

A population-based analysis of patterns of care in patients with high-risk non-muscle-invasive bladder cancer from Alberta, Canada

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ABSTRACT

Introduction: Approximately three-quarters of patients newly diagnosed with bladder cancer have non-muscle-invasive disease (NMIBC). Among these patients, those with high-risk (HR) features should be managed more aggressively in an attempt to circumvent the elevated risk of recurrence/progression. Population-based data on the incidence of HR-NMIBC and receipt of guideline-recommended care are limited.

Methods: This retrospective, observational study gathered data from multiple linked provincial (Alberta) healthcare databases to describe baseline characteristics, treatment patterns, and survival outcomes in a population of individuals diagnosed with HR-NMIBC from 2010–2020. Data for all patients aged >18 years with T1, Tis, or high-grade Ta NMIBC (“high-risk”) were analyzed using basic statistics, multivariate regression analyses and the Kaplan-Meier method.

Results: Of 6837 de novo NMIBC patients identified, 3874 (57%) were categorized as HR-NMIBC. The majority (82%) were male, with a median age of 72 years, and approximately half had a Charlson comorbidity index score ≥ 1 . Following initial transurethral resection of bladder tumor (TURBT), 61% of the cohort received no adjuvant bacillus Calmette-Guérin (BCG) or chemotherapy, while 36% received BCG, 3% gemcitabine, and 1% mitomycin C. Patients underwent a median of four TURBT procedures. ‘Adequate BCG’ (≥ 5 induction doses + ≥ 2 maintenance doses) was received by 32% of BCG-treated and 12% of all HR-NMIBC patients. Survival was improved in patients receiving adequate BCG.

Conclusion: Data from this large, real-world population highlights poor use of induction/maintenance BCG therapy following TURBT among patients with HR-NMIBC.

KEY MESSAGES

- Real-world data from Alberta, Canada, shows only 39% of high-risk non-muscle-invasive bladder cancer (HR-NMIBC) patients in the study received CUA guideline-recommended adjuvant treatment with bacillus Calmette-Guérin (BCG) or chemotherapy following transurethral resection of bladder tumor (TURBT).
- Of those who received BCG, only 1/3 received a schedule considered adequate for prolonged disease-free survival.

INTRODUCTION

Bladder cancer (BCa) is the fifth most common type of cancer in Canada (8.1% of cancer diagnoses) and tenth most common cancer worldwide.^{1–3} It is a disease that disproportionately affects men (male:female incidence is 3:1) and the elderly (average age at diagnosis is 73 years).¹ Approximately 70–80% of individuals with BCa are diagnosed with non-muscle invasive bladder cancer (NMIBC).^{1,4}

NMIBC is a heterogeneous disease with a risk of disease recurrence or progression that varies based on T stage, tumour grade, tumour size, number of tumours, and prior disease recurrence.¹ Risk indices, which include the European Organisation for Research and Treatment of Cancer (EORTC) scale, the European Association of Urology (EAU) risk score, and the Club Urologico Espanol de Tratamiento Oncologico (CUETO) tool, offer a means of categorizing NMIBC into low-, intermediate- or high-risk (HR) categories that guide treatment.^{5,6}

Over the past two decades, treatment algorithms for this disease have not changed.^{7,8} Primary treatment of NMIBC consists of one or several transurethral resection of bladder tumour (TURBT) procedures.^{4,9,10} To improve prognosis and minimize recurrence, treatment with chemotherapy or bacillus Calmette-Guérin (BCG) is recommended following TURBT.^{1,9,10} For low risk NMIBC, this entails a single instillation of chemotherapy (mitomycin C, gemcitabine, doxorubicin, epirubicin, or pirarubicin), whereas adjuvant induction and maintenance chemotherapy or immunotherapy (BCG) are additionally recommended for intermediate risk NMIBC.^{1,9,10} For HR-NMIBC, standard of care treatment is adjuvant intravesical induction and maintenance BCG.^{1,9,10} Radical cystectomy may also be considered for individuals with very high risk features, BCG-unresponsive HR-NMIBC, or endoscopically unresectable disease.^{1,9,10} Even with TURBT and adjuvant intravesical treatment, intravesical recurrence occurs in up to 70% of cases with 10%–30% progressing to muscle invasive bladder cancer (MIBC) which has a 50% mortality rate within five years.^{4,11}

