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

Geoffrey Gotto[1], Nimira S. Alimohamed[2], Girish S. Kulkarni[3], Peter C. Black[4], Wassim Kassouf[5], Andrea Kokorovic[6], Bernhard J. Eigl[7], Normand Blais[8], Aly-Khan A. Lalani[9], Winson Y. Cheung[10,11], Mariet Stephen[11,12], Brendan J.W. Osborne[13], Christopher J.D. Wallis[14]

[1]Departments of Surgery and Oncology, University of Calgary, Calgary, AB, Canada; [2]Division of Medical Oncology, Department of Medicine, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; [3]Divisions of Urology and Surgical Oncology, Department of Surgery, University Health Network, University of Toronto, Toronto, ON, Canada; [4]Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; [5]Division of Urology, Department of Surgery, McGill University Health Center, Montreal, QC, Canada; [6]Department of Urology, Dalhousie University, Halifax, NS, Canada; [7]BC Cancer, Vancouver, BC, Canada; [8]Division of Medical Oncology and Hematology, Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; [9]Department of Oncology, Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; [10]Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; [11]Oncology Outcomes, Calgary, AB, Canada; [12]Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; [13]Janssen Inc., Toronto, ON, Canada; [14]Urologic Oncology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

Cite as: Gotto G, Alimohamed NS, Kulkarni GS, et al. A population-based analysis of patterns of care in patients with high-risk non-muscle-invasive bladder cancer from Alberta, Canada. *Can Urol Assoc J* 2025;19(10):302-10. http://dx.doi.org/10.5489/cuaj.9110

Published online July 8, 2025

Appendix available at *cuaj.ca*

See related commentary on page 311

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.

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

INTRODUCTION

Bladder cancer (BCa) is the fifth most common type of cancer in Canada (8.1% of cancer diagnoses) and the 10th most common cancer worldwide.[1-3] It is a disease that disproportionally 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 heterogenous disease with a risk of disease recurrence or progression that varies based on T stage, tumor grade, tumor size, number of tumors, and prior disease recurrence.[1] Risk indices, which include the European Organization for Research and Treatment of Cancer (EORTC) scale, the European Association of Urology (EAU) risk score, and the Club Urologico Espanol de Tratemiento 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 tumor (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

KEY MESSAGES

- Real-world data from Alberta, Canada, show 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.
- Of those who received BCG, only 1/3 received a schedule considered adequate for prolonged disease-free survival.

chemotherapy or immunotherapy (BCG) are additionally recommended for intermediate-risk NMIBC.[1,9,10]

For HR-NMIBC, the 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 bladder cancer 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 (two tertiary, four regional, and 11 community centers) and 4.5 million provincial residents. The databases used 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 Supplementary Table 1 [available at *cuaj.ca*] for a full description of databases used). 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, AB, 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 tumors without nodal or distant metastasis (N0M0) 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 (Supplementary Table 2; available at *cuaj.ca*). Prespecified baseline characteristics of interest (sex, age, residence, T stage, tumor grade, and index year) were determined by the variables collected in the databases used. 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[24] the year prior to bladder cancer 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 six doses with a gap no longer than five 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 intervals,[1] 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 one-year, two-year, and five-year survival, along with the corresponding 95% confidence intervals (95% CI).

Data analysis

Baseline characteristics and treatment patterns are described using the mean (standard deviation [SD]) for continuous symmetrically distributed data, median (interquartile range [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-squared tests for categorical variables and ANOVA for continuous variables) 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, tumor 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 31, 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., one-year, two-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 identified, 3874 (56.7%) were categorized as HR-NMIBC (Table 1). The annual incidence of HR-NMIBC ranged from approximately 8–10 per 100 000 and was generally stable over the study period (Supplementary Table 3; available at *cuaj.ca*).[29] In the HR-NMIBC cohort, 82% were male, and the median age was 72 years. Tumor stage was T1 in 50%, Ta in 33%, and Tis in 17% of HR-NMIBC patients. Approximately half of HR-NMIBC patients had a Charlson comorbidity index (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 (Supplementary Table 4; available at *cuaj.ca*).

