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

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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 (T2-4N0-1M0) 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.

KEY MESSAGES

- Curative intent treatment (radical cystectomy or TURBT and chemoradiotherapy) was received by 58% of patients in Alberta diagnosed with de novo MIBC patients 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.

INTRODUCTION

Bladder cancer (BCa) accounts for 8% of all cancer diagnoses in Canada, with around 9,000 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 tumour 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 tumour (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 not receive NAC should be offered adjuvant cisplatin-based combination chemotherapy.[3] For patients who are ineligible for RC or prefer bladder preservation, TMT (+/- 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% to 78%.[7–12] Given the rapidly evolving treatment landscape, these disparities highlight significant barriers within current practice patterns which 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 (2 tertiary, 4 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 utilized (see Table S1 for a full description of the databases utilized). 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] Pathological re-staging 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 prior to 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. Pre-specified baseline characteristics of interest (sex, age, residence, comorbidity index, T stage, N stage, tumour grade, and index year) were determined by the variables collected in the databases utilized. Index year was collected as a continuous variable. Age was collected as a continuous variable and categorized as ≤65, 66-75, and ≥76 years. Charlson comorbidities were identified by validated claims-based algorithms, as defined in Quan et al. (2005),[19] in the year prior to bladder cancer 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. 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 2-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 (SD) for continuous symmetrically distributed data, median (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 +/- chemotherapy +/- RT), using standardized mean differences (SMDs), where values < 0.1 reflect no meaningful imbalance, and p-values (i.e. chi-square tests for categorical variables and ANOVA for continuous variables), whereby values less than 0.05 were considered to be statistically significant. The number and proportion of individuals missing data for each covariate are summarized but not included in analyses.

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 31st, 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 significance 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 to 3.0 per 100,000 and was generally stable over the study period (see Table S2).[23] Baseline characteristics are outlined in Table 1. Overall, the majority of patients were male (77%) with a median age of 73 years, the majority had a tumour stage of T2 (68%) and N0 (76%), and 50% had a Charlson Comorbidity Index (CCI) of one or higher.

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, ≥97%) and 12%

(n=75) received AC. Partial cystectomy was performed in 2% of patients (n=23). Among the 641 patients (50%) who did not undergo cystectomy, 116 (18%) received TMT, 156 (24%) received radiation therapy 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 (Table S3a/b and S4a/b; Figure S1 and S2) revealed that patients who received no treatment or RT only were predominantly aged ≥76 years (73% and 86%, respectively) and had a Charlson Comorbidity Index (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=0 (61% and 67%, respectively). Cystectomy was more frequently performed in patients with T3 or T4 tumours compared to T2 tumours (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 between 2010 and 2014 to 78% among those diagnosed 2018 and 2020 (**Figure S2**).

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 years (0.6-0.8) among those who were untreated, and 0.6 years (0.4-0.8) for those who received RT alone. (Figure S3).

In Cox multivariable regression analysis, the strongest predictors of inferior survival were age ≥66 years (vs. ≤65 yrs), CCI score of 1 or more (vs. 0), and a T4 tumour stage (vs. T2). Treatment with NAC, RC alone, TMT, or adjuvant chemotherapy 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 radiation therapy 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 generally 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, median OS was significantly improved with 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) and this was consistent with historical outcomes reported in the pivotal Grossman et al. study which demonstrated a median OS 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 median OS 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) (Table 2), advanced age and comorbidity burden (Table S4b), and poor OS among patients receiving RT alone (Figure S3). 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 bladder cancer care, providing a valuable foundation for targeted improvements at the level of

the health-care system.[45] Evidence further supports that multidisciplinary review, timely referral 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 follow-up 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 methodological 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 pathological 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 geographical 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.