Such high recurrence and progression rates require intense surveillance and repeated lines of treatment, making the estimated lifetime treatment cost of BCa among the highest of all malignancies.¹² Costs related to managing HR-NMIBC are substantially higher than those for low-risk NMIBC.¹³ This, coupled with limited real-world evidence, particularly in the Canadian setting,¹⁴ means the true burden of disease and patterns of care for HR-NMIBC remain unknown. To better understand the current Canadian landscape, we aimed to assess baseline characteristics, treatment patterns, and overall survival (OS) in a real-world cohort of individuals diagnosed with HR-NMIBC in Alberta, Canada between 2010 and 2020.

METHODS

Study design and setting

This study is a retrospective, observational, cohort study of individuals diagnosed with *de novo* HR-NMIBC between 2010 and 2020. The primary objective of the study was to characterize patterns of care for patients with HR-NMIBC in a Canadian real-world setting.

To this end, data related to cancer diagnosis, patient and disease characteristics, treatment, and outcomes were sourced from multiple population-level health administrative databases in Alberta, Canada, covering 17 cancer centers (2 tertiary, 4 regional and 11 community centers) and 4.5 million provincial residents. The databases utilized included the Alberta cancer registry (ACR), pharmaceutical information network (PIN), health practitioner claims, discharge abstract database (DAD), and national ambulatory care reporting system

(NACRS) databases (see Table S1 for a full description of databases utilized). Coded data were deterministically linked (100% linkage rate) using unique lifetime identifier numbers; i.e., each patient has a number that is used across all Alberta healthcare databases. Patients were followed from diagnosis until last known contact with the healthcare system, end of 2021, or death, whichever occurred first.

Database linkage, data cleaning, statistical analyses, and generation of study results were conducted by the University of Calgary's Oncology Outcomes (O2) research group (Calgary, Alberta, Canada). This study was approved by the Health Research Ethics Board of the Alberta Cancer Committee (ID: HREBA-CC-0141).

Participants

Eligible patients were those aged ≥ 18 years presenting with T1, Tis, or Ta tumours without nodal or distant metastasis (NOMO) and high-risk features (HR-NMIBC). Disease stage was defined using the most recent edition of the American Joint Committee on Cancer (AJCC) TNM staging guidelines available at the time of diagnosis.¹⁵⁻¹⁷ To classify disease grade, the 1973 World Health Organization (WHO) definition was used for individuals diagnosed prior to 2018, as only cellular differentiation was collected in the registry during that time.¹⁸ The 2004/2016 WHO definition was used for individuals diagnosed since 2018.^{19,20} High risk was defined as T1, Tis, or high-grade Ta (HG-Ta) pathology based on EAU criteria, using available data.⁹ Patients with disease characteristics not meeting these criteria were excluded (e.g., Ta + grade 2).

Variables/data collection

Procedural codes for the variables of interest were compiled by the study investigators (see Table S2). Pre-specified baseline characteristics of interest (sex, age, residence, T stage, tumour grade, and index year) and were determined by the variables collected in the databases utilized. Index year was collected as a continuous variable. Age was collected as a continuous variable and categorized as ≤ 65 , 66-75, and ≥ 76 , in alignment with disease and treatment characteristics, and published literature.^{1,21-23} Charlson comorbidities were identified by searching codes as defined in Quan et al. (2005),²⁴ the year prior to BCa diagnosis. Rural vs. urban residence was classified based on standard methodology.²⁵⁻²⁷

Treatment related variables of interest included type, number of procedures/cycles, and duration. Treatments of interest included TURBT, BCG, gemcitabine, mitomycin C, and cystectomy (partial or radical). The number of TURBT procedures, including the initial diagnostic TURBT was observed for the overall population and by T stage. First therapy following initial TURBT was noted and time to therapy was calculated as the time from diagnosis to first treatment. Therapies recorded after TURBT were considered adjuvant since single instillation therapy on the day of initial TURBT was not captured. Induction BCG was operationalized as repeated or successive dispensations of BCG up to 6 doses with a gap no longer than 5 weeks between each dose; maintenance BCG was defined as repeated or successive dispensations of BCG following induction treatment, up to a total of 36 months, with a gap no

longer than 240 days between each dose. Adequate BCG was defined as 5-6 doses of induction and ≥ 2 doses of maintenance BCG treatment.²⁸ Gaps between BCG doses of longer than 240 days (up to 180 days as per recommended dosing intervals¹ plus an additional 60 days to account for variations in dosing schedule) were presumed to be treatment for recurrent disease and were excluded. Duration of treatment was calculated as the date from first (induction/maintenance) dispensation to the date of last (induction/maintenance) dispensation.

