

A population-based analysis of patterns of care in patients with de novo muscle-invasive bladder cancer from Alberta, Canada

Nimira S. Alimohamed¹, Geoffrey Gotto², Girish S. Kulkarni³, Peter C. Black⁴, Wassim Kassouf⁵, Srikala S. Sridhar⁶, Andrea Kokorovic⁷, Bernhard J. Eigl⁸, Normand Blais⁹, Aly-Khan A. Lalani¹⁰, Winson Y. Cheung^{11,12}, Mariet Stephen^{12,13}, Brendan J.W. Osborne¹⁴, Christopher J.D. Wallis¹⁵

¹Division of Medical Oncology, Arthur J.E. Child Comprehensive Cancer Centre, University of Calgary, Calgary, AB, Canada; ²Departments of Surgery and Oncology, University of Calgary, Calgary, AB, Canada; ³Divisions of Urology and Surgical Oncology, Department of Surgery, University Health Network, University of Toronto, Toronto, ON, Canada; ⁴Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; ⁵Department of Surgery (Urology), McGill University Health Center, Montreal, QC, Canada; ⁶Division of Medical Oncology, University of Toronto, Princess Margaret Cancer Centre, Toronto, ON, Canada; ⁷Department of Urology, Dalhousie University, Halifax, NS, Canada; ⁸BC Cancer, Vancouver, BC, Canada; ⁹Division of Medical Oncology and Hematology, Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; ¹⁰Department of Oncology, Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; ¹¹Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; ¹²Oncology Outcomes, Calgary, AB, Canada; ¹³Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; ¹⁴Johnson & Johnson Innovative Medicine, Toronto, ON, Canada; ¹⁵Urologic Oncology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

Cite as: Alimohamed NS, Gotto G, Kulkarni GS, et al. A population-based analysis of patterns of care in patients with de novo muscle-invasive bladder cancer from Alberta, Canada. *Can Urol Assoc J* 2025;19(12):393-402. <http://dx.doi.org/10.5489/cuaj.9111>

Published online August 28, 2025

Appendix available at cuaj.ca

ABSTRACT

INTRODUCTION: Approximately 25% of patients diagnosed with bladder cancer have muscle-invasive disease (MIBC). While real-world data have highlighted opportunities to improve curative-intent treatment rates, comprehensive population-level data in Canada are limited. This study aimed to assess patterns of care and outcomes in a real-world cohort of MIBC in Canada.

METHODS: This retrospective, observational study describes baseline characteristics, treatment patterns, and overall survival (OS) of individuals with de novo MIBC diagnosed between 2010 and 2020 in Alberta, Canada. Data from adult patients with MIBC (T2-T4, N0/I, M0) were obtained from administrative databases and analyzed using basic statistics, multivariate regression analyses, and the Kaplan-Meier method.

RESULTS: We identified 1292 patients with de novo MIBC. Of these, 76% were male with a median age of 73 years, 68% had cT2, and 76% had cN0 disease; approximately half had a Charlson comorbidity index (CCI) ≥ 1 . Overall, 25% did not receive active treatment, while 58% received curative-intent treatment (49% underwent radical cystectomy [RC] and 9% received chemoradiotherapy), and 17% received some form of non-curative-intent treatment. Of those who underwent RC, 45% received neoadjuvant chemotherapy (NAC). Median overall survival (mOS) in the entire cohort was 2.1 years (95% confidence interval 1.9–2.4). Key predictors of inferior survival were age ≥ 76 years, CCI score of ≥ 1 , T4 tumor stage, or not receiving NAC.

CONCLUSIONS: This real-world analysis highlights opportunities to improve outcomes for patients with MIBC. Increasing access to curative-intent treatments, particularly in the elderly and those with comorbidities, is likely to enhance patient care and outcomes.

INTRODUCTION

Bladder cancer (BCa) accounts for 8% of all cancer diagnoses in Canada, with around 9000 incident cases per year.¹⁻³ The male:female incidence is 3:1, and the average age at diagnosis is 73 years.¹ At diagnosis, 70% are non-muscle-invasive (NMIBC), 25% are muscle-invasive (MIBC), and 5% are already metastatic. Histologically, 90% are urothelial pathology — pure or mixed.³ MIBC is characterized by aggressive tumor biology, leading to a 40–50% five-year mortality rate, despite intensive treatment.³

Guideline-recommended locoregional management of T2-4aN1M0 MIBC involves cisplatin-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) or trimodal therapy (TMT; transurethral resection of bladder tumor [TURBT] + chemoradiotherapy) in eligible patients.³ Cystectomy should occur 4–6 weeks, and at most 10 weeks, after completion of NAC to optimize survival.³ High-risk patients, those with residual T2+ or node-positive disease after NAC and RC, or those ineligible for or refusing cisplatin-based NAC, can be offered adjuvant checkpoint inhibition with nivolumab for one year.⁴ Patients with pT2-4 and/or pN1-3 disease after cystectomy who are eligible for and did

KEY MESSAGES

- Curative intent treatment (radical cystectomy or TURBT and chemoradiotherapy) was received by 58% of patients in Alberta diagnosed with de novo MIBC from 2010–2020, whereas 25% of patients went untreated.
- The median OS of the entire MIBC cohort was 2.1 years, reinforcing the urgency to improve on curative-intent treatment options for patients with MIBC.
- In this cohort, patients undergoing cystectomy + chemotherapy had a median OS of 6.9 years. Patients treated with cystectomy alone had a median OS of 3.5 years.
- This study provides valuable insights into treatment patterns and outcomes in real-world patients with de novo MIBC, helping to guide future research and drive advancements in patient care.

not receive NAC should be offered adjuvant cisplatin-based combination chemotherapy.³ For patients who are ineligible for RC or prefer bladder preservation, TMT (\pm NAC) is the recommended alternative, with outcomes appearing similar to those undergoing RC based on a propensity analysis.⁵ Unfortunately, despite curative-intent treatment, 50% of patients will recur or develop metastatic disease.^{5,6}

Despite the high risk of disease progression and poor prognosis associated with untreated MIBC, real-world data from various jurisdictions indicate that curative-intent therapy, with RC (with or without perioperative chemotherapy) or chemoradiotherapy, is administered at suboptimal rates, ranging from 37–78%.^{7–12} Given the rapidly evolving treatment landscape, these disparities highlight significant barriers within current practice patterns that may adversely impact outcomes for patients with potentially curable MIBC; however, population-based studies assessing contemporary care patterns for MIBC remain limited, particularly in Canada.¹³

This study aimed to evaluate baseline characteristics, treatment patterns, and overall survival (OS) in a real-world cohort of individuals diagnosed with de novo MIBC over a 10-year period in Alberta, Canada.

METHODS

Study design and setting

We conducted a retrospective, observational cohort study of individuals diagnosed with de novo MIBC between 2010 and 2020. The primary objective of the study was to characterize patterns of care related to MIBC in a Canadian real-world setting.

Data related to cancer diagnosis, patient and disease characteristics, treatment, and outcomes were retrieved from numerous population-level administrative databases in Alberta, Canada, covering 17 cancer centers (two tertiary, four regional, and 11 community centers) and 4.5 million provincial residents. The Alberta Cancer Registry (ACR), Pharmaceutical Information Network (PIN), health practitioner claims, Discharge Abstract Database (DAD), ARIA (electronic medical records), and National Ambulatory Care Reporting System (NACRS) databases were used (Supplementary Table 1, available at cuaj.ca, for a full description of the databases used). Unique lifetime identifier numbers were used to link coded data (100% linkage rate) between the databases. Patients were followed from diagnosis until last known contact with the healthcare system, end of 2021, or death, whichever occurred first.

The Oncology Outcomes (O2) research group (Calgary, Alberta, Canada) conducted database linkage, data cleaning, statistical analyses, and generation of study results. Approval for the study was granted 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 de novo MIBC (T2–T4, N0/1, M0) at TURBT, defined using the most recent edition of the American Joint Committee on Cancer (AJCC) TNM staging guidelines available at the time of diagnosis.^{14–16} Pathologic restaging information was not available. Stage and grade information were extracted from databases using a hierarchical approach that included pathology, imaging, and subsequent clinical records. The 1973 World Health Organization (WHO) definition of disease grade was used for individuals diagnosed before 2018, as only cellular differentiation was collected in the registry during that time.¹⁷ The 2004/2016 WHO definition was used for individuals diagnosed since 2018.¹⁸ Patients with disease characteristics not meeting these criteria were excluded.

Variables/data collection

Procedural codes for the variables of interest were compiled by the study investigators. Prespecified baseline characteristics of interest (sex, age, residence, comorbidity index, T stage, N stage, tumor grade, and index year) were determined by the variables collected in the databases used. The index year was collected as a continuous variable. Age was collected as a continuous variable and categorized as ≤ 65 , 66–75, and ≥ 76 years. Charlson comorbidities were identified by validated claims-based algorithms, as defined in Quan et al,¹⁹ in the year prior to BCa diagnosis. Rural vs. urban residence was classified based on standard methodology.^{20–22}

Treatment-related variables of interest included type (cystectomy, chemotherapy, and radiation therapy) and duration. The number of patients undergoing partial or radical cystectomy, and/or receiving chemotherapy and/or radiation was observed for the overall population and by baseline characteristic. TURBT operations were not included. NAC was any chemotherapy on or after the date of diagnosis but prior to the date of the first cystectomy procedure. Adjuvant chemotherapy (AC) was any chemotherapy on or after but within 180 days of the date of the first cystectomy procedure.

Receipt of radiation therapy (RT) and systemic therapy within two years of the index date were also examined among individuals who did not undergo cystectomy. Radiation dose was not captured in the studied databases. Radiation in combination with chemotherapy was assumed to be bladder-preserving therapy (with TURBT). OS was examined for the overall population, as well as by treatment modality.

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 among de novo MIBC and stratified by: 1) surgical management (cystectomy vs. none), and 2) treatment modality (cystectomy \pm chemotherapy \pm RT), using standardized mean differences (SMDs), where values <0.1 reflect no meaningful imbalance, and p-values (i.e., Chi-squares tests for categorical variables and ANOVA for continuous variables) less than 0.05 were considered to be statistically significant. The number and proportion of individuals missing data for each covariate are summarized but not included in analyses.

Table 1. Baseline characteristics of individuals diagnosed with de novo MIBC in Alberta, Canada, from 2010–2020

Variable	MIBC N=1292
Male, n (%)	977 (75.6)
Urban residence, n (%)	1053 (81.5)
Age at Dx, years, mean (SD)	72.7 (11.5)
Age at Dx, years, median [IQR]	73.0 [64.0, 81.0]
Age at Dx, categories, n (%)	
≤ 65	342 (26.5)
66–75	373 (28.9)
≥ 76	577 (44.7)
Charlson comorbidity index score, n (%)	
0	648 (50.2)
1	374 (28.9)
≥ 2	270 (20.9)
cT stage, n (%)	
T2	881 (68.2)
T3	167 (12.9)
T4	244 (18.9)
cN stage, n (%)	
N0	982 (76.0)
N1–3	240 (18.6)
Missing	70 (5.4)
Tumor grade, n (%)	
High	1185 (91.7)
Low/Intermediate	32 (2.5)
Missing	75 (5.8)
Year of diagnosis, n (%)	
2010–2014	576 (44.6)
2015–2020	716 (55.4)

Dx: diagnosis; IQR: interquartile range; MIBC: muscle-invasive bladder cancer; SD: standard deviation.

OS was defined as the time between diagnosis (index date) or treatment initiation to death from any cause. Kaplan-Meier curves were estimated to calculate the median survival, along with the corresponding 95% confidence intervals (95% CI). For the estimation of OS, individuals were censored at the time of last known contact with the healthcare system or December 31,

Table 2. Treatment type and duration among individuals diagnosed with de novo MIBC in Alberta, Canada, from 2010–2020

Variable, n (%)	De novo MIBC N=1292
Radical cystectomy (RC) ^a	628 (48.6)
RC + chemotherapy	326 (25.2)
RC + neoadjuvant chemotherapy (NAC) ^b	281 (44.7)
Cisplatin-based	272-280 (96.8–99.6)
Other	<10 (0.4–3.2) ^d
Duration of NAC, mos, median [IQR] ^c	2.2 [1.5, 2.5]
RC + adjuvant chemotherapy (AC) ^f	75 (11.9)
Cisplatin-based	52 (69.3)
Other	23 (30.7)
Duration of AC, mos, median [IQR]	2.1 [0.9, 4.2]
RC with no chemotherapy	302 (23.4)
Partial cystectomy	23 (1.8)
Partial cystectomy + chemotherapy ^b	14-22 (60.9–95.7)
Partial cystectomy with no chemotherapy	<10 ^d (4.3–39.1)
Radiation therapy	272 (21.1)
Chemoradiation	116 (9.0)
Radiation therapy (RT) only	156 (12.1)

^aA very small number of individuals (n<10) underwent both partial and radical cystectomy. These individuals were excluded from the estimated number of partial cystectomy procedures and classified as radical cystectomy to prevent suppression of dependent data (i.e., partial cystectomy numbers). ^bNeoadjuvant therapy was defined as therapy received between the index date and date of cystectomy. ^cAdjuvant therapy was defined as therapy received within 9 months (273 days) of the date of cystectomy. ^dIn accordance with data privacy legislation, cells with fewer than 10 individuals were suppressed and labelled “n<10”. Any dependencies that would allow for the derivation of cell counts <10 are labelled as “not reportable”. ^eReceived within 2 years of the index date, examined among individuals who did not undergo cystectomy (n=641) and includes chemoradiation therapy. AC: adjuvant chemotherapy; FU: fluorouracil; IQR: interquartile range; MIBC: muscle-invasive bladder cancer; NAC: neoadjuvant chemotherapy; N/R: not reportable; RC: radical cystectomy; RT: radiation therapy; w/o: without.

2021, whichever occurred first, and was accounted for using the Kaplan-Meier estimator. To quantify the magnitude of association between the baseline characteristics and OS, Cox regression analysis was used. All baseline variables were examined and adjusted in the multivariable analyses.

Analyses were conducted using R version 4.2.2. All statistical tests were two-sided, with statistical signifi-

Table 2 (cont'd). Treatment type and duration among individuals diagnosed with de novo MIBC in Alberta, Canada, from 2010–2020

Variable, n (%)	De novo MIBC N=1292
Chemotherapy only	46 (3.6)
Chemotherapy regimen ^a	162 (25.3)
Platinum + gemcitabine	61 (37.7)
Platinum	31 (19.1)
Platinum + etoposide	N/R ^d
Platinum + gemcitabine + paclitaxel	N/R ^d
Platinum + gemcitabine + pembrolizumab	<10 ^d
Other platinum combo	16 (9.9)
5-FU/capecitabine	11 (6.8)
Other	15 (9.3)
Duration of chemotherapy, mos, median [IQR]	2.3 [0.9, 5.3]
No treatment	323 (25.0)

^aA very small number of individuals (n<10) underwent both partial and radical cystectomy. These individuals were excluded from the estimated number of partial cystectomy procedures and classified as radical cystectomy to prevent suppression of dependent data (i.e., partial cystectomy numbers). ^bNeoadjuvant therapy was defined as therapy received between the index date and date of cystectomy. ^cAdjuvant therapy was defined as therapy received within 9 months (273 days) of the date of cystectomy. ^dIn accordance with data privacy legislation, cells with fewer than 10 individuals were suppressed and labelled “n<10”. Any dependencies that would allow for the derivation of cell counts <10 are labelled as “not reportable”. ^eReceived within 2 years of the index date, examined among individuals who did not undergo cystectomy (n=641) and includes chemoradiation therapy. AC: adjuvant chemotherapy; FU: fluorouracil; IQR: interquartile range; MIBC: muscle-invasive bladder cancer; NAC: neoadjuvant chemotherapy; N/R: not reportable; RC: radical cystectomy; RT: radiation therapy; w/o: without.

cance defined at the 0.05 alpha level. In accordance with data privacy legislation, cells with fewer than 10 individuals were suppressed and labelled “<10.” Any dependencies that would allow for the derivation of cell counts <10 are labelled as “not reportable.”

RESULTS

Baseline characteristics

This study identified 1292 patients diagnosed with de novo MIBC between 2010 and 2020. The annual incidence was approximately 2.5–3.0 per 100 000, and was generally stable over the study period (Supplementary Table 2; available at cuaj.ca).²³ Baseline characteristics are outlined in Table 1. Overall, the majority of patients

were male (77%), with a median age of 73 years. Most had a tumor stage of T2 (68%) and N0 (76%), and 50% had a Charlson comorbidity index (CCI) of ≥ 1 .

Treatment patterns

In this real-world analysis of patients diagnosed with de novo MIBC, 58% received curative-intent local treatment, including RC in 628 patients and TMT in 116 patients. Among those who underwent RC, 45% (n=281) received NAC (predominantly cisplatin-based, $\geq 97\%$) and 12% (n=75) received AC. Partial cystectomy was performed in 2% of patients (n=23). Among the 641 (50%) patients who did not undergo cystectomy, 116 (18%) received TMT, 156 (24%) received RT alone, and 46 (7%) received systemic chemotherapy alone. A total of 323 patients (25%) did not receive any active treatment (Table 2). Due to data limitations in this analysis, it was not possible to determine which patients receiving TMT also received NAC.

Baseline characteristics stratified by treatment type (Supplementary Figures 1, 2, Supplementary Tables 3A, 3B, 4A, 4B; available at cuaj.ca) revealed that patients who received no treatment or RT only were predominantly aged ≥ 76 years (73% and 86%, respectively) and had a CCI score ≥ 1 (67% and 64%, respectively). In contrast, those who underwent cystectomy or received perioperative chemotherapy were ≤ 75 years (77% and 86%, respectively) with a CCI of 0 (61% and 67%, respectively). Cystectomy was more frequently performed in patients with T3 or T4 tumors compared to T2 tumors (83% and 60% vs. 42%, respectively) and in those with lymph node-positive disease (74% for N1-3 vs. 42% for N0). Additionally, 11% of patients with T2 MIBC and 10% of those with N0 disease received chemoradiotherapy without cystectomy. Rates of cystectomy were similar between males and females, as well as between individuals residing in urban and rural areas. Year of diagnosis did not significantly impact treatment trends, except for an observed increase in the overall rate of any treatment over time, from 72% among those diagnosed from 2010–2014 to 78% among those diagnosed from 2018–2020 (Supplementary Figure 2; available at cuaj.ca).

Median OS in this de novo MIBC cohort was 2.1 (1.9–2.4) years (Figure 1). The median OS varied significantly by treatment type ($p < 0.01$); mOS was 6.9 years (4.7–not reached) in those who received any perioperative chemotherapy and cystectomy, 3.5 years (2.4–5.1) in those who underwent cystectomy alone, 2.1 years (1.7–3.2) in those who received TMT, 0.7

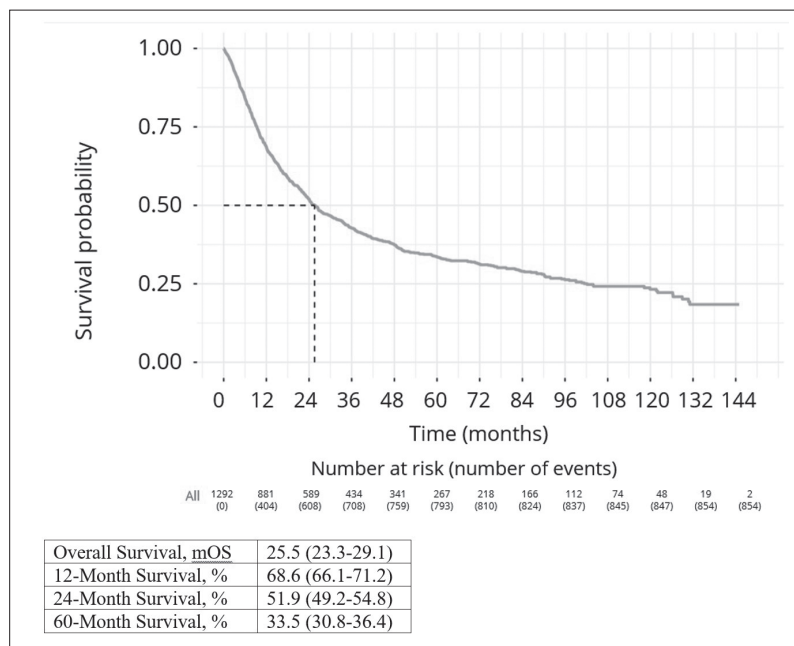


Figure 1. Overall survival from date of diagnosis among individuals with de novo muscle-invasive bladder cancer (MIBC) diagnosed from 2010–2020 in Alberta, Canada. OS: overall survival.

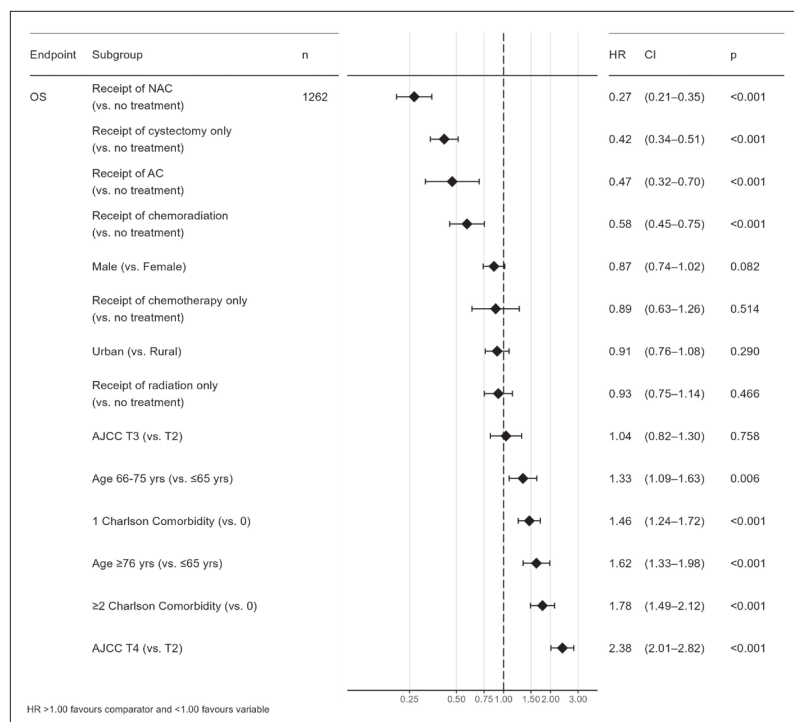


Figure 2. Cox multivariate regression analysis showing predictors of overall survival among individuals with de novo muscle-invasive bladder cancer (MIBC) diagnosed in Alberta, Canada, from 2010–2020. AC: adjuvant chemotherapy; CI: confidence interval; HR: hazard ratio; NAC: neoadjuvant chemotherapy; OS: overall survival.

years (0.6–0.8) among those who were untreated, and 0.6 years (0.4–0.8) for those who received RT alone (Supplementary Figure 3; available at cuaj.ca).

Table 3. Summary of treatments received in contemporary population-based MIBC cohorts

Study country; data source; year	Number of patients; key inclusion; characteristics	Treatments				
		RC	NAC + RC	Chemo + RT	Chemo or RT alone	No Tx
(Present study) Canada; Alberta provincial databases; 2010–2020	N=1292 T2–4N0–3M0	23% RC alone (n=302) 49% any RC (n=628)	22% (n=281)	9% (n=116)	16% (n=202)	25% (n=323)
John et al (2021)⁹ UK; 2016	N=2519 T2–4N0M0; 75% CCI=0	15% RC alone (n=368) 23% any RC (n=588)	9% (n=220)	14% (n=352)	N/A	26% (n=650)
Flegar et al (2022)¹⁰ Germany; 2006–2017	N=24534, N=7292 (2017) BCa stage ≥T2	78% any RC in 2017	16% *chemo+RC ± RT	N/A	N/A	6% in 2017
Fletcher et al (2020)¹¹ USA; 2004–2013	N=48651 T≥2N0M0; 79% T2	25% RC first (not incl NAC) (n=12348)	9% (n=4222); 15% in 2014	5% (n=2554)	18% (n=8533)	39% (n=19016); 34% in 2014
Richters et al (2022)¹² Netherlands; 2018–2020	N=3484 non-advanced MIBC	31% RC only (n=1090) 45% any RC (n=1571)	14% (n=481)	13% (n=437)	22% (n=767)	20% (n=709)

AC: adjuvant chemotherapy; BCa: bladder cancer; CCI: Charlson comorbidity index; IC: induction chemotherapy; IV: intravenous; MIBC: muscle-invasive bladder cancer; N/A: data not available; NAC: neoadjuvant chemotherapy; RC: radical cystectomy; RT: radiation therapy; SEER: Surveillance, Epidemiology, and End Results; TURBT: transurethral resection of bladder tumor.

In Cox multivariable regression analysis, the strongest predictors of inferior survival were age ≥ 66 years (vs. ≤ 65 yrs), CCI score of ≥ 1 (vs. 0), and a T4 tumor stage (vs. T2). Treatment with NAC, RC alone, TMT, or AC was associated with a significantly lower risk of death compared to no treatment (Figure 2).

DISCUSSION

This study provides comprehensive, population-level data on the characteristics, treatment patterns, and outcomes of patients diagnosed with de novo MIBC in Alberta. Over the 10-year study period, nearly 1300 patients were diagnosed with de novo MIBC. Of these, 49% underwent RC, 2% underwent partial cystectomy, 9% received TMT, 12% received RT alone, 4% received chemotherapy alone, and 25% did not receive active treatment. Among patients who underwent RC, NAC and AC were administered to 45% and 12%, respectively. In this dataset, it was not possible to determine which patients receiving TMT also received preceding NAC.

A comparison of selected contemporary (i.e., data collected 2010 or later) and broad (i.e., provincial or national) population-based MIBC cohorts is summarized in Table 3. Findings from this Alberta cohort gen-

erally demonstrate similar or higher rates of guideline-recommended treatment compared to other regions, highlighting the region's adherence to evidence-based care. Additionally, these findings align with international trends, where real-world practice reflects a nuanced approach to curative-intent therapy, balancing patient age and comorbidities with treatment recommendations.^{9–13,24–29}

While definitive surgery, chemotherapy, and TMT have established contraindications, no strict eligibility profile based solely on age or CCI has been defined, underscoring the importance of individualized treatment decision-making.^{3,30–36} Although performance status data were not available from the datasets used in this study, incorporating this information in future studies could further refine our understanding of functional status and treatment eligibility. Furthermore, a deeper understanding of referral patterns, multidisciplinary review, physician preferences, and patient decision-making can reveal key opportunities to enhance care delivery and ensure more patients receive optimal, guideline-based treatment.^{36,37}

In this real-world analysis of patients with newly diagnosed MIBC, mOS was significantly improved with

Table 3 (cont'd). Summary of treatments received in contemporary population-based MIBC cohorts

Study country; data source; year	Number of patients; key inclusion; characteristics	Treatments				
		NAC + RC	RC + AC	RC + Chemo	RC alone	Associated with NAC
Studies in MIBC patients who received cystectomy						
Canada; Alberta provincial databases; 2010-2020 (present study)	N=628 T2-4N0-3M0	45% (n=281)	12% (n=75)	52% (n=326)	48% (n=302)	N/A
Macleod et al (2019) ²⁵ USA; SEER-Medicare data; 2004-2013	N=3826 Age >65; 50% T2	18% (n=676)	17% (n=666) *+ n=109 counted in NAC group	35% (n=1342)	65% (n=2484)	Female gender, lower comorbidity, married status, and lower stage disease (all p<0.05)
Benidir et al (2021) ²⁴ Canada; ON; 2002-2016	N=2791 *Excludes patients who received chemo and did not undergo RC	17% (n=484); 35% in 2015	10% (n=277)	27% (n=761)	73% (n=2030)	N/A
Hermans et al (2016) ²⁶ Netherlands; 1995-2013	N=10 338 cTa/is, T1-4, N0-3, M0-1 (M1 retroperitoneal lymphadenopathy)	7% (n=725); 21% in 2013 *Includes IC	2% (n=183)	N/A	86% (n=8936)	IC: younger age, ≥cT3, ≥cN1, treatment in academic/teaching hospitals (all p<0.05)
Booth et al (2018) ¹³ ON; 1994-2013	N=4250 MIBC+cystectomy	8.8% (n=372) 27% in 2013	19.5% (n=827)	26.6% (n=1129) 42% in 2013	73.4% (n=3121)	N/A
Körner and Jensen (2022) ²⁷ Denmark; 2013-2019	N=1032 Age ≤75 years and T≥2	58% (n=594)	N/A	N/A	42.4% (n=438)	Lower CCI
Jerlström et al (2020) ²⁸ Sweden; 2011-2015	N=1340 MIBC; 74% T2, 84% N0	39% (n=519) *Min 2 cycles	N/A	N/A	N/A	Younger, higher education, better physical status, and more advanced bladder cancer
Fletcher (see above)						Younger age, white race, better education, and treatment at a high-volume facility

AC: adjuvant chemotherapy; BCa: bladder cancer; CCI: Charlson comorbidity index; IC: induction chemotherapy; IV: intravenous; MIBC: muscle-invasive bladder cancer; N/A: data not available; NAC: neoadjuvant chemotherapy; RC: radical cystectomy; RT: radiation therapy; SEER: Surveillance, Epidemiology, and End Results; TURBT: transurethral resection of bladder tumor.

NAC. Patients who underwent RC + perioperative chemotherapy had a mOS of 6.9 years compared to those who underwent RC alone (mOS of 3.5 years). This was consistent with historical outcomes reported in the pivotal Grossman et al study, which demonstrated a mOS of 6.4 years for NAC plus RC and 3.8 years for RC alone.³⁸ Similarly, these findings align with a real-world study from Quebec, where patients undergoing cystectomy alone had a mOS of 3.7 years.³⁹ While survival was notably lower among those who did not undergo RC, further interpretation or direct comparison to other populations remains challenging due to the heterogeneity within patient cohorts.⁴⁰

This is particularly relevant for those receiving TMT, chemotherapy alone, or RT alone, as the majority were likely unfit for RC.³

In this real-world dataset, treatment intent (i.e., palliative vs. curative) is not recorded and could not be inferred based on dose, as radiation dose details were unavailable; however, several factors suggest a predominance of palliative-intent RT in this cohort, including the low use of concomitant radio-sensitizing chemotherapy (n=116/272), advanced age and comorbidity burden, and poor OS among patients receiving RT alone. Consequently, these findings likely reflect patient selection and baseline characteristics

rather than the intrinsic efficacy of the respective treatment modalities.

Optimizing the use of curative-intent therapies has the potential to significantly improve long-term outcomes for patients with MIBC.⁴¹ Enhancing treatment delivery requires a deeper understanding of the factors influencing adherence to guideline-recommended care. Key opportunities for improvement include advancing therapies with novel mechanisms of action, expanding supportive care measures, strengthening patient advocacy and education, and personalizing care plans.^{42,43}

Encouragingly, data from the Swedish national cancer database (BladderBase) have demonstrated a survival benefit with curative-intent therapy, even among frail patient subsets.⁴⁴ In Canada, referral pathway audits have identified areas for enhancement in BCa care, providing a valuable foundation for targeted improvements at the healthcare system level.⁴⁵ Evidence further supports that multidisciplinary review, timely referral to medical oncology, and treatment at academic centers are associated with greater treatment uptake and improved outcomes.^{11,13,46-48} Addressing these challenges presents a significant opportunity, as eligibility for emerging therapies increasingly depends on specialized diagnostics and coordinated multidisciplinary care, reinforcing the importance of comprehensive and proactive treatment strategies.

This dataset represents one of the most comprehensive evaluations of baseline characteristics and treatment patterns among Canadian patients with de novo MIBC. By encompassing a broad, population-based cohort across the province of Alberta, it provides valuable insights into real-world practice patterns while minimizing selection bias. In contrast to center-specific real-world data, which can be heavily influenced by referral patterns and physician preferences,⁴⁹ provincial-level data offer a more representative reflection of standard clinical practice. Additionally, the study's setting within Alberta's single-payer, universal healthcare system reduces the risk of bias related to differential loss to followup from transitions between healthcare providers.

Importantly, stage at initial diagnosis was determined using the provincial cancer registry, a more precise method for case identification compared to datasets relying solely on International Classification of Diseases (ICD) codes. This methodologic strength further enhances the reliability of the findings in capturing contemporary treatment patterns related to disease characteristics.

Limitations

Many of the limitations in our study arise from the nature of administrative data and the gaps in the

information available for analysis. Specifically, the lack of longitudinal diagnostic data (with only the stage at diagnosis being recorded) hindered our ability to assess pathologic restaging after treatment. Additionally, details regarding performance status, suitability for surgery or chemotherapy, and treatment decision-making (including the intent of therapy) were not available for further investigation.

It is also important to note that our data pertain solely to de novo MIBC patients, whose prognosis may differ from that of patients with NMIBC who have progressed to MIBC. Lastly, our findings may not be generalizable to other MIBC populations in different provinces or countries, as varying system, environmental, and geographic factors could influence outcomes.

CONCLUSIONS

Data from this retrospective, population-based study highlight important insights into treatment patterns and outcomes for patients with de novo MIBC. While 58% of patients received curative-intent therapy (including RC or TMT), 25% went without active treatment, thus highlighting the potential for improvement. This study emphasizes the need for further research to better understand the factors influencing treatment decisions, ultimately aiming to enhance outcomes for real-world patients with MIBC.

COMPETING INTERESTS: 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 (institution) from AstraZeneca and EMD Serono. Dr. Gotto has received honoraria from Astellas, AstraZeneca, Bayer, EMD Serono, Ferring, Janssen, McKesson, Merck, Pfizer, Sanofi, and Tolmar. Dr. Kulkarni has been an advisory board member for AAA/Novartis, Abbvie, Astellas, BMS, EnGene, EMD Serono, Ferring, Johnson&Johnson, Knight Therapeutics, Merck, Pfizer, Theralase, and Verity; a consultant for AstraZeneca, 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 Theralase; 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. Sridhar has received consulting fees from Astellas, AstraZeneca, Bayer, BMS, Eisai, EMD Serono, Hoffmann-La Roche, Immunomedics, Ipsen, Janssen, Merck, Pfizer, and Seagen; honoraria from Bayer, EMD Serono, Pfizer, and Seagen; and meeting attendance/travel from EMD Serono. Dr. Kokorovic has received consultancy fees from Astellas, Bayer, Ferring, Janssen, Knight Therapeutics, Pfizer, and Tolmar; and honoraria from Janssen. Dr. Eigl has received honoraria from EMD Serono, Gilead, Janssen, Pfizer, and Seagen; 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 Serono (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. Mr. Cheung and Ms. Stephen are employed by Janssen. Mr. Osborne is employed by J&J Innovative Medicine. Dr. Wallis has received

consulting fees from Janssen Oncology, Nanostics Inc, Precision Point Specialty, and Sesen Bio; honoraria/travel from Abbvie, Astellas, AstraZeneca, Bayer, EMD Serono, Haymarket Media, Healing and Cancer Foundation, Knight Therapeutics, Merck, Science & Medicine, TerSera, and Tolmar; and research funding from Bayer, Knight Therapeutics, and Tolmar.

FUNDING: Funding for the study, medical writing, and project management was provided by Johnson & Johnson Innovative Medicine (Toronto, ON, Canada).

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

REFERENCES

- 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.
- 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>
- Kulkarni GS, Black PC, Sidhar SS, et al. Canadian Urological Association guideline: Muscle-invasive bladder cancer. *Can Urol Assoc J* 2019;13:230-8. <https://doi.org/10.5489/cuoj.5902>
- Clinical Practice Guideline. GU-013, Alberta, Canada: Cancer Care Alberta.
- Zlotta AR, Ballas LK, Niemierko A, et al. Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: A multi-institutional propensity score matched and weighted analysis. *Lancet Oncol* 2023;24:669-81. [https://doi.org/10.1016/S1473-2045\(23\)00170-5](https://doi.org/10.1016/S1473-2045(23)00170-5)
- Ghoneim MA, Abdel-Latif M, el-Mekresh M, et al. Radical cystectomy for carcinoma of the bladder: 2,720 consecutive cases 5 years later. *J Urol* 2008;180:121-7. <https://doi.org/10.1016/j.juro.2008.03.024>
- Herzberg H, Ventura Y, Lifshitz K, et al. Natural history and health care burden of non-curative treatment for muscle-invasive bladder cancer. *Urol Oncol* 2024;S1078-1439(24)00365-X.
- Westergren D-O, Gärdmark T, Lindhagen L, et al. A nationwide, population based analysis of patients with organ confined, muscle invasive bladder cancer not receiving curative intent therapy in Sweden from 1997 to 2014. *J Urol* 2019;202:905-12. <https://doi.org/10.1097/JU.0000000000000350>
- John JB, Varughese MA, Cooper N, et al. Treatment allocation and survival in patients diagnosed with nonmetastatic muscle-invasive bladder cancer: An analysis of a national patient cohort in England. *Eur Urol Focus* 2021;7:359-65. <https://doi.org/10.1016/j.euf.2020.01.013>
- Flegar L, Kraywinkel K, Zacharis A, et al. Treatment trends for muscle-invasive bladder cancer in Germany from 2006 to 2019. *World J Urol* 2022;40:1715-21. <https://doi.org/10.1007/s00345-022-04017-z>
- Fletcher SA, Harmouch SS, Krimphove MJ, et al. Characterizing trends in treatment modalities for localized muscle-invasive bladder cancer in the pre-immunotherapy era. *World J Urol* 2018;36:1767-74. <https://doi.org/10.1007/s00345-018-2371-y>
- Richters A, Leliveld AM, Goossens-Laan CA, et al. Sex differences in treatment patterns for non-advanced muscle-invasive bladder cancer: A descriptive analysis of 3484 patients of the Netherlands Cancer Registry. *World J Urol* 2022;40:2275-81. <https://doi.org/10.1007/s00345-022-04080-6>
- Booth CM, Karim S, Brennan K, et al. Perioperative chemotherapy for bladder cancer in the general population: Are practice patterns finally changing? *Urol Oncol* 2018;36:89.e13-20. <https://doi.org/10.1016/j.urolonc.2017.11.015>
- American Joint Committee on Cancer. *AJCC cancer staging manual*. New York, NY: Springer New York. Epub ahead of print 2002. <https://doi.org/10.1007/978-1-4757-3656-4>
- Edge SB, American Joint Committee on Cancer (eds). *AJCC cancer staging manual*. 7th ed. New York, NY: Springer, 2010.
- Amin MB, American Joint Committee on Cancer, American Cancer Society (eds). *AJCC cancer staging manual*. 8th ed. Chicago IL: American Joint Committee on Cancer, Springer, 2017.
- 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. Bladder Consensus Conference Committee. *Am J Surg Pathol* 1998;22:1435-48. <https://doi.org/10.1097/00000478-199812000-00001>
- 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>
- 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>
- 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>
- 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>
- 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>
- Alberta population estimates: Data tables. Open Government. <https://open.alberta.ca/opendata/alberta-population-estimates-data-tables> (accessed 16 April 2024).
- Benidir T, Herrera-Caceres J, Wallis C, et al. Population-based analysis of perioperative chemotherapy use, interventions requiring hospitalization and atheroembolic events among patients with non-metastatic muscle-invasive bladder cancer. *Cancer Med* 2021;10:2636-44. <https://doi.org/10.1002/cam4.3805>
- Macleod LC, Yabes JG, Yu M, et al. Trends and appropriateness of perioperative chemotherapy for muscle-invasive bladder cancer. *Urol Oncol* 2019;37:462-9. <https://doi.org/10.1016/j.urolonc.2019.04.006>
- Hermans TJN, Fransen van de Putte EE, Horenblas S, et al. Perioperative treatment and radical cystectomy for bladder cancer—a population based trend analysis of 10,338 patients in the Netherlands. *Eur J Cancer* 2016;54:18-26. <https://doi.org/10.1016/j.ejca.2015.11.006>
- Körner SK, Jensen JB. A population-based retrospective analysis on variation in use of neoadjuvant chemotherapy depending on comorbidity in patients with muscle-invasive bladder cancer undergoing cystectomy in Denmark in the period 2013–2019. *Scand J Urol* 2022;56:34-8. <https://doi.org/10.1080/21681805.2021.2002400>
- Jerlström T, Chen R, Liedberg F, et al. No increased risk of short-term complications after radical cystectomy for muscle-invasive bladder cancer among patients treated with preoperative chemotherapy: A nation-wide register-based study. *World J Urol* 2020;38:381-8. <https://doi.org/10.1007/s00345-019-02770-2>
- Bream MJ, Maurice MJ, Altschuler J, et al. Increased use of cystectomy in patients 75 and older: A contemporary analysis of survival and perioperative outcomes from the national cancer database. *Urology* 2017;100:72-8. <https://doi.org/10.1016/j.urol.2016.08.054>
- Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer* 2006;107:506-13. <https://doi.org/10.1002/cncr.22031>
- Kaushik D, Shi Z, Liss MA, et al. Screening logs from a pilot randomized controlled trial of radical cystectomy versus chemoradiation therapy for muscle-invasive bladder cancer. *Urol Oncol* 2020;38:4.e1-6. <https://doi.org/10.1016/j.urolonc.2019.09.008>
- Gofrit ON, Meirovitz A, Frank S, et al. Trimodal therapy in T2-4aNOMO bladder cancer—how to select the best candidate? *Cancer Med* 2020;9:8491-7. <https://doi.org/10.1002/cam4.3478>
- Posielski N, Koenig H, Ho O, et al. Use of neoadjuvant chemotherapy in elderly patients with muscle-invasive bladder cancer: A population-based study, 2006–2017. *Oncol* 2022;36:21-33. <https://doi.org/10.46883/2022.25920939>
- D'Andrea D, Black PC, Zargar H, et al. Association of age with response to preoperative chemotherapy in patients with muscle-invasive bladder cancer. *World J Urol* 2021;39:4345-54. <https://doi.org/10.1007/s00345-021-03793-4>
- VanderWalde NA, Chi MT, Hurria A, et al. Treatment of muscle invasive bladder cancer in the elderly: Navigating the trade-offs of risk and benefit. *World J Urol* 2016;34:3-11. <https://doi.org/10.1007/s00345-015-1708-z>
- Sfakianos JP, Galsky MD. Neoadjuvant chemotherapy in the management of muscle-invasive bladder cancer: Bridging the gap between evidence and practice. *Urol Clin North Am* 2015;42:181-7, viii. <https://doi.org/10.1016/j.ucl.2015.01.002>
- Robinson AG, Izard JP, Booth CM. The role of population-based observational research in bladder cancer. *Bladder Cancer* 2015;1:123-31. <https://doi.org/10.3233/BLC-150018>
- Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349:859-66. <https://doi.org/10.1056/NEJMoa022148>
- Zakaria AS, Santos F, Kassouf W, et al. Survival after radical cystectomy for bladder cancer in relation to prior non-muscle invasive disease in Quebec. *Urol Int* 2016;97:49-53. <https://doi.org/10.1159/000444093>

40. Caballero JM, Gili JM, Pereira JC, et al. Systematic review of population-based bladder cancer registries: How criteria heterogeneity affects the comparison of incidences. *Cancer Med* 2023;12:7540-51. <https://doi.org/10.1002/cam4.5494>
41. Martini A, Sfakianos JP, Renström-Koskela L, et al. The natural history of untreated muscle-invasive bladder cancer. *BJU Int* 2020;125:270-5. <https://doi.org/10.1111/bju.14872>
42. Kamat AM, Mathew P. Bladder cancer: Imperatives for personalized medicine. *Oncol* 2011;25:951-8, 960.
43. Fontes MS, de Almeida DVP, Cárcano F, et al. Precision medicine for urothelial carcinoma: An international perspective. *Urol Oncol* 2024;S1078-1439(23)00360-5.
44. Häggström C, Rowley M, Liedberg F, et al. Latent heterogeneity of muscle-invasive bladder cancer in patient characteristics and survival: A population-based nation-wide study in the Bladder Cancer Data Base Sweden (BladderBaSe). *Cancer Med* 2023;12:13856-64. <https://doi.org/10.1002/cam4.5981>
45. Vanin Moreno N, Whitehead M, Siemens DR. Real-life benchmarking bladder cancer care: A population-based study. *Can Urol Assoc J* 2023;17:268-73. <https://doi.org/10.5489/cuaj.8231>
46. Walraven JEW, Ripping TM, Oddens JR, et al. The influence of multidisciplinary team meetings on treatment decisions in advanced bladder cancer. *BJU Int* 2023;131:244-52. <https://doi.org/10.1111/bju.15856>
47. Varughese M. Overcoming the chasm between evidence and routine practice for bladder cancer; just a quixotic notion? *Clin Oncol* 2021;33:e274-84. <https://doi.org/10.1016/j.clon.2021.03.008>
48. Gotto GT, Shea-Budgell MA, Rose MS, et al. Predictors of referral for neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer and changes in practice over time. *Can Urol Assoc J* 2015;9:236-41. <https://doi.org/10.5489/cuaj.2722>
49. Jarada TN, O'Sullivan DE, Brenner DR, et al. Selection bias in real-world data studies used to support health technology assessments: A case study in metastatic cancer. *Curr Oncol* 2023;30:1945-53. <https://doi.org/10.3390/curroncol30020151>

CORRESPONDENCE: Dr. Nimira S. Alimohamed, Division of Medical Oncology, University of Calgary, Calgary, AB, Canada; Nimira.Alimohamed@albertahealthservices.ca