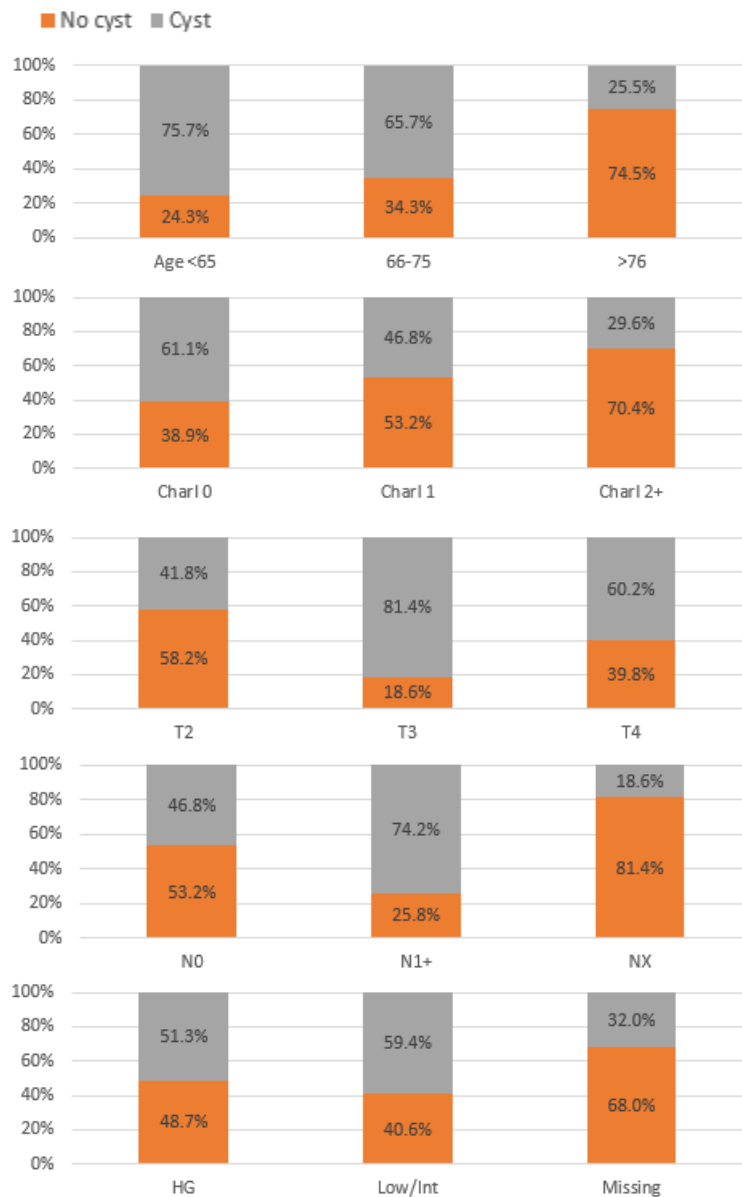
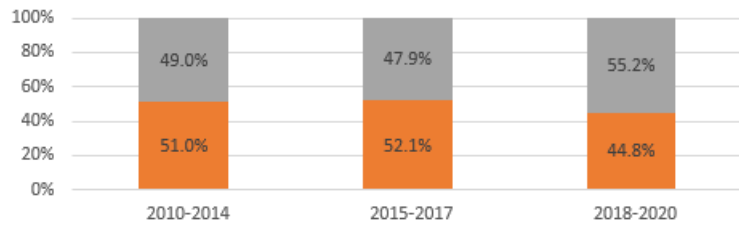