OS was defined as the time between diagnosis (first TURBT or index date) to death from any cause. Kaplan-Meier curves were estimated and used to calculate the median survival as well as the 1-year, 2-year, and 5-year survival along with the corresponding 95% confidence intervals (95% CI).

Data analysis

Baseline characteristics and treatment patterns are described using the mean (SD) for continuous symmetrically distributed data, median (IQR) for continuous skewed data, and frequency (%) for categorical data. The distribution of baseline characteristics was compared between: 1) high-risk vs. low/intermediate-risk *de novo* NMIBC, 2) T1, Ta, and Tis in HR-NMIBC, and 3) *de novo* HR-NMIBC individuals who received vs. did not receive BCG therapy, using standardized mean differences (SMDs), where values < 0.1 reflect no meaningful imbalance, and p-values (i.e. chi-square tests for categorical variables and ANOVA for continuous variables), whereby values less than 0.05 are considered to be statistically significant. The number and proportion of individuals missing data for each covariate are summarized but not included in analyses.

To quantify the magnitude of association between the baseline characteristics and receipt of BCG therapy, multivariable logistic regression analysis was used. Based on *a priori* expert opinion, the following variables were included as covariates in the multivariable analyses: age at diagnosis, sex, rural vs. urban residence, number of Charlson comorbidities, T stage, tumour grade, and year of diagnosis (2015-2020 vs. 2010-2014).

Survival outcomes are described from diagnosis and from initiation of BCG therapy. For the estimation of OS, individuals were censored at the time of last known contact with the healthcare system or December 31st, 2021, whichever occurred first and was accounted for by the Kaplan-Meier estimator. The median OS and survival rate at specific time-points of interest (e.g. 1-year, 2-year) were estimated along with the 95% CI. ; Analyses were conducted using R version 4.2.2. All statistical tests were two-sided with statistical significance defined at the 0.05 alpha level. A second analyst quality checked the codes performed by the primary analyst.

RESULTS

Baseline characteristics

Of 6837 *de novo* NMIBC patients that were identified, 3874 (56.7%) were categorized as HR-NMIBC (Table 1). The annual incidence of HR-NMIBC ranged from approximately 8 to 10 per 100,000 and was generally stable over the study period (see Table S3).²⁹ In the HR-NMIBC cohort, 82% were male and the median age was 72 years. Tumour stage was T1 in 50%, Ta in

33%, and Tis in 17% of HR-NMIBC patients. Approximately half of HR-NMIBC patients had a CCI ≥ 1 . In comparison to those with low or intermediate risk NMIBC, high risk patients were more often male, older, and had more comorbidities at baseline (see Table S4).

Treatment patterns

Patients underwent a median of 4 (IQR: 2-6) TURBT procedures with a median interval of 6.4 months (IQR: 0.2-24.7) between procedures. Few patients (9.7%) underwent cystectomy and timing was highly variable. See Table 2 for further details. Following initial TURBT, 60.8% of the cohort did not receive adjuvant BCG or chemotherapy, while 35.6% received BCG, 2.9% gemcitabine, and 0.6% mitomycin C.

Of those treated with adjuvant BCG, 28.3% received only one induction dose and 56.9% completed 5 or 6 doses. BCG-treated patients were predominantly male (83.9%), had T1 tumours (52%) and had a CCI of 0-1 (83.5%) (Table S5). BCG induction therapy was initiated a median of 3.6 [2.2, 6.6] months after diagnosis. At least one BCG maintenance dose was given to 59.0% of those who received induction treatment and the majority (86.7%) of those patients received two or more maintenance doses. ‘Adequate BCG’ (≥ 5 induction doses + ≥ 2 maintenance doses) was received by 32.0% of BCG-treated and 11.5% of all HR-NMIBC patients.