Treatment patterns

Patients underwent a median of four (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 (Table 2). 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 five or six doses. BCG-treated patients were predominantly male (83.9%), had T1 tumors (52%), and had a CCI of 0–1 (83.5%) (Supplementary Table 5; available at *cuaj.ca*). 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 use were younger age, fewer comorbidities, rural residence, and being diagnosed 2010–2014 (Figure 1 and Supplementary Table 6; available at *cuaj.ca*).

OS in this HR-NMIBC cohort was 10.3 years (95% CI 9.7–10.9) with one- and two-year survival rates of 94.7% and 88.6%, respectively (Supplementary Figure 1; available at *cuaj.ca*). 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).

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.

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 classifica-

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.

tion, 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 1/3 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 (odds ratio [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 five-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 that, if required, a restaging TURBT should be performed within six 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 U.S. (2.6 months).[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 4500 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 use among those diagnosed in 2015–2020 vs. 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

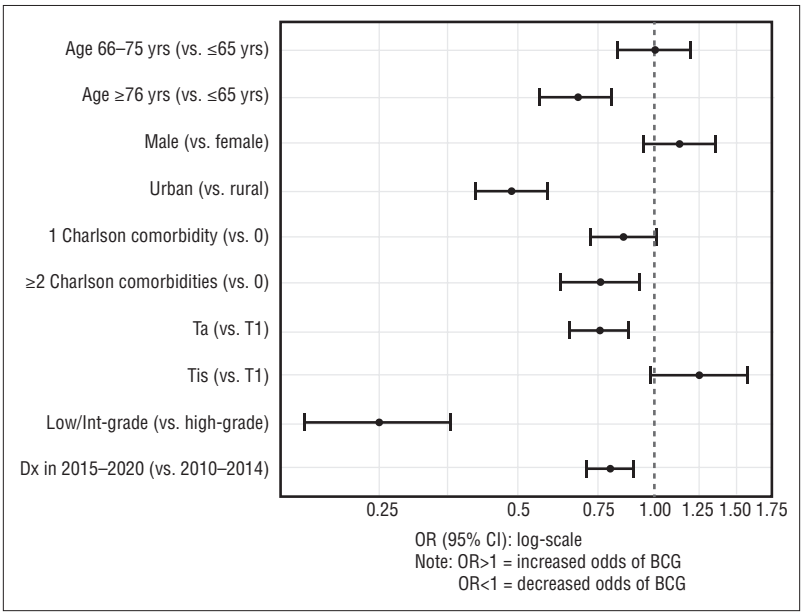
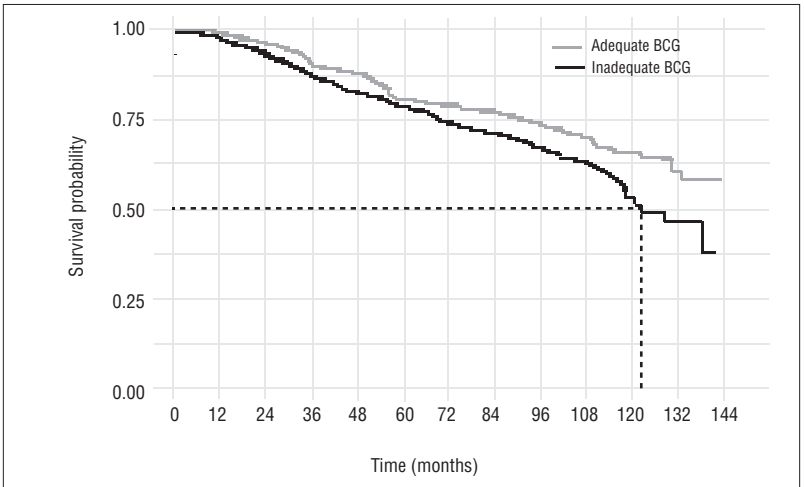


Figure 1. Predictors of bacillus Calmette-Guérin (BCG) initiation among individuals with high-risk non-muscle-invasive bladder cancer (HR-NMIBC) diagnosed in Alberta, Canada, from 2010–2020. Notes: Individuals missing information on disease grade were excluded from the analyses (n=345; 8.9% of total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



Number at risk (number of events)													
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, NR)	0.991 (0.982, 1.000)	0.966 (0.949, 0.983)	0.808 (0.770, 0.848)
Inadequate BCG	122.8 (117.8, NR)	0.982 (0.972, 0.993)	0.928 (0.908, 0.949)	0.792 (0.756, 0.829)