APPENDIX

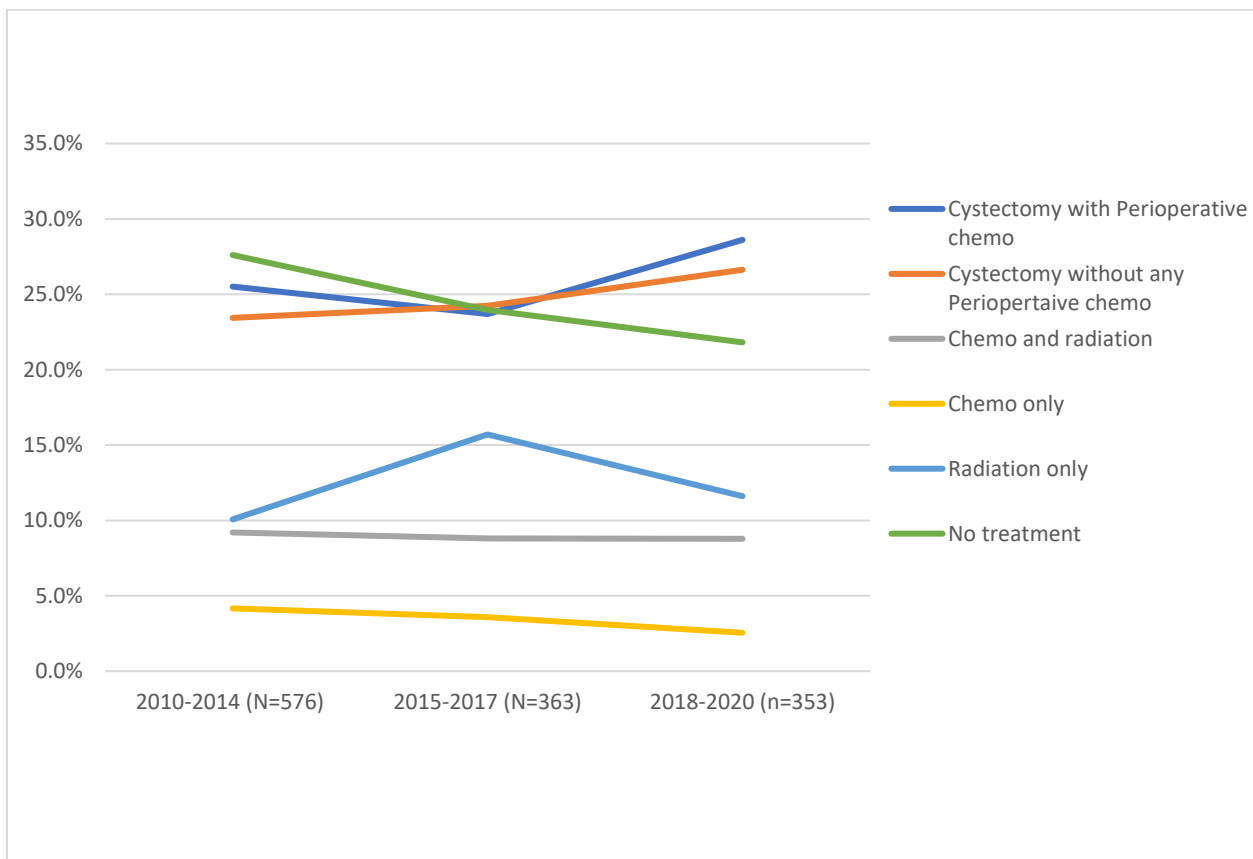
Supplementary Figure 1. Proportion of de novo MIBC patients exposed to cystectomy vs. no cystectomy by baseline category. Charl: Charlson comorbidity index; Cyst: cystectomy; Dx: diagnosis; Gr: grade; HG: high-grade; IQR: interquartile range; Low/Int: low/intermediate; MIBC: muscle-invasive bladder cancer; SD, standard deviation.