In multivariable regression analysis, the strongest predictor of receipt of BCG in HR-NMIBC was high-grade disease. Other features associated with higher BCG utilization were younger age, fewer comorbidities, rural residence, and being diagnosed 2010-2014. Table S6, Figure 1.

OS in this HR-NMIBC cohort was 10.3 years (95% CI: 9.7-10.9 years) with 1- and 2-year survival rates of 94.7% and 88.6%, respectively (Figure S1). The OS from the initiation of BCG among individuals with HR-NMIBC was 11.6 years (95% CI: 10.2-not reached) and the five-year survival was 77.9% (95% CI: 75.6-80.4) (data not shown). Analysis of survival based on BCG treatment adequacy showed a median OS of 10.2 years (95% CI: 9.8-not reached) among patients receiving inadequate BCG and a longer median OS not reached (95% CI: 11.1-not reached) in patients receiving adequate BCG (Figure 2).;

DISCUSSION

This dataset represents, to the best of our knowledge, one of the largest and most comprehensive studies assessing NMIBC practice patterns in Canada. In this Alberta cohort, 62%, 28% and 10% of *de novo* NMIBC were stage Ta, T1, and Tis, respectively, compared to 70%, 20%, and 10% generally reported.³⁰ Nearly half (48%) were high grade and 57% were categorized as high-risk. This is higher than studies applying WHO 2004 grading or EAU risk classification, in which 31-40% of NMIBCs were high grade and 27-43% were high risk.³¹⁻³⁴

A large proportion of patients (61%) did not receive guideline recommended adjuvant treatment with BCG or chemotherapy following initial TURBT. BCG treatment is recommended for all HR-NMIBC patients, but only 1 in 3 initiated BCG treatment and, of those, only 32% (11% of all HR-NMIBC patients) received a schedule of induction and maintenance considered

‘adequate’ to reduce the risk of recurrence and progression.¹ Diagnosis in 2015-2020 was associated with decreased odds of BCG initiation compared to diagnosis in 2010-2014. Increased age (≥ 76 years) was found to be a significant negative predictor (OR=0.66, $p < 0.001$) of treatment with BCG in the Alberta cohort, despite data that supports its tolerability in older patients.^{35,36} Finally, the 5-year OS rate of 79% from BCG initiation is similar to that observed in the landmark South West Oncology Group (SWOG) randomized trial with maintenance BCG (83%).³⁷ To the best of our knowledge, our study is the first to show a possible OS advantage of adequate BCG over inadequate BCG in a real-world setting, with caution that this data may be confounded by cases of early recurrence and consequent BCG discontinuation.

In the Alberta cohort of BCG-treated patients, BCG was initiated a median of 3.6 months after the initial TURBT. Canadian Urological Association (CUA) management guidelines note, if required, a restaging TURBT should be performed within 6 weeks of the first TURBT, and BCG would typically be initiated 2-4 weeks after that (i.e. the longest time from initial TURBT to BCG recommended is 2.5 months).¹ The 3.6 month delay is also longer than the median seen in real-world observations using the Surveillance Epidemiology and End Results (SEER) database in the US (2.6 mos).³⁸ In a retrospective study of high grade T1 NMIBC, compared to the group that received BCG earliest (6-10 weeks post TURBT), postponing time to BCG initiation was associated with an increased risk of recurrence and progression (by at least 50% and 200% for every week of delay, respectively).³⁹

Rates of BCG delivery vary widely in the literature (3-86%) and comparison is difficult due to differing study methodologies.¹⁴ However, rates of use in the Alberta dataset (40%) are in line with results from a systematic literature review by Mori et al. that noted 32.5% compliance with administration of adjuvant intravesical BCG in nearly 4,500 patients with NMIBC.⁴⁰ Other real-world research using the SEER database has shown that 21% of HR-NMIBC cases received low intensity care.⁴¹ While BCG contraindications are rare, medical fitness/frailty may account for some patients not initiating BCG or only receiving one dose due to treatment frequency/invasiveness. While serious toxicity occurs in only 5% of patients treated with BCG, local and systemic adverse events are common, which may, in part, explain why only 1/3 of treated patients received adequate BCG.^{40,42,43}

