The use of perioperative chemotherapy in patients undergoing radical cystectomy for bladder cancer in Quebec, Canada, 2000–2016

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Abstract

Introduction: Despite its proven benefit, studies have reported poor use of perioperative chemotherapy (POC) in bladder cancer patients undergoing radical cystectomy (RC). We evaluated POC use in Quebec between January 2000 and September 2016.

Methods: Using provincial health administrative databases, data were retrospectively collected from patients from two years before RC until December 2016 or death. Logistic regression was used to identify variables predicting POC use. Survival analyses were conducted using Cox regression. Analyzed covariates were age, sex, comorbidities, year of RC, residence and hospital region, distance to hospital, hospital type and size, and hospital's and surgeon's RC volume.

Results: A total of 790/4656 patients (17.0%) received POC. Neoadjuvant chemotherapy (NAC) use increased in recent years: 3.5% (2009), 11.2% (2012), and 20.7% (2015). POC use was increased in patients with recent surgery, a younger age, less comorbidities, residing closer to the hospital of surgery, and a high surgeon's RC volume ($p<0.05$). For patients treated between 2013 and 2016, a younger age (odds ratio [OR] 0.71; 95% confidence interval [CI] 0.64–0.80 per five years), shorter distance to the hospital (OR 0.88; 95% CI 0.77–0.99 per 50 km), surgery in an academic hospital (OR 1.86; 95% CI 1.06–3.29), and recent surgery (OR 1.34; 95% CI 1.14–1.58 per year) independently predicted NAC use. These NAC users had a significantly higher overall survival rate than patients without POC (hazard ratio 0.73; 95% CI 0.55–0.97). Limitations include missing data on pathological staging.

Conclusions: NAC/POC use increased in Quebec but was lower compared to most developed countries. Its use was lower in patients residing further from the hospital and in those treated in non-academic hospitals.

Introduction

Radical cystectomy (RC) is the standard treatment for patients with localized muscle-invasive bladder cancer.[1] In the early 2000s, randomized clinical trials concluded that patients with cT2–T4A urothelial carcinoma had better clinical outcomes when treated with neoadjuvant cisplatin-based combination chemotherapy.[2-4] These findings resulted in the recommendation of neoadjuvant chemotherapy (NAC) for this patient population in several guidelines, including those by the Canadian Urological Association in 2019.[1,5] More recent studies have further underscored the benefit of NAC use.[6,7] If patients have not received NAC, they are recommended to receive adjuvant cisplatin-based combination chemotherapy (AC) when having pT3–T4 disease and/or positive lymph nodes at surgery, as randomized controlled trials showed improved progression-free survival (PFS) and overall survival (OS) in these patients.[1,8]

However, the uptake of perioperative chemotherapy (POC) in clinical practice has been slow and varies across the world. In Nordic European countries, NAC is considered for all eligible patients.[9] In 2016, 47% of all Swedish patients with muscle-invasive bladder cancer received cisplatin-based combination chemotherapy prior to cystectomy.[10] In Japan, 83% of patients with cT2 or more advanced muscle-invasive bladder cancer received NAC in 2005–2016.[11] Other countries have been less successful in the implementation of NAC. For example, in the National Cancer Database in the United States, NAC was administered to 32.2% of patients undergoing RC for muscle-invasive bladder cancer in 2014,[12] and in South Korea, this percentage was only 8.4% in 2010–2013.[13] For Canada, the most recent data is available from the Ontario Cancer Registry, in which POC and NOC use were 35% and 19% in 2009–2013, compared to 23% and 4% in 1994–2008, respectively.[14] While this is a significant improvement, POC use differed across regions in Ontario, and was lower in older patients, patients with a lower socioeconomic status, and those treated by low-volume surgeons.

We studied POC use in a large cohort of bladder cancer patients undergoing RC in the Canadian province of Quebec between 2000 and 2016. We evaluated changes in chemotherapy use over the years, determinants for POC use and the clinical outcome of patients based on NAC and AC use.

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Methods

Study design, data acquisition, and study population

This is a retrospective study of patients undergoing RC for bladder cancer in Quebec. The study has been approved by the research ethics board of the McGill University Health Centre (project number 2014-1059; latest renewal August 31, 2018). The cohort was collected using data from the Quebec provincial health administrative agencies Régie de l'assurance maladie du Québec (RAMQ), Ministère de la Santé et des Services Sociaux (MSSS), and Institut de la statistique du Québec (ISQ). In total, 5148 patients were identified who underwent RC between January 2000 and September 2016. This included all RCs conducted in the province in this timeframe, since these surgeries are only conducted in public hospitals in Quebec. During a rigorous selection process, we excluded 492 patients who had RC for other indications than bladder cancer or who had their cystectomy performed by surgeons other than urologists, as previously described.[15]

All patient data were collected from two years before the RC until death or the last day the patient was known to be alive before January 1, 2017. The collected data consisted of all medical procedures performed in public hospitals, all hospital and emergency room admissions, intensive care unit stays, all prescribed medication bought in outpatient pharmacies by individuals covered by the Public Prescription Drug Insurance Plan (universal health coverage), and all deaths (including date and cause of death) in Quebec.

Data analyses

NAC use was defined as patients who had a medical act code for chemotherapy administration within the three months preceding the index date. Patients were considered to have received AC when they had a code for chemotherapy within 90 days after postoperative hospital discharge and did not have NAC.

Charlson comorbidity index is a number between 0 and 33 based on a patient's age and comorbidities,[16,17] and was estimated by evaluation of filed diagnostic codes and medication specifically used for certain diseases. We included codes filed both prior to and after RC in our calculation of comorbidity indices. All patients had a minimum index of 2, since all patients had a solid tumor. Region of residence and hospital were categorized into three groups: urban regions included cities with >400 000 inhabitants, rural regions did not have a city with >100 000 inhabitants, and an intermediate group included all regions with cities of 100 000–400 000 inhabitants. Distance between a patient's residence and the hospital of RC was calculated as the driving distance between the center of a patient's postal code and the hospital, as described previously.[15] University-affiliated hospitals included all hospitals that train urology residents. Hospital size was determined based on the number of beds (<250, 250–499, or ≥500 beds). A hospital's or surgeon's RC volume was calculated by dividing the total number of RCs by the years between the first and last RC for bladder cancer of that hospital/surgeon in our database.

OS was calculated as the time between RC and death (or last followup). We described the definition of bladder cancer-specific deaths previously.[15] Patients who died from other causes than bladder cancer were censored at the time of death in bladder cancer-specific survival calculations. Recurrence-free survival was defined as the time between RC and first administration of chemo- or radiotherapy after surgery, or death due to bladder cancer. All chemo- and radiotherapy administered within three months after postoperative hospital discharge was considered adjuvant and/or salvage therapy and, therefore, this was not considered a recurrence. Instead, these patients were considered to have recurred when there was an interval of ≥3 months between the adjuvant/salvage therapy and new chemo- or radiotherapy, or when the patients died from bladder cancer.

Statistical analyses

All statistical analyses were conducted using Stata (v15.1, Statacorp, College Station, TX, U.S.). Baseline characteristics were displayed as the median with interquartile range (IQR) for continuous variables. Odds ratios (OR) and their respective 95% confidence intervals (CI) were calculated using univariable and multivariable logistic regression models. In the multivariable models, we mutually adjusted for all variables included in the univariable analysis. In these analyses, year of surgery, age, Charlson comorbidity index, distance between the patient's residence and hospital of surgery, and hospital's and surgeons' RC volume were analyzed as continuous variables. Sex, region of residence, region of the hospital of surgery, and hospital type and size were analyzed as categorical variables. Patients with missing data were excluded from multivariable analyses. Survival analyses were conducted using the Kaplan-Meier method.[18] Followup time was calculated using the reverse Kaplan-Meier method.[19] Hazard ratios (HR) were calculated using Cox regression.[20] In multivariable Cox proportional hazards models, we adjusted for the same variables as in logistic regression models.

Results

We identified 4656 patients with bladder cancer who had a RC performed in Quebec between January 2000 and September 2016. Of these, 324 (7.0%) and 466 (10.0%)

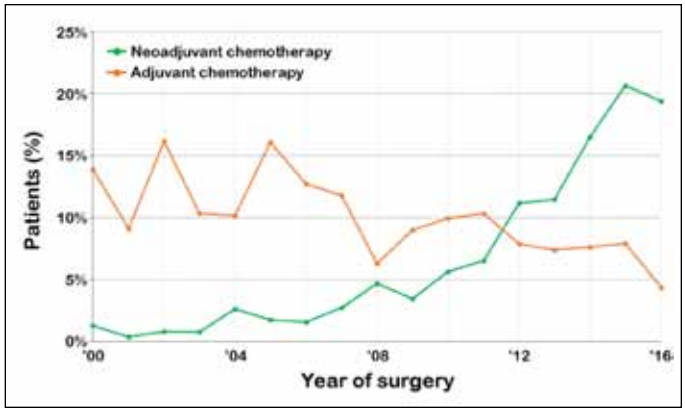

Fig. 1. Percentage of patients receiving neoadjuvant and adjuvant chemotherapy, by year.

received NAC or AC, respectively. Over the years, the use of NAC has been increasing, with rates surpassing 10% in 2012, and 20% in 2015 (Fig. 1). Between 2000 and 2011, 9–17% of patients received AC per year; however, AC use dropped below 8% after 2011. Baseline and surgery characteristics of patients are displayed in Table 1. Median age of patients receiving POC was 64 years (IQR 58–70) vs. 70 years (IQR 63–76) in the rest of the cohort (OR 0.76 per five-year increment; 95% CI 0.73–0.79) (Table 2). Approximately three-quarters of the patients were male. Patients receiving POC had a significantly lower Charlson comorbidity index (median 5 vs. 7; OR 0.78; 95% CI 0.75–0.81). Slightly over half of the patients were treated in university-affiliated hospitals. The median time between the last cystoscopy/transurethral resection of the bladder (TURB) and RC was 49 days (IQR 28–76), 42 days (IQR 27–62 days), and 126 days (IQR 56–167 days) for patients who did not receive POC and those who received AC or NAC, respectively.

In a multivariable analysis (Table 2), year of surgery, age, Charlson comorbidity index, distance between the residence and hospital, hospital size, and hospital's and

Table 1. Baseline characteristics

	No perioperative chemotherapy	Perioperative chemotherapy	Neoadjuvant chemotherapy	Adjuvant chemotherapy
Number of patients	3866	790	324	466
Age	70 (63–76)	64 (58–70)	64 (58–69)	64 (58–70)
Sex				
Male	2939 (76.0%)	607 (76.8%)	243 (75.0%)	364 (78.1%)
Female	927 (24.0%)	183 (23.2%)	81 (25.0%)	102 (21.9%)
Charlson comorbidity index	7 (5–8)	5 (4–7)	5 (4–7)	5 (4–7)
Index ≥10	12.9% (499/3866)	3.8% (30/790)	2.2% (7/324)	4.9% (23/466)
Region of residence				
Regions with cities with >400 000 inhabitants	1454 (37.6%)	291 (36.8%)	110 (34.0%)	181 (38.8%)
Regions with cities with 100 000–400 000 inhabitants	2121 (54.9%)	450 (57.0%)	194 (59.9%)	256 (54.9%)
Rural regions (largest city in region <100 000 inhabitants)	265 (6.9%)	39 (4.9%)	14 (4.3%)	25 (5.4%)
Unknown	26 (0.7%)	10 (1.3%)	6 (1.9%)	4 (0.9%)
Region of hospital of surgery				
Regions with cities with >400 000 inhabitants	2301 (59.5%)	475 (60.1%)	197 (60.8%)	278 (59.7%)
Regions with cities with 100 000–250 000 inhabitants	1524 (39.4%)	309 (39.1%)	127 (39.2%)	182 (39.1%)
Rural regions (largest city in region <100 000 inhabitants)	41 (1.1%)	6 (0.8%)	0 (0.0%)	6 (1.3%)
Distance (in km) between residence and hospital	20 (8–77)	21 (9–57)	24 (11–59)	19 (8–57)
Type of hospital				
University-affiliated hospital	1960 (50.7%)	427 (54.1%)	199 (61.4%)	228 (48.9%)
Other hospital	1906 (49.3%)	363 (45.9%)	125 (38.6%)	238 (51.1%)
Hospital size				
<250 beds	287 (7.4%)	53 (6.7%)	12 (3.7%)	41 (8.8%)
250–499 beds	1888 (48.8%)	432 (54.7%)	152 (46.9%)	280 (60.1%)
≥500 beds	1691 (43.7%)	304 (38.5%)	159 (49.1%)	145 (31.1%)
Unknown	0 (0.0%)	1 (0.1%)	1 (0.3%)	0 (0.0%)
Radical cystectomy volume/active year				
Hospital	13.4 (7.8–32.2)	13.8 (7.8–32.2)	16.1 (9.9–32.2)	12.8 (5.8–32.2)
Surgeon	7.3 (4.7–13.1)	8.6 (4.9–13.4)	10.3 (5.7–13.4)	8.1 (4.7–13.4)
Time (days) from last cystoscopy/TURB to surgery	49 (28–76)	56 (32–118)	126 (56–167)	42 (27–62)

Continuous variables are displayed as the median (interquartile range). Categorical variables are displayed as patient number (percentage). TURB: transurethral resection of the bladder.

Table 2. Predictors for perioperative chemotherapy use

	Univariable	Multivariable[1]
Year of surgery (per 1-year increment)	**1.06 (1.04–1.08)**	**1.06 (1.05–1.08)**
Age (per 5-year increment)	**0.76 (0.73–0.79)**	**0.81 (0.77–0.86)**
Sex (female; ref.: male)	0.96 (0.80–1.15)	0.94 (0.78–1.14)
Charlson's comorbidity index, per-point increment	**0.78 (0.75–0.81)**	**0.88 (0.84–0.92)**
Region of residence (ref.: regions with cities with >400 000 inhabitants)		
Regions with cities with 100 000–400 000 inhabitants	1.06 (0.90–1.25)	1.06 (0.84–1.33)
Rural regions (largest city in region <100 000 inhabitants)	0.74 (0.51–1.05)	1.14 (0.60–2.20)
Region of hospital of surgery (ref.: regions with cities with >400 000 inhabitants)		
Regions with cities with 100 000–400 000 inhabitants	0.98 (0.84–1.15)	0.93 (0.71–1.21)
Rural regions (largest city in region <100 000 inhabitants)	0.71 (0.30–1.68)	1.10 (0.38–3.17)
Distance between residence and hospital (per 50 km increase)	**0.96 (0.93–0.99)**	**0.91 (0.86–0.97)**
Type of hospital, university-affiliated	1.14 (0.98–1.33)	1.02 (0.77–1.34)
Hospital size (ref.: ≥500 beds)		
250–499 beds	**1.27 (1.08–1.49)**	**1.45 (1.20–1.76)**
<250 beds	1.03 (0.75–1.41)	1.01 (0.70–1.45)
Hospital's radical cystectomy volume (per 5/active year increment)	1.02 (1.00–1.05)	**0.91 (0.87–0.96)**
Surgeon's radical cystectomy volume (per 5/active year increment)	**1.13 (1.06–1.20)**	**1.33 (1.16–1.52)**

Values represent odds ratios with 95% confidence intervals. [1]All variables were mutually adjusted for each other.

surgeon's RC volume were independent predictors for POC use, with adjusted ORs of 1.06 (95% CI 1.05–1.08 per one-year increment), 0.81 (95% CI 0.77–0.86 per five-year increment), 0.88 (95% CI 0.84–0.92, per point increment), 0.91 (95% CI 0.86–0.97 per 50 km increase), 1.45 (95% CI 1.20–1.76 comparing hospitals with 250–499 beds to those with ≥500 beds), 0.91 (95% CI 0.87–0.96 per five/active year increment), 1.33 (95% CI 1.16–1.52, per five/active year increment), respectively. When analyzing patients who received NAC and AC as separate groups, independent predictors for NAC (Supplementary Table 1) were year of surgery (adjusted OR 1.30; 95% CI 1.26–1.35), age (adjusted OR 0.76; 95% CI 0.71–0.82), surgery in a university-affiliated hospital (adjusted OR 1.69; 95% CI 1.12–2.55), and hospital's RC volume (adjusted OR 0.89; 95% CI 0.82–0.96). Year of surgery (adjusted OR 0.95; 95% CI 0.93–0.97), age (adjusted OR 0.87; 95% CI 0.82–0.92), Charlson comorbidity index (adjusted OR 0.86; 95% CI 0.81–0.91), distance to the hospital (adjusted OR 0.90; 95% CI 0.83–0.97), surgery in a university-affiliated hospital (adjusted OR 0.70; 95% CI 0.50–1.00), hospital size (adjusted OR 1.71; 95% CI 1.34–2.17), and surgeon's RC volume (adjusted OR 1.34; 95% CI 1.14–1.59) independently predicted AC use (Supplementary Table 2).

With a median followup time of 7.4 years (95% CI 7.0–7.7), median OS, bladder cancer-specific, and recurrence-free survival were 3.3 years (95% CI 3.0–3.6 years), 6.5 years (95% CI 5.8–7.4), and 4.6 years (95% CI 4.0–5.1), respectively. Patients who received AC had significantly worse OS (adjusted HR 1.32; 95% CI 1.17–1.48), bladder cancer-specific survival (adjusted HR 1.66; 95% CI 1.45–1.89), and recurrence-free survival (adjusted HR 1.71; 95% CI 1.51–1.93) than those without AC (Fig. 2). Intriguingly, patients who received NAC also had significantly worse bladder cancer-specific survival (adjusted HR 1.29; 95% CI 1.05–1.57) and recurrence-free survival (adjusted HR 1.66; 95% CI 1.45–1.89) (Figs. 2B, 2C).

Next, we evaluated whether we could identify specific subgroups who had a worse or better clinical outcome when receiving NAC (Table 3). OS was significantly worse in patients who received NAC in the years 2000–2012 compared to those not receiving NAC in the same period (adjusted HR 1.41; 95% CI 1.13–1.76). In 2013–2016, patients who had received NAC had significantly better OS rates in univariable analyses (OR 0.73; 95% CI 0.55–0.97), but this difference was not significant when adjusting for differences in baseline characteristics (adjusted OR 0.78; 95% CI 0.58–1.06). Similar results were observed for bladder cancer-specific survival, in which the adjusted HR for NAC use was 1.59 (95% CI 1.24–2.03) for those treated in 2000–2012, and 0.87 (95% CI 0.62–1.21) for those treated in 2013–2016. Indeed, when comparing Kaplan-Meier curves of patients treated in 2013–2016, there was significant separation of the OS curves (Fig. 3A), while the bladder cancer-specific and recurrence-free survival curves were mostly overlapping (Figs. 3B, 3C). Patients treated with NAC in 2013–2016 had significantly better OS compared to those without NAC (Supplementary Fig. 1). Furthermore, comparing patients treated with NAC in 2000–2012 to those treated with NAC in 2013–2016, survival had significantly improved in recent years (Supplementary Fig. 2). For all other subgroups evaluated (Table 3), patients in all subgroups tended to have a worse bladder cancer-specific survival when receiving NAC compared to those without NAC. Bladder cancer-specific survival was significantly worse for patients receiving NAC and aged <70 years (adjusted HR 1.38; 95% CI 1.09–1.75), men (adjusted HR 1.28; 95% CI 1.02–1.61), patients with a Charlson comorbidity index below (adjusted HR 1.29; 95% CI 1.01–1.66), or at/above 7 (adjusted HR