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. NR: not reached.

advocated prioritization of HR-NMIBC and/or dose and schedule reductions[1] that would still be captured as "adequate BCG" within the administrative databases as searched. In a U.S.-based assessment of the impact of supply shortage on BCG use, 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 use 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., tumor 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 use, 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 underuse 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), 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, provides 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., tumor multifocality, tumor 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), 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 use of adjuvant induction and maintenance BCG therapy following TURBT among patients with HR-NMIBC. Additional research is recommended to identify reasons for underuse so that strategies can be applied that support guideline-recommended therapy among HR-NMIBC patients in real-world settings.

COMPETING INTERESTS: Dr. Gotto has received honoraria from Astellas, AstraZeneca, Bayer, EMD Serono, Ferring, Janssen, McKesson, Merck, Pfizer, Sanofi, and Tolmar. Dr. Alimohamed has held advisory/consultancy roles

with AbbVie, AstraZeneca, Bayer, BMS, EMD Serono, Gilead, Janssen, Merck, Pfizer, and Seagen; and has received research funding (to institution) from AstraZeneca and EMD Serono. Dr. Kulkarni has served on advisory boards for AAA/Novartis, AbbVie, Astellas, BMS, EMD Serono, EnGene, Ferring, Johnson&Johnson, Knight Therapeutics, Merck, Pfizer, Theralase, and Verity; has consulted for Astra Zeneca, Johnson&Johnson , Photocure, TerSera, and Verity; and has participated in clinical trials supported by BMS, CG Oncology, EnGene, Ferring, Johnson&Johnson, Merck, Pfizer, Seagen, Theralase, and Verity. Dr. Black has been an advisory board member or equivalent for AbbVie, AstraZeneca, Astellas, Bayer, BMS, CG Oncology, Combat, EMD Serono, Ferring, Janssen, Merck, Nonagen, Nanobot, NanOlogy, Pfizer, Photocure, Prokarium, Sumitomo, TerSera, Tolmar, and Verity; a speaker's bureau member for Bayer, Janssen, Pfizer, and TerSera; has participated in clinical trials supported by CG Oncology, Genentech, Janssen, Pacific Edge, Pfizer, and Therelase; and holds a shared patent with Veracyte. Dr. Kassouf has held consultant or advisory roles with Astellas, AstraZeneca, Bayer, BMS, EMD Serono, Ferring, Janssen, Merck, Pfizer, Photocure, Roche, Seagen, and Sesen Bio; and has participated in clinical trials supported by BMS, CG Oncology, Janssen, Pfizer, Roche, and Theralase. Dr. Kokorovic has been a consultant for Astellas, Bayer, Ferring, Janssen, Knight Therapeutics, Pfizer, and Tolmar; and has received honoraria from Janssen. Dr. Eigl has received honoraria from EMD Serono, Gilead, Janssen, Pfizer, and Seagen; has received research funding from Pfizer and travel expenses from EMD Serono. Dr. Blais does not report any competing personal or financial interests related to this work. Dr. Lalani has received grants/research support from BMS (Inst), BioCanRx (Inst), EMD Serrono (Inst), Ipsen (Inst), Novartis (Inst), and Roche (Inst); and honoraria from Astellas, AstraZeneca, Bayer, BMS, Eisai, EMD Serono, Ipsen, Janssen, McKesson, Merck, Novartis, Pfizer, Roche, and TerSera. Dr. Cheung has received grants/research support from Janssen. Dr. Stephen has received grants/research support from Janssen. Mr. Osborne is employed by J&J Innovative Medicine. Dr. Wallis has received consulting fees from Janssen Oncology, Nanostics Inc, Precision Point Specialty LLC, SESEN Bio; honoraria/travel from AbbVie, Astellas, Astra Zeneca, Bayer, EMD Serono, Haymarket Media, Healing and Cancer Foundation, Knight Therapeutics, Merck, Science & Medicine Canada, TerSera, and Tolmar; and research funding from Knight Therapeutics and Tolmar.

FUNDING: Funding for the study, medical writing, and project management was provided by Janssen Canada Inc.