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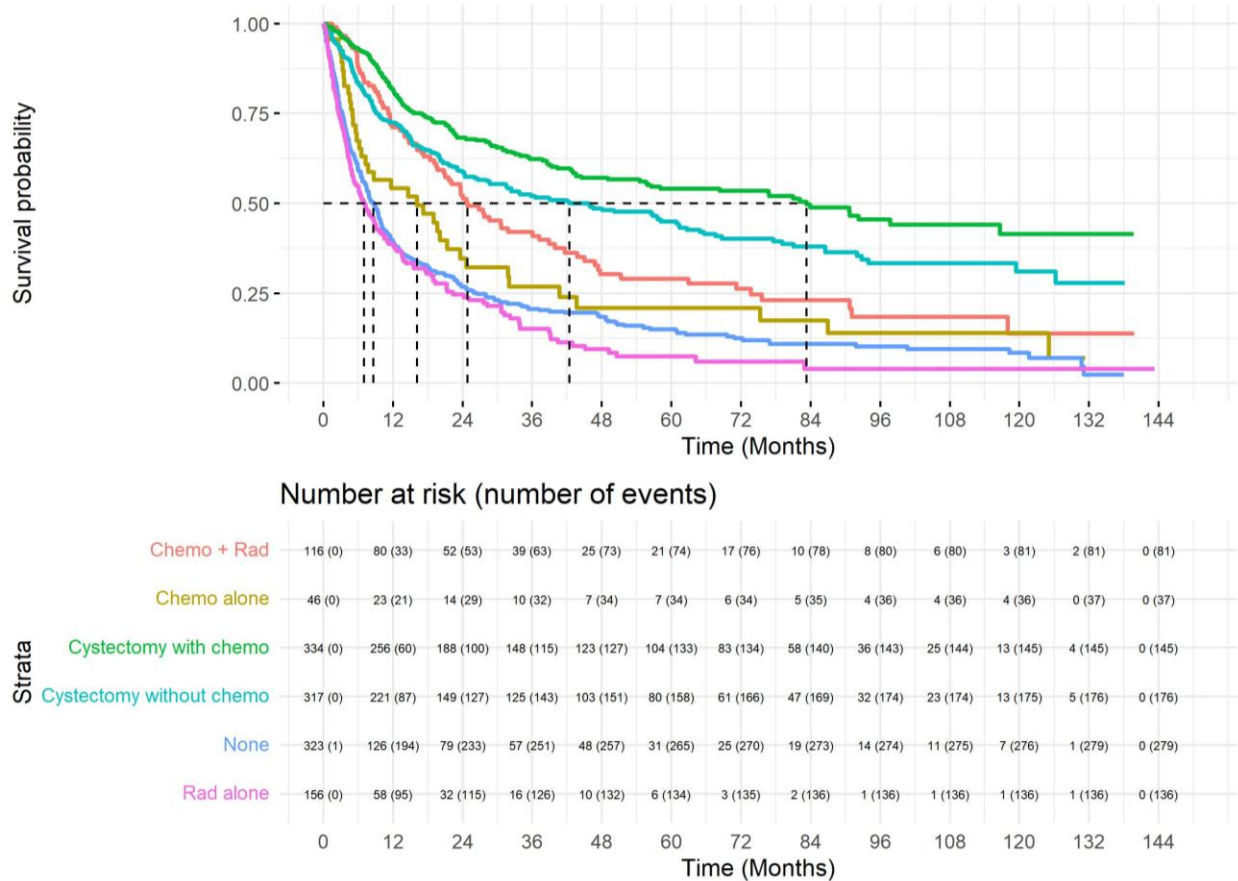


Supplementary Figure 2. Proportion of de novo MIBC patients exposed to each treatment by timeframe of diagnosis.



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Supplementary Figure 3. Overall survival from date of diagnosis among individuals with de novo MIBC by treatment modality in Alberta, Canada, diagnosed from 2010–2020.



Treatment group	Median, months (95% CI)	12-month	24-month	60-month
Cystectomy with chemotherapy ^a	83.3 (55.9, –)	0.816 (0.775, 0.859)	0.682 (0.632, 0.736)	0.541 (0.485, 0.604)
Cystectomy without chemotherapy ^b	42.4 (28.7, 61.4)	0.725 (0.677, 0.776)	0.585 (0.532, 0.644)	0.449 (0.393, 0.514)
Chemoradiation	24.8 (20.8, 38.9)	0.712 (0.633, 0.800)	0.523 (0.437, 0.626)	0.290 (0.212, 0.398)
Chemotherapy alone	16.2 (7.3, 24.6)	0.542 (0.415, 0.707)	0.347 (0.230, 0.523)	0.209 (0.113, 0.386)
No treatment	8.6 (7.3, 10.0)	0.395 (0.345, 0.452)	0.268 (0.224, 0.322)	0.150 (0.113, 0.198)

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Radiation alone	7.0 (5.1, 10.0)	0.387 (0.318, 0.472)	0.246 (0.185, 0.326)	0.074 (0.039, 0.142)
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^aThis group includes patients who received partial cystectomy + chemotherapy (n=8). ^bThis group includes patients who received partial cystectomy + no chemotherapy (n=15). Chemo: chemotherapy; MIBC: muscle-invasive bladder cancer; OS: overall survival; rad: radiation; Tx: treatment.