The decrease in odds of BCG utilization among those diagnosed in 2015-2020 versus 2010-2014 prompted consideration of the potential effect the BCG supply shortage may have had on BCG initiation. The shortage in Canada is not expected to have had a significant impact on BCG receipt since management guidelines advocated prioritization of HR-NMIBC and/or dose and schedule reductions¹ that would still be captured as “adequate BCG” within the administrative databases as searched. In a US-based assessment of the impact of supply shortage on BCG utilization, it was found that utilization rates decreased 5.9% in the shortage period.²² The true impact in Canada could be assessed by comparing BCG utilization from 2021 onward, to our study results, given the Health Canada approval of the Russian BCG-I strain in late 2020 and the subsequent resolution of BCG supply issues in Canada.⁴⁴

It is important to note that the definition of high-risk applied to the Alberta cohort was likely inclusive of some patients who, with more information available about risk factors (e.g., tumour size, multifocality), would have actually been classified as intermediate risk by current EAU or American Urological Association (AUA) criteria.^{10,32} In the absence of this information, patients with T1 low/intermediate grade (n=99), and Ta high grade (n=1275) disease were assumed to be high-risk, regardless of other risk factors, according to the EAU risk stratification recommendations at the time.⁴⁵ This may explain the high proportion of high-risk NMIBC in the Alberta cohort compared to populations classified by other criteria. However, classification method is not expected to influence the rate of BCG utilization, since clinical practice supports the use of BCG in all Ta high grade NMIBC.⁴⁶

In a systematic literature review including 160 publications related to HR-NMIBC, the percentage of high-grade cases was 92%,¹⁴ compared to 85% in the Alberta cohort, where grade data was missing for 9% of patients. Given the prognostic significance of grade for progression and disease-specific mortality in NMIBC, and the strong emphasis placed on proper assessment and reporting of grade for risk stratification and treatment,¹ this may represent an opportunity for improvement in clinical practice or data capture.

Considering the potential impact of under-treatment on long term outcomes for patients with HR-NMIBC, additional research is warranted to identify reasons for the underutilization and delays in the provision of guideline recommended therapy in this population. A starting point, highlighted in our dataset, would be to explore barriers to decreasing the interval between TURBT and the start of BCG induction therapy. Interestingly, rural residence did not appear to negatively impact receipt of BCG therapy in this cohort of patients from Alberta, rather, rural patients were more likely to receive BCG treatment. Further explorations might include patient and physician beliefs (including differences between urban and rural), and attitudes and experiences related to BCG efficacy and tolerability.¹³ Finally, ongoing research, such as the recently published network meta-analysis suggesting a reduction in the incidence of BCG-induced lower urinary tract symptoms with certain medications, provide strategies clinicians can consider for improving BCG adherence.⁴⁷

Limitations

Many of the limitations in our study relate to the nature of administrative data and gaps in information available to explore. For instance, some covariates used in the AUA, EORTC, CUETO, or EUA risk indices (e.g., tumour multifocality, tumour size, histologic subtype, prior recurrence, or lymphovascular invasion) were not captured in the Alberta databases and so more detailed stratification of HR-NMIBC was not possible in this study.^{6,10,32,48} Another limitation of this administrative data is the lack of diagnostic information over time (i.e., only stage at diagnosis is captured), therefore restricting the ability to analyze changes in disease stage or grade over time or relate those to treatment changes. Additionally, nuances related to treatment decisions, tolerability, and response are not available and require different study methodologies to elucidate.

Unfortunately, limitations in the collection of this administrative data also preclude the evaluation of endpoints more appropriate for early stage cancer, such as recurrence-free, progression-free, or disease-specific survival,⁴⁹ and confounding limits the sound interpretation of OS results. Furthermore, comparison to other real-world data is restricted by fundamental differences in study design, inclusion criteria, patient/disease characteristics, and treatment interventions received.¹⁴ Our findings reflect a *de novo* HR-NMIBC population in Alberta, Canada and may not be generalizable to a broader HR-NMIBC population.

CONCLUSIONS

Data from this large, population-based, retrospective study highlight poor utilization of adjuvant induction and maintenance BCG therapy following TURBT among patients with HR-NMIBC. Additional research is recommended to identify reasons for underutilization so that strategies can be applied that support guideline recommended therapy among HR-NMIBC patients in real-world settings.