ACKNOWLEDGEMENTS: Medical writing and project management services were provided by Stevie Kenyon of Placencia Holdings Ltd. Database linkage, data cleaning, statistical analyses, and generation of study results were conducted by the Oncology Outcomes (O2) research group.

REFERENCES

1. Bhindi B, Kool R, Kulkarni GS, et al. Canadian Urological Association guideline on the management of non-muscle-invasive bladder cancer: Full-text. *Can Urol Assoc J* 2021;15:E424-60.
2. Brenner DR, Poirier A, Woods RR, et al. Projected estimates of cancer in Canada in 2022. *CMAJ* 2022;194:E601-7. https://doi.org/10.1503/cmaj.212097
3. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209-49. https://doi.org/10.3322/caac.21660
4. Miyake M, Nishimura N, Fujii T, et al. Recent advancements in the diagnosis and treatment of non-muscle invasive bladder cancer: Evidence update of surgical concept, risk stratification, and BCG-treated disease. *Int J Urol* 2023;30:944-57. https://doi.org/10.1111/iju.15263
5. Isharwal S, Konety B. Non-muscle invasive bladder cancer risk stratification. *Indian J Urol* 2015;31:289-96. https://doi.org/10.4103/0970-1591.166445
6. Soukup V, Čapoun O, Cohen D, et al. Risk stratification tools and prognostic models in non-muscle-invasive bladder cancer: A critical assessment from the European Association of Urology non-muscle-invasive bladder cancer guidelines panel. *Eur Urol Focus* 2020;6:479-89. https://doi.org/10.1016/j.euf.2018.11.005
7. Lenis AT, Lec PM, Chamie K, et al. Bladder cancer: A review. *JAMA* 2020;324:1980-91. https://doi.org/10.1001/jama.2020.17598
8. Boormans JL, Zwarthoff EC. Limited funds for bladder cancer research and what can we do about it. *Bladder Cancer* 2016;2:49-51. https://doi.org/10.3233/BLC-150042
9. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2013. *Eur Urol* 2013;64:639-53. https://doi.org/10.1016/j.eururo.2013.06.003
10. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. *J Urol* 2016;196:1021-9. https://doi.org/10.1016/j.juro.2016.06.049
11. Kulkarni GS, Black PC, Sridhar SS, et al. Canadian Urological Association guideline: Muscle-invasive bladder cancer. *Can Urol Assoc J* 2019;13:230-8. https://doi.org/10.5489/cuaj.5902
12. Global Burden of Disease Health Financing Collaborator Network. Evolution and patterns of global health financing 1995–2014: Development assistance for health, and government, prepaid private, and out-of-pocket health spending in 184 countries. *Lancet* 2017;389:1981-2004.
13. Grabe-Heyne K, Henne C, Mariappan P, et al. Intermediate and high-risk non-muscle-invasive bladder cancer: An overview of epidemiology, burden, and unmet needs. *Front Oncol* 2023;13:1170124. https://doi.org/10.3389/fonc.2023.1170124
14. Musat MG, Kwon CS, Masters E, et al. Treatment outcomes of high-risk non-muscle invasive bladder cancer (HR-NMIBC) in real-world evidence (RWE) studies: Systematic literature review (SLR). *Clin Outcomes Res* 2022;14:35-48. https://doi.org/10.2147/CEOR.S341896
15. American Joint Committee on Cancer. *AJCC cancer staging manual*. 6th ed. New York, NY: Springer; 2002. https://doi.org/10.1007/978-1-4757-3656-4
16. American Joint Committee on Cancer. *AJCC cancer staging manual*. 7th ed. New York, NY: Springer; 2010.
17. American Joint Committee on Cancer. *AJCC cancer staging manual*. 8th ed. Chicago, IL: Springer; 2017.