Supplementary Table 1. Description of databases use
Alberta Cancer Registry (ACR)
Cancer is a reportable disease within the province of Alberta. The ACR captures information on all individuals diagnosed with cancer within the province of Alberta (200,000+ cases). This database also includes information related to cancer morphology and stage which are captured from pathology, physician, and laboratory reports, electronic medical records, along with patient charts. In addition, this database houses information on the date and cause of death along with the last known date of follow-up which are captured via vital statistics and the population registry. The database currently captures individuals diagnosed with cancer between 2004-2020 and has follow-up data until the end of 2020.
ARIA (Electronic Medical Records)
The ARIA database consists of electronic medical records for all 17 provincial cancer centers (2 tertiary centers, 4 regional and 11 community centers) covering 4.5 million residents of Alberta. This database contains information related to patient care including information on systemic therapies (including the date and dose of each agent within each cycle of each chemotherapy regimen), radiation therapy, treatment facility, and visits with cancer physicians (including specialty type).
Discharge Abstract Database (DAD)
The DAD database captures information for each instance where an individual has been discharged from an inpatient hospital bed. This database contains International Classification of Diseases, Tenth Revision – Canadian Enhancement (ICD-10-CA) diagnostic codes for the most responsible diagnosis and secondary diagnoses. Information is also captured on procedures that occurred during the hospitalization. Such procedures are coded according to the Canadian Classification of Health Interventions (CCI) system. In addition, information on the date and the duration of the hospitalization are also available as are information on aspects of patient costs such as the resource intensity weight. Data accuracy and quality are assessed on a regular basis by hospital administration and the Canadian Institute for Health Information (CIHI).
National Ambulatory Care Reporting System Database (NACRS)
The NACRS database captures information on all inpatient and outpatient use of ambulatory care services. This database contains ICD-10-CA diagnostic codes and the date of service. As with the DAD, data accuracy and quality are assessed on a regular basis by hospital administration and the Canadian Institute for Health Information (CIHI).
Practitioner Claims Database (PC)
The PC database captures physician and allied practitioner claims used for reimbursement and shadow-billing purposes that have been processed by the Alberta government. This database includes information such as the processed claim amount, diagnostic codes (ICD-9-CM:

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International Classification of Diseases, Ninth Revision – Clinical Modification), and health service codes (CCP: Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures).
Pharmaceutical Information Network Database (PIN)
The PIN database captures information on all prescription drugs dispensed from community pharmacies in the province. Information within the PIN database is collected from community pharmacists and includes information on the drug name, dose, and quantity dispensed. Complete information from this database is available starting in 2010. While data are available prior to 2010, these data are incomplete since they were collected prior to the enactment of regulations that mandated the collection of pharmacy dispensary records which occurred in 2007.

Supplementary Table 2. Annual incidence of de novo MIBC in Alberta, Canada from 2010–2020			
Year	Population (n)	De novo MIBC (N=1292)	
		Cases (n)	Incidence (95% CI)
2010	3732082	111	3.0 (2.4-3.6)
2011	3789030	116	3.1 (2.5-3.7)
2012	3874548	103	2.7 (2.2-3.2)
2013	3981011	118	3.0 (2.5-3.5)
2014	4083648	128	3.1 (2.6-3.7)
2015	4144491	135	3.3 (2.7-3.9)
2016	4196061	106	2.5 (2.1-3.1)
2017	4241100	122	2.9 (2.4-3.4)
2018	4298275	112	2.6 (2.1-3.1)
2019	4361694	119	2.7 (2.3-3.3)
2020	4421876	122	2.8 (2.3-3.3)

CI: confidence interval; MIBC: muscle-invasive bladder cancer.

