HR-NMIBC.17

Only one study was identified that proposed combination intravesical chemotherapy (gemcitabine and docetaxel) for the treatment of HR-NMIBC patients who failed BCG therapy. The median TTR was 6.8 months for the overall population and 9.5 months for patients who underwent subsequent cystectomy.97 Intermediate-risk (IR) patients treated with adjuvant chemotherapy (mitomycin C, epirubicin, or doxorubicin) carried a high risk of recurrence (5-year RFS 44%), but a lower risk of long-term progression (5-year PFS 88%).104

Only two studies reported median OS in high-risk or high-grade NMIBC,67,109 of which one reported OS by treatment with radical cystectomy in high-grade NMIBC (Figure 4).67 In the case of patients with HR-NMIBC and T1 HG disease, early radical cystectomy was associated with longer median OS compared with patients not undergoing cystectomy and receiving endoscopic management, with or without intravesical therapy (72.4 vs 64 months; Figure 4).67 The lowest median OS was reported in the study of patients with high-risk disease specifically (median OS of 52.8 months), which classified high-risk as stage Ta, T1, or CIS (grade III [poorly differentiated]) or IV (undifferentiated); and tumor size ≥3 cm.109
Clinical Outcomes at Follow-Up

The median follow-up for CSS ranged from 12 to 130 months across 30 studies that reported CSS at follow-up. There was no observed trend in the proportion of HR-NMIBC patients dying due to cancer (CSS) with increasing length of follow-up (Figure 5A). Median follow-up for OS ranged from 23 to 130 months across the 21 studies that reported this.

Likewise, there was no evident trend in survival outcomes with increasing duration of follow-up. Notably, one study by Gordon et al reported the lowest percentage of patients who were alive at follow-up (9.8%) out of the 21 studies, which was seen in patients with HR-NMIBC who did not undergo re-TURBT after a median follow-up period of 50 months.

Treatment discontinuation rates were primarily related to the proportion of patients completing maintenance BCG therapy. Studies showed that overall treatment compliance among high-risk patients is poor, with approximately half of patients completing maintenance therapy (ranging from 29% to 59%). In the overall NMIBC population, as few as 15% of the patients complete maintenance therapy.

Discussion

Findings from this SLR identified that treatment patterns and survival outcomes in HR-NMIBC are varied in real-world clinical practice. Due to the heterogeneity in outcomes measured and patient populations, it is difficult to accurately determine if real-world outcomes are consistent with clinical trial data. Nonetheless, in comparing against the landmark South West Oncology Group (SWOG) randomized trial, 5-year OS, PFS, and RFS with maintenance BCG were 83%, 76%, and 60%, respectively, which are largely in line with outcomes from several RWE studies identified in this SLR (Figure 3).

Various methods used across studies to identify and define high-risk patients contribute to the heterogeneity reported in the literature. The high-risk population included in studies was not always standardized in terms of disease stages and grades. While most studies agreed that T1 HG-disease is categorized as high-risk NMIBC, some also include other criteria such as Ta HG, Ta LG multiple recurrent tumors, multifocal, or large tumors.

Treatment guidelines recommend the use of adjuvant induction BCG after TURBT followed by maintenance BCG, typically ranging from 1 to 3 years in patients with high-risk disease. Findings from this SLR showed there is no consistent approach to the treatment of HR-NMIBC in the real-world following upfront TURBT. The use of BCG in real-world clinical practice is largely consistent with guidelines with regards to the use of BCG induction therapy, which was used in all patients in the majority of studies. However, the use of maintenance therapy is more variable and less consistent, with less than a quarter of studies reporting that all high-risk patients received BCG maintenance therapy. Overall, BCG was found to be the mainstay therapy in HR-NMIBC in the real-world setting, with other therapies including mitomycin C, chemotherapy, and surgery used less frequently and less consistently. There is a wide variation in treatment patterns indicating that the real-world clinical management of HR-NMIBC is not standardized.

BCG is an effective therapy, and patients receiving maintenance BCG have a lower risk of recurrence and disease progression than those only receiving induction therapy or re-TURBT, no further treatment, or not completing maintenance therapy. However, the improvements reported with BCG in terms of survival, TTR, and TTP vary across studies. This may be due to differences in the proportion of patients with non-primary tumors and in those completing maintenance BCG. Patients undergoing early radical cystectomy have a significantly lower risk of mortality than initial local treatment with intravesical BCG, yet no difference in cancer-specific mortality was found between up-front or delayed cystectomy after BCG. High rates of disease recurrence in high-risk
patients are associated with lower 5-year RFS and a high disease burden, based on the need to undergo repeated TURBT or radical cystectomy.27,46,54

Overall, disease recurrence and survival outcomes seen in the real-world setting are heterogeneous. This heterogeneity may be influenced by inconsistent use of treatments in clinical practice, variations in the patient populations included in studies, as well as differences in the methodology and data sources used across studies. RWE studies comparing the efficacy of intravesical BCG and chemo- or immunotherapy are scarce, and outcomes reported to date are variable. There is a need to better understand the factors associated with the use of BCG and other intravesical therapies or surgical procedures in HR-NMIBC, as well as their effectiveness in the real-world.

**Limitations**

The generalization of results may be limited by the heterogeneous nature of real-world data due to variations across studies in their design, patient populations, data collection, reporting, and methodologies. The high variability of
population characteristics and therapeutic strategies made it difficult to derive average scores for key efficacy outcomes of CSS, OS, PFS, and RFS in HR-NMIBC, so results were instead reported by the individual studies. Another key factor contributing to data heterogeneity is the variability of criteria used to define high-risk disease in RWE studies. For this reason, all outcomes should be interpreted in the context of the clinical characteristics (ie, tumor stage and grade, response to prior therapy, tumor characteristics) of the HR-NMIBC population. Further, the observational nature of RWE means that caution should be exercised when comparing outcomes across different studies due to differences in the representativeness of the patient populations and differences in study design.

Conclusion
BCG treatment rates and survival outcomes in HR-NMIBC vary in the real world, with better survival seen in patients completing maintenance BCG, in those responding to treatment generally, and not progressing to muscle-invasive disease. There is a need to better understand the factors associated with BCG use and discontinuation and to develop an effective treatment that improves outcomes in HR-NMIBC.

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