18. Epstein JI, Amin MB, Reuter VR, et al. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. *Am J Surg Pathol* 1998;22:1435-48. https://doi.org/10.1097/00000478-199812000-00001
19. Eble J, Sauter G, Epstein J, et al. *Pathology and genetics of tumours of the urinary system and male genital organs*. WHO classification of tumours. 3rd ed. Lyon, France: IARC; 2004. Available from: Https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Pathology-And-Genetics-Of-Tumours-Of-The-Urinary-System-And-Male-Genital-Organs-2004
20. Humphrey PA, Moch H, Cubilla AL, et al. The 2016 WHO classification of tumours of the urinary system and male genital organs: Part B—prostate and bladder tumours. *Eur Urol* 2016;70:106-19. https://doi.org/10.1016/j.eururo.2016.02.028
21. Lin W, Pan X, Zhang C, et al. Impact of age at diagnosis of bladder cancer on survival: A Surveillance, Epidemiology, and End Results-based study 2004–2015. *Cancer Control* 2023;30:10732748231152322. https://doi.org/10.1177/10732748231152322
22. Chun B, He M, Jones C, et al. Variation in statewide intravesical treatment rates for non-muscle invasive bladder cancer during the Bacillus Calmette-Guérin drug shortage. *Urology* 2023;177:74-80. https://doi.org/10.1016/j.urology.2023.02.044
23. Shariat SF, Sfakianos JP, Droller MJ, et al. The effect of age and gender on bladder cancer: A critical review of the literature. *BJU Int* 2010;105:300-8. https://doi.org/10.1111/j.1464-410X.2009.09076.x
24. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-9. https://doi.org/10.1097/01.mlr.0000182534.19832.83
25. Shiff NJ, Lix LM, Joseph L, et al. The prevalence of systemic autoimmune rheumatic diseases in Canadian pediatric populations: Administrative database estimates. *Rheumatol Int* 2015;35:569-73. https://doi.org/10.1007/s00296-014-3136-6
26. Garies S, Youngson E, Soos B, et al. Primary care EMR and administrative data linkage in Alberta, Canada: Describing the suitability for hypertension surveillance. *BMJ Health Care Inform* 2020;27:e100161. https://doi.org/10.1136/bmjhci-2020-100161
27. Murphy GK, McAlister FA, Eurich DT. Cardiovascular medication utilization and adherence among heart failure patients in rural and urban areas: A retrospective cohort study. *Can J Cardiol* 2015;31:341-7. https://doi.org/10.1016/j.cjca.2014.11.024
28. Center for Drug Evaluation and Research. Bacillus Calmette-Guérin-unresponsive nonmuscle invasive bladder cancer: Developing drugs and biologics for treatment. *FDA Guidance for Industry* 2018. Available from: Https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bacillus-calmette-guerin-unresponsive-nonmuscle-invasive-bladder-cancer-developing-drugs-and
29. Alberta population estimates: Data tables. *Open Government*. Available from: Https://open.alberta.ca/opendata/alberta-population-estimates-data-tables (accessed 16 Apr 2024).
30. Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: Epidemiology, staging and grading, and diagnosis. *Urology* 2005;66:4-34. https://doi.org/10.1016/j.urology.2005.07.062
31. Rieken M, Shariat SF, Kluth L, et al. Comparison of the EORTC tables and the EAU categories for risk stratification of patients with nonmuscle-invasive bladder cancer. *Urol Oncol* 2018;36:8.e17-24. https://doi.org/10.1016/j.urolonc.2017.08.027