Supplementary Table 3A. Baseline characteristics of the de novo MIBC cohort, stratified by receipt of cystectomy (within category proportions), from Alberta, Canada from 2010–2020					
Variable	Overall N=1292	No cystectomy n=641	Any cystectomy^a c=651	p	SMD
Male, n (%)	977 (75.6)	475 (74.1)	502 (77.1)	0.232	0.07
Urban residence, n (%)	1053 (81.5)	508 (79.3)	545 (83.7)	0.046	0.115
Age at index, categories, n (%)				<0.001	1.018
≤65 years	342 (26.5)	83 (12.9)	259 (39.8)		
66–75 years	373 (28.9)	128 (20.0)	245 (37.6)		
≥76 years	577 (44.7)	430 (67.1)	147 (22.6)		
Age at index, years, mean (SD)	72.7 (11.5)	78.3 (10.4)	67.2 (9.8)	<0.001	1.097
Charlson comorbidity index score, n (%)				<0.001	0.508
0	648 (50.2)	252 (39.3)	396 (60.8)		
1	374 (28.9)	199 (31.0)	175 (26.9)		
≥2	270 (20.9)	190 (29.6)	80 (12.3)		
T stage at initial Dx, n (%)				<0.001	0.58
T2	881 (68.2)	513 (80.0)	368 (56.5)		
T3	167 (12.9)	31 (4.8)	136 (20.9)		
T4	244 (18.9)	97 (15.1)	147 (22.6)		
N stage at initial Dx, n (%)				<0.001	0.539
N0	982 (76.0)	522 (81.4)	460 (70.7)		
N1	240 (18.6)	62 (9.7)	178 (27.3)		
Missing	70 (5.4)	57 (8.9)	13 (2.0)		
Tumor grade, n (%)				0.003	0.19
High	1185 (91.7)	577 (90.0)	608 (93.4)		
Low/intermediate	32 (2.5)	13 (2.0)	19 (2.9)		
Missing	75 (5.8)	51 (8.0)	24 (3.7)		
Year of Index, n (%)				0.097	0.121
2010–2014	576 (44.6)	294 (45.9)	282 (43.3)		
2015–2017	363 (28.1)	189 (29.5)	174 (26.7)		
2018–2020	353 (27.3)	158 (24.6)	195 (30.0)		

^aThis number includes patients who received radical cystectomy (n=628, including n<10 who also received partial cystectomy) or partial cystectomy (n=23). Dx: diagnosis; MIBC: muscle-invasive bladder cancer; SD: standard deviation; SMD: standardized mean difference.

Supplementary Table 3B. Baseline characteristics of the de novo MIBC cohort, stratified by receipt of cystectomy (within variable proportions), from Alberta, Canada from 2010–2020			
Variable	Overall (N=1292)	No cystectomy (n=641)	Any cystectomy^a (n=651)
Male, n (%)	977 (100)	475 (48.6)	502 (51.4)
Female	315 (100)	166 (52.7)	149 (47.3)
Urban residence, n (%)	1053 (100)	508 (48.2)	545 (51.8)
Rural	239 (100)	133 (55.6)	96 (40.2)
Age at index, years, mean (SD)	72.7 (100)	78.3 (10.4)	67.2 (9.8)
Age at index, categories, n (%)			
≤65 years	342 (100)	83 (24.3)	259 (75.7)
66–75 years	373 (100)	128 (34.3)	245 (65.7)
≥76 years	577 (100)	430 (74.5)	147 (25.5)
Charlson comorbidity index score, n (%)			
0	648 (100)	252 (38.9)	396 (61.1)
1	374 (100)	199 (53.2)	175 (46.8)
≥2	270 (100)	190 (70.4)	80 (29.6)
T stage at initial Dx, n (%)			
T2	881 (100)	513 (58.2)	368 (41.8)
T3	167 (100)	31 (18.6)	136 (81.4)
T4	244 (100)	97 (39.8)	147 (60.2)
N stage at initial Dx, n (%)			
N0	982 (100)	522 (53.2)	460 (46.8)
N1	240 (100)	62 (25.8)	178 (74.2)
Missing	70 (100)	57 (81.4)	13 (18.6)
Tumor grade, n (%)			
High	1185 (100)	577 (48.7)	608 (51.3)
Low/intermediate	32 (100)	13 (40.6)	19 (59.4)
Missing	75 (100)	51 (68.0)	24 (32.0)
Year of index, n (%)			
2010–2014	576 (100)	294 (51.0)	282 (49.0)
2015–2017	363 (100)	189 (52.1)	174 (47.9)
2018–2020	353 (100)	158 (44.8)	195 (55.2)

^aThis number includes patients who received radical cystectomy (n=628, including n<10 who also received partial cystectomy) or partial cystectomy (n=23). Dx: diagnosis; MIBC: muscle-invasive bladder cancer; SD: standard deviation.

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Supplementary Table 4A. Baseline characteristics of the de novo MIBC cohort, stratified by receipt of therapy (within category proportions), from Alberta, Canada from 2010–2020								
Variable	Overall (N=1292)	Cystectomy with perioperative chemo^a (n=334)	Cystectomy without any perioperative chemo^b (n=317)	Chemo and radiation (n=116)	Chemo only (n=46)	Radiation only (n=156)	No treatment (n=323)	p
Female, n (%)	315 (24.3)	62 (20.7)	87 (27.4)	17 (14.7)	11 (23.9)	43 (27.5)	95 (29.4)	0.002
Male	977 (75.6)	272 (81.4)	230 (72.6)	99 (85.3)	35 (76.1)	113 (72.4)	228 (70.6)	
Rural residence, n (%)	239 (18.5)	50 (14.9)	56 (17.6)	N/R ^c	<10 ^c	32 (20.5)	63 (19.5)	0.200
Urban residence	1053 (81.5)	284 (85.0)	261 (82.3)	N/R ^c	N/R ^c	124 (79.5)	260 (80.5)	
Mean age at index, years, mean (SD)	72.7 (11.5)	65.5 (8.9)	69.0 (10.5)	70.7 (10.4)	71.2 (10.1)	82.2 (7.5)	80.2 (9.7)	<0.001
Age at index, categories, n (%)								<0.001
≤65 years	342 (26.5)	154 (46.1)	105 (33.1)	34 (29.3)	N/R ^c	<10 ^c	29 (9.0)	
66–75 years	373 (28.9)	133 (39.8)	112 (35.3)	39 (33.6)	N/R ^c	N/R ^c	58 (18.0)	
≥76 years	577 (44.7)	47 (14.1)	100 (31.5)	43 (37.1)	17 (37.0)	134 (85.9)	236 (73.1)	
Charlson comorbidity index score, n (%)								<0.001
0	648 (50.2)	225 (67.4)	171 (53.9)	62 (53.4)	26 (56.5)	56 (35.9)	108 (33.4)	
1	374 (28.9)	80 (24.0)	95 (30.0)	N/R ^c	N/R ^c	49 (31.4)	98 (30.3)	
≥2	270 (20.9)	29 (8.7)	51 (16.1)	N/R ^c	<10 ^c	51 (32.7)	117 (36.2)	
T stage at initial Dx, n (%)								<0.001
T2	881 (68.2)	218 (65.3)	150 (47.3)	100 (86.2)	37 (80.4)	122 (78.2)	254 (78.6)	

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T3	167 (12.9)	52 (15.6)	84 (26.5)	<10 ^c	<10 ^c	<10 ^c	15 (4.6)	
T4	244 (18.9)	64 (19.2)	83 (26.2)	N/R ^c	<10 ^c	N/R ^c	54 (16.7)	
N stage at initial Dx, n (%)								<0.0 01
N0	982 (76.0)	236 (70.7)	224 (70.7)	95 (81.9)	32 (69.6)	133 (85.3)	262 (81.1)	
N1	240 (18.6)	N/R ^c	N/R ^c	N/R ^c	N/R ^c	N/R ^c	N/R ^c	
Missing	70 (5.4)	N/A	N/A	N/A	N/A	N/A	N/A	
Tumor grade, n (%)								0.03 3
High	1185 (91.7)	319 (95.5)	289 (91.2)	106 (91.3)	41 (89.1)	146 (93.6)	284 (87.9)	
Low/inter mediate	32 (2.6)	N/R ^c	N/R ^c	N/R ^c	N/R ^c	N/R ^c	N/R ^c	
Missing	75 (5.8)	N/A	N/A	N/A	N/A	N/A	N/A	
Year of index, n (%)								0.20 0
2010–20 14	576 (44.6)	147 (44.0)	135 (42.6)	53 (45.7)	24 (52.2)	58 (37.2)	159 (49.2)	
2015–20 17	363 (28.1)	86 (25.7)	88 (27.8)	N/R ^c	N/R ^c	57 (36.5)	87 (26.9)	
2018–20 20	353 (27.3)	101 (30.2)	94 (29.7)	N/R ^c	<10 ^c	41 (26.3)	77 (23.8)	

^aThis group includes patients who received partial cystectomy + chemotherapy (n=8). ^bThis group includes patients who received partial cystectomy + no chemotherapy (n=15). ^cIn 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.” Chemo: chemotherapy; Dx: diagnosis; MIBC: muscle-invasive bladder cancer; N/A: not available; SD: standard deviation.

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Supplementary Table 4B. Baseline characteristics of the de novo MIBC cohort, stratified by receipt of therapy (within variable proportions), from Alberta, Canada from 2010–2020							
Variable	Overall (N=1292)	Cystectomy with perioperative chemo^a (n=334)	Cystectomy without any perioperative chemo^b (n=317)	Chemo and radiation (n=116)	Chemo only (n=46)	Radiation only (n=156)	No treatment (n=323)
Female, n (%)	315 (100)	62 (19.7)	87 (27.6)	17 (5.4)	11 (3.5)	43 (13.7)	95 (30.2)
Male	977 (100)	272 (27.8)	230 (23.5)	99 (10.1)	35 (3.6)	113 (11.6)	228 (23.3)
Rural residence, n (%)	239 (100)	50 (20.9)	56 (23.4)	N/R ^c	<10 ^c	32 (13.4)	63 (26.4)
Urban residence	1053 (100)	284 (27.0)	261 (24.8)	N/R ^c	N/R ^c	124 (11.8)	260 (24.7)
Mean age at index, years, mean (SD)	72.7 (11.5)	65.5 (8.9)	69.0 (10.5)	70.7 (10.4)	71.2 (10.1)	82.2 (7.5)	80.2 (9.7)
Age at index, categories, n (%)							
≤65 years	342 (100)	154 (45.0)	105 (30.7)	34 (9.9)	N/R ^c	<10 ^c	29 (8.5)
66–75 years	373 (100)	133 (35.7)	112 (30.0)	39 (10.5)	N/R ^c	N/R ^c	58 (15.5)
≥76 years	577 (100)	47 (8.1)	100 (17.3)	43 (7.5)	17 (2.9)	134 (23.2)	236 (40.9)
Charlson comorbidity index score, n (%)							
0	648 (100)	225 (34.7)	171 (26.4)	62 (9.9)	26 (4.0)	56 (8.6)	108 (16.7)
1	374 (100)	80 (21.4)	95 (25.4)	N/R ^c	N/R ^c	49 (13.1)	98 (26.2)
≥2	270 (100)	29 (10.7)	51 (18.9)	N/R ^c	<10 ^c	51 (18.9)	117 (43.3)
T stage at initial Dx, n (%)							
T2	881 (100)	218 (24.7)	150 (17.0)	100 (11.4)	37 (4.2)	122 (13.8)	254 (28.8)
T3	167 (100)	52 (31.1)	84 (50.3)	<10 ^c	<10 ^c	<10 ^c	15 (9.0)

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T4	244 (100)	64 (26.2)	83 (34.0)	N/R ^c	<10 ^c	N/R ^c	54 (22.1)
N stage at initial Dx, n (%)							
N0	982 (100)	236 (24.0)	224 (22.8)	95 (9.7)	32 (3.3)	133 (13.5)	262 (26.7)
N1	240 (100)	N/R ^c	N/R ^c	N/R ^c	N/R ^c	N/R ^c	N/R ^c
Missing	70 (100)	N/A	N/A	N/A	N/A	N/A	N/A
Tumor grade, n (%)							
High	1185 (100)	319 (26.9)	289 (24.4)	106 (8.9)	41 (3.5)	146 (12.3)	284 (24.0)
Low/intermediate	32 (100)	N/R ^c	N/R ^c	N/R ^c	N/R ^c	N/R ^c	N/R ^c
Missing	75 (100)	N/A	N/A	N/A	N/A	N/A	N/A
Year of index, n (%)							
2010–2014	576 (100)	147 (25.5)	135 (23.4)	53 (9.2)	24 (4.2)	58 (10.1)	159 (27.6)
2015–2017	363 (100)	86 (23.7)	88 (24.2)	N/R ^c	N/R ^c	57 (15.7)	87 (24.0)
2018–2020	353 (100)	101 (28.6)	94 (26.6)	N/R ^c	<10 ^c	41 (11.6)	77 (21.8)

^aThis group includes patients who received partial cystectomy + chemotherapy (n=8). ^bThis group includes patients who received partial cystectomy + no chemotherapy (n=15). ^cIn 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.” Chemo: chemotherapy; Dx: diagnosis; MIBC: muscle-invasive bladder cancer; N/A: not available; SD: standard deviation.