DRAFT

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FIGURES AND TABLES

Figure 1. Predictors of bacillus Calmette-Guérin (BCG) initiation among individuals with high-risk non-muscle-invasive bladder cancer (HR-NMIBC) diagnosed in Alberta, Canada from 2010–2020. Notes: Individuals missing information on disease grade were excluded from the analyses (n=345; 8.9% of total cohort). CI: confidence interval; Dx: diagnosis; Low/Int: low/intermediate.

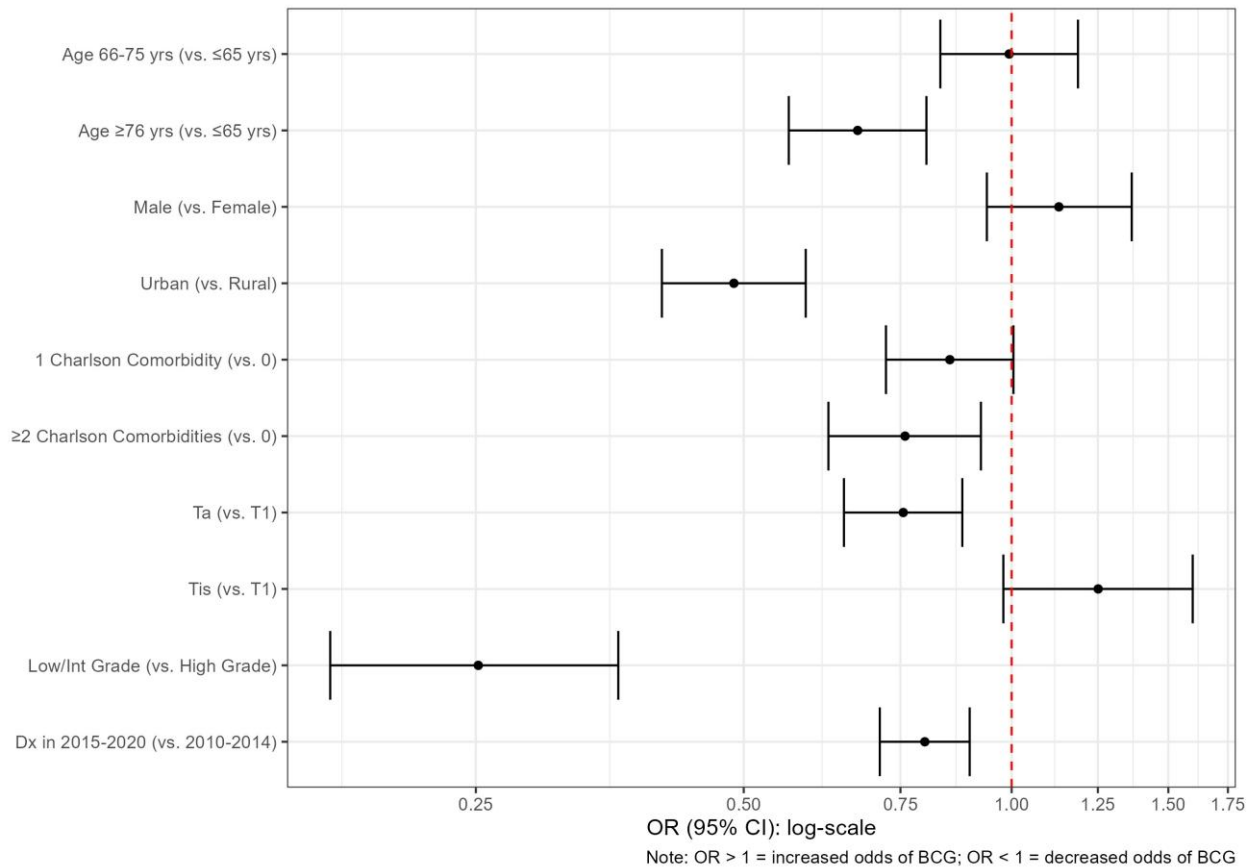
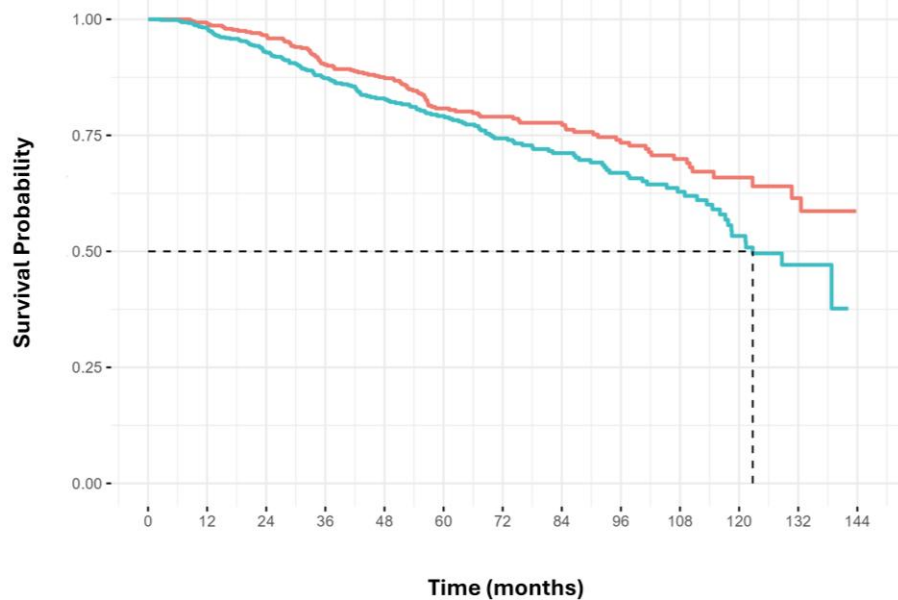