32. Sylvester RJ, Rodríguez O, Hernández V, et al. European Association of Urology (EAU) prognostic factor risk groups for non-muscle-invasive bladder cancer (NMIBC) incorporating the WHO 2004/2016 and WHO 1973 classification systems for grade: An update from the EAU NMIBC guidelines panel. *Eur Urol* 2021;79:480-8. https://doi.org/10.1016/j.eururo.2020.12.033
33. Mangrud OM, Waalen R, Gudlaugsson E, et al. Reproducibility and prognostic value of WHO1973 and WHO2004 grading systems in TaT1 urothelial carcinoma of the urinary bladder. *PLoS One* 2014;9:e83192. https://doi.org/10.1371/journal.pone.0083192
34. Pan C-C, Chang Y-H, Chen K-K, et al. Prognostic significance of the 2004 WHO/ISUP classification for prediction of recurrence, progression, and cancer-specific mortality of non-muscle-invasive urothelial tumors of the urinary bladder: A clinicopathologic study of 1,515 cases. *Am J Clin Pathol* 2010;133:788-95. https://doi.org/10.1309/AJCP12MRVVHTCKEJ
35. Krajewski W, Rodríguez Faba O, Breda A, et al. Analysis of age influence on oncological results and toxicity of BCG immunotherapy in non-muscle invasive bladder cancer. *World J Urol* 2020;38:3177-82. https://doi.org/10.1007/s00345-020-03130-1
36. Inoue T, Miyake M, Nishimura N, et al. Association of increased age with decreased response to intravesical instillation of Bacille Calmette-Guérin in patients with high-risk non-muscle invasive bladder cancer: Retrospective multi-institute results from the Japanese Urological Oncology Research Group JUOG-UC-1901-BCG. *Urology* 2022;167:158-64. https://doi.org/10.1016/j.urology.2022.05.034
37. Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance Bacillus Calmette-Guérin immunotherapy for recurrent Ta, T1 and carcinoma in situ transitional cell carcinoma of the bladder: A randomized Southwest Oncology Group study. *J Urol* 2000;163:1124-9. https://doi.org/10.1016/S0022-5347(05)67707-5
38. Petrilla AA, Silverstein AR, Eccleston A, et al. Time to event following Bacillus Calmette-Guérin therapy initiation in Medicare beneficiaries with intermediate- to high-risk non-muscle invasive bladder cancer, 2010–2019. *J Clin Oncol* 2023;41:473. https://doi.org/10.1200/JCO.2023.41.6_suppl.473
39. Krajewski W, Moschini M, Chorbińska J, et al. Delaying BCG immunotherapy onset after transurethral resection of non-muscle-invasive bladder cancer is associated with adverse survival outcomes. *World J Urol* 2021;39:2545-52. https://doi.org/10.1007/s00345-020-03522-3
40. Mori K, Miura N, Babjuk M, et al. Low compliance to guidelines in nonmuscle-invasive bladder carcinoma: A systematic review. *Urol Oncol* 2020;38:774-82. https://doi.org/10.1016/j.urolonc.2020.06.013
41. Strope SA, Ye Z, Hollingsworth JM, et al. Patterns of care for early stage bladder cancer. *Cancer* 2010;116:2604-11. https://doi.org/10.1002/cncr.25007
42. Lamm DL, van der Meijden PM, Morales A, et al. Incidence and treatment of complications of bacillus Calmette-Guérin intravesical therapy in superficial bladder cancer. *J Urol* 1992;147:596-600. https://doi.org/10.1016/S0022-5347(17)37316-0
43. Herr HW, Dalbagni G. Intravesical bacille Calmette-Guérin (BCG) in immunologically compromised patients with bladder cancer. *BJU Int* 2013;111:984-7. https://doi.org/10.1111/j.1464-410X.2012.11778.x
44. Regulatory decision summary for Verity-BCG. Available from: Https://dhpp.hpfb-dgpsa.ca/review-documents/resource/RDS00744 (accessed 24 Jul 2024).
45. Babjuk M, Böhle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2016. *Eur Urol* 2017;71:447-61. https://doi.org/10.1016/j.eururo.2016.05.041
46. Bree KK, Hensley PJ, Lobo N, et al. All high-grade Ta tumors should be classified as high risk: Bacillus Calmette-Guérin response in high-grade Ta tumors. *J Urol* 2022;208:284-91. https://doi.org/10.1097/JU.0000000000002678
47. Chen Z, Chen X, Li D, et al. Comparison of treatments for preventing lower urinary tract symptoms after BCG immunotherapy of bladder tumors: A systematic review and network meta-analysis. *BMC Urol* 2025;25:19. https://doi.org/10.1186/s12894-024-01675-6
48. van Rhijn BWG, Hentschel AE, Bründl J, et al. Prognostic value of the WHO1973 and WHO2004/2016 classification systems for grade in primary Ta/T1 non-muscle-invasive bladder cancer: A multicenter European Association of Urology non-muscle-invasive bladder cancer guidelines panel study. *Eur Urol Oncol* 2021;4:182-91. https://doi.org/10.1016/j.euo.2020.12.002
49. Kamat AM, Sylvester RJ, Böhle A, et al. Definitions, end points, and clinical trial designs for non-muscle-invasive bladder cancer: Recommendations from the International Bladder Cancer Group. *J Clin Oncol* 2016;34:1935-44. https://doi.org/10.1200/JCO.2015.64.4070

CORRESPONDENCE: Dr. Geoffrey Grotto, Southern Alberta Institute of Urology, Calgary, AB Canada; drgotto@gmail.com