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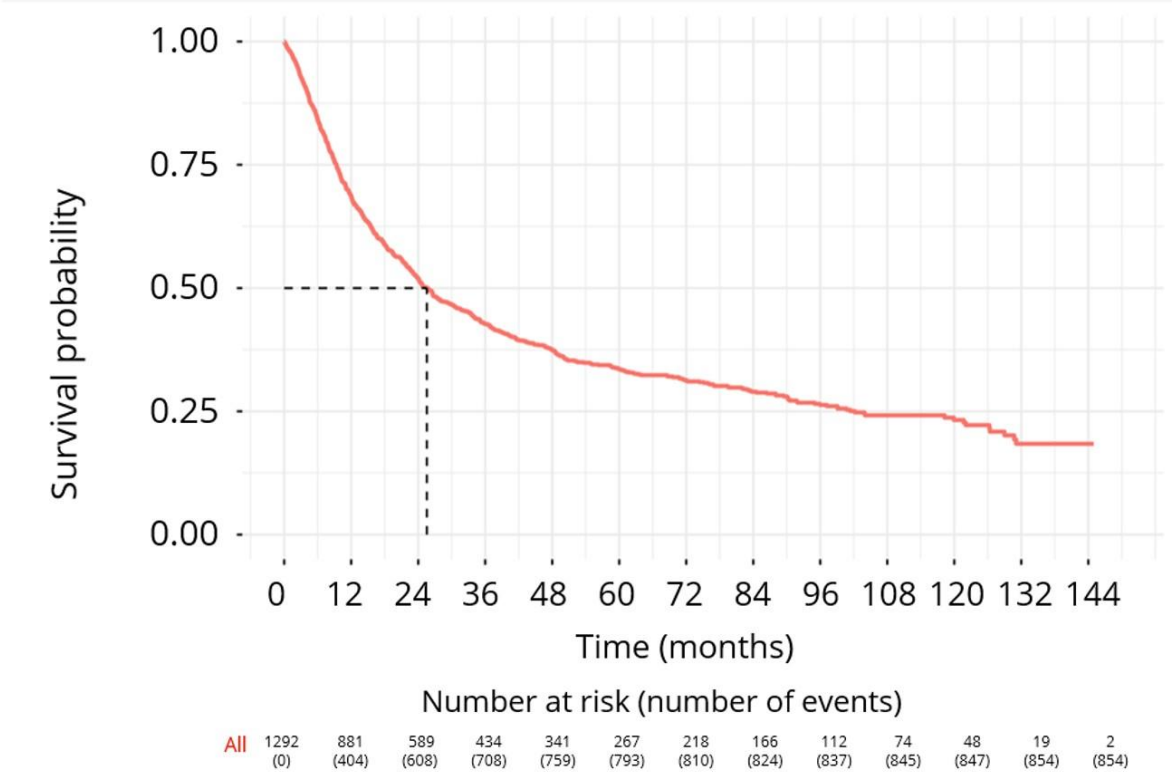
FIGURES AND TABLES

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.



Overall Survival, mOS	25.5 (23.3-29.1)
12-Month Survival, %	68.6 (66.1-71.2)
24-Month Survival, %	51.9 (49.2-54.8)
60-Month Survival, %	33.5 (30.8-36.4)