Figure 2. Overall survival from date of diagnosis among individuals with de novo high-risk non-muscle-invasive bladder cancer (HR-NMIBC) receiving adequate or inadequate bacillus Calmette-Guérin (BCG) treatment in Alberta, Canada, diagnosed from 2010–2020. OS: overall survival.



	Number at risk (number of events)												
	0	12	24	36	48	60	72	84	96	108	120	132	144
Adequate BCG	445 (0)	439 (4)	417 (15)	379 (42)	344 (54)	255 (77)	191 (82)	158 (85)	119 (93)	82 (98)	41 (102)	24 (104)	0 (105)
Inadequate BCG	624 (0)	612 (11)	516 (43)	407 (71)	328 (90)	265 (104)	208 (119)	155 (127)	115 (135)	75 (141)	45 (150)	13 (154)	0 (155)

Characteristic	Median, months	12-Month	24-Month	60-Month
Adequate BCG	132.6 (105, 155)	0.991 (0.982, 1.000)	0.966 (0.949, 0.983)	0.808 (0.770, 0.848)
Inadequate BCG	122.8 (117.8, 127.8)	0.982 (0.972, 0.993)	0.928 (0.908, 0.949)	0.792 (0.756, 0.829)

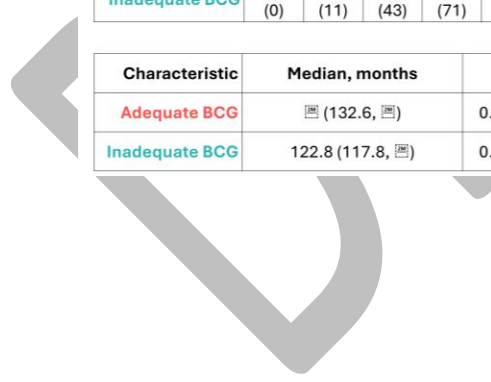


Table 1. Baseline characteristics of the HR-NMIBC cohort		
Variable	Overall n=6837	HR-NMIBC n=3874
Male, n (%)	5363 (78.4)	3181 (82.1)
Urban residence, n (%)	5679 (83.1)	3244 (83.7)
Age at Dx, years, mean (SD)	69.7 (11.9)	71.4 (11.2)
Age at Dx, years, median [IQR]	71.0 [62.0, 78.0]	72.0 [64.0, 80.0]
Age at Dx, categories, n (%)		
≤65	2344 (34.3)	1138 (29.4)
66–75	2170 (31.7)	1233 (31.8)
≥76	2323 (34.0)	1503 (38.8)
Charlson comorbidity index score, n (%)		
0	3672 (53.7)	2019 (52.1)
1	1952 (28.6)	1113 (28.7)
≥2	1213 (17.7)	742 (19.2)
T stage, n (%)		
T1	1934 (28.3)	1934 (49.9)
Ta	4238 (62.0)	1275 (32.9)
Tis	665 (9.7)	665 (17.2)
Tumor grade (%)		
High	3287 (48.1)	3287 (84.8)
Low/intermediate	3205 (46.9)	242 (6.2)
Missing	345 (5.0)	345 (8.9)
T stage + tumor grade		
T1 + high-grade	1732 (25.3)	1732 (44.7)
T1 + low/intermediate-grade	99 (1.4)	99 (2.6)
T1 + missing grade	103 (1.5)	103 (2.7)
Ta + high-grade	1275 (18.6)	1275 (32.9)
Ta + low/intermediate-grade	2963 (43.3)	0 (0.0)
Tis + high-grade	280 (4.1)	280 (7.2)
Tis + low/intermediate-grade	143 (2.1)	143 (3.7)
Tis + missing	242 (3.5)	242 (6.2)
Year of diagnosis (%)		
2010–2014	2898 (42.4)	1616 (41.7)
2015–2020	4075 (59.6)	2258 (58.3)

Dx: diagnosis; HR-NMIBC: high-risk non-muscle-invasive bladder cancer; IQR: interquartile range; SD: standard deviation.

Table 2. Treatment patterns and duration among individuals diagnosed with HR-NMIBC in Alberta, Canada from 2010–2020	
Variable	HR-NMIBC n=3874
Any TURBT, n (%)	3802 (98.1)
Time between TURBT procedures, mos, median [IQR]	6.4 [0.2, 24.7]
TURBT procedures, #, n (%)	
1	69 (1.8)
2	972 (25.6)
3	218 (5.7)
4	961 (25.3)
≥5	1582 (41.6)
First treatment type, n (%)	
BCG	1381 (35.6)
Gemcitabine	113 (2.9)
Mitomycin C	24 (0.6)
None	2356 (60.8)
Time to first treatment (BCG, gemcitabine, or mitomycin C), mos, median [IQR]*	3.7 [2.3, 7.5]
Any BCG treatment, n (%)	1389 (35.9)
Adequate BCG, n (%)	445 (32.0)
BCG induction duration, mos, median [IQR]	1.2 [0.2, 1.4]
Time to first BCG induction dose, mos, median [IQR]	3.6 [2.2, 6.6]
BCG induction doses, #, n (%)	
1	393 (28.3)
2	58 (4.2)
3	109 (7.8)
4	38 (2.7)
5	209 (15.0)
6	582 (41.9)
BCG maintenance duration, mos, median [IQR]	3.6 [0.9, 4.3]
Time to first BCG maintenance dose, mos, median [IQR]	8.5 [6.6, 13.0]

BCG maintenance doses, #, n (%)	
1	109 (13.3)
2	156 (19.0)
3	121 (14.8)
4	75 (9.2)
5	101 (12.3)
6	185 (22.6)
≥7	72 (8.8)
Any gemcitabine, n (%)	253 (6.5)
Gemcitabine duration, mos, median [IQR]	2.8 [1.4, 7.8]
Gemcitabine cycles, n (%)	
1	26 (10.3)
2	16 (6.3)
3	11 (4.3)
4	13 (5.1)
5–9	104 (41.1)
≥10	83 (32.8)
Any mitomycin C, n (%)	45 (1.2)
Mitomycin C duration, mos, median [IQR]	0.9 [0.2, 3.0]
≥2 Mitomycin C cycles, n (%)	25 (55.6)
Any cystectomy, n (%)	376 (9.7)
Radical	333 (8.6)
Partial	43 (1.1)
Time to cystectomy, mos, median [IQR]	13.9 [6.3, 25.6]

*Among those who received BCG, gemcitabine, or mitomycin C. BCG: bacillus Calmette-Guérin; HR-NMIBC: high-risk non-muscle-invasive bladder cancer; IQR: interquartile range; mos: months; SD: standard deviation; TURBT: transurethral resection of bladder tumor.