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

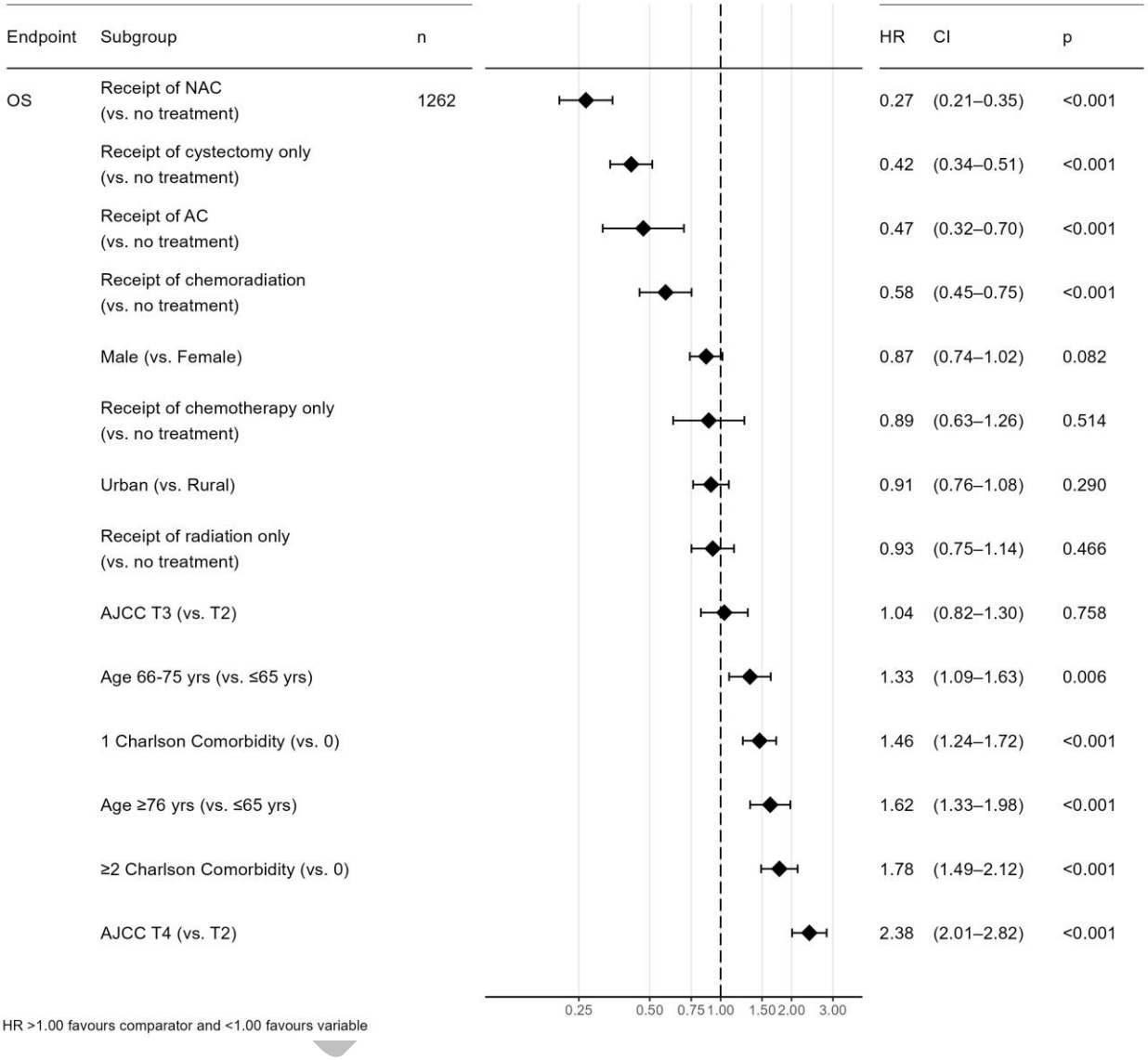


Table 1. Baseline characteristics of individuals diagnosed with de novo MIBC in Alberta, Canada, from 2010–2020	
Variable	**MIBC N=1292**
Male, n (%)	977 (75.6)
Urban residence, n (%)	1053 (81.5)
Age at Dx, years, mean (SD)	72.7 (11.5)
Age at Dx, years, median [IQR]	73.0 [64.0, 81.0]
Age at Dx, categories, 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.

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]	2.2 [1.5, 2.5]
RC + adjuvant chemotherapy (AC)[c]	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)
Chemotherapy only	46 (3.6)
Chemotherapy regimen[e]	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)

[a]A 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). [b]Neoadjuvant therapy was defined as therapy received between the index date and date of cystectomy. [c]Adjuvant therapy was defined as therapy received within 9 months

(273 days) of the date of cystectomy. [d]In 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". [e]Received 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.

Table 3. Summary of treatments received in contemporary population-based MIBC cohorts						
Study country; data source; year	**Number of patients; key inclusion; characteristics**	**Treatments**				
Studies including all patients with MIBC		**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)
Studies in MIBC patients who received cystectomy		**NAC+RC**	**RC+AC**	**RC+ Chemo**	**RC alone**	**Associated with NAC:**
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)	Gemale gender, lower comorbidity, married status, and lower stage disease (all p<0.05)
Benidir et al (2021)[24]	N=2791	17% (n=484);	10% (n=277)	27% (n=761)	73% (n=2030)	N/A

Canada; ON; 2002–2016	**excludes patients who received chemo and did not undergo RC*	35% in 2015				
Hermans et al (2016)[26] Netherlands; 1995–2013	N=10338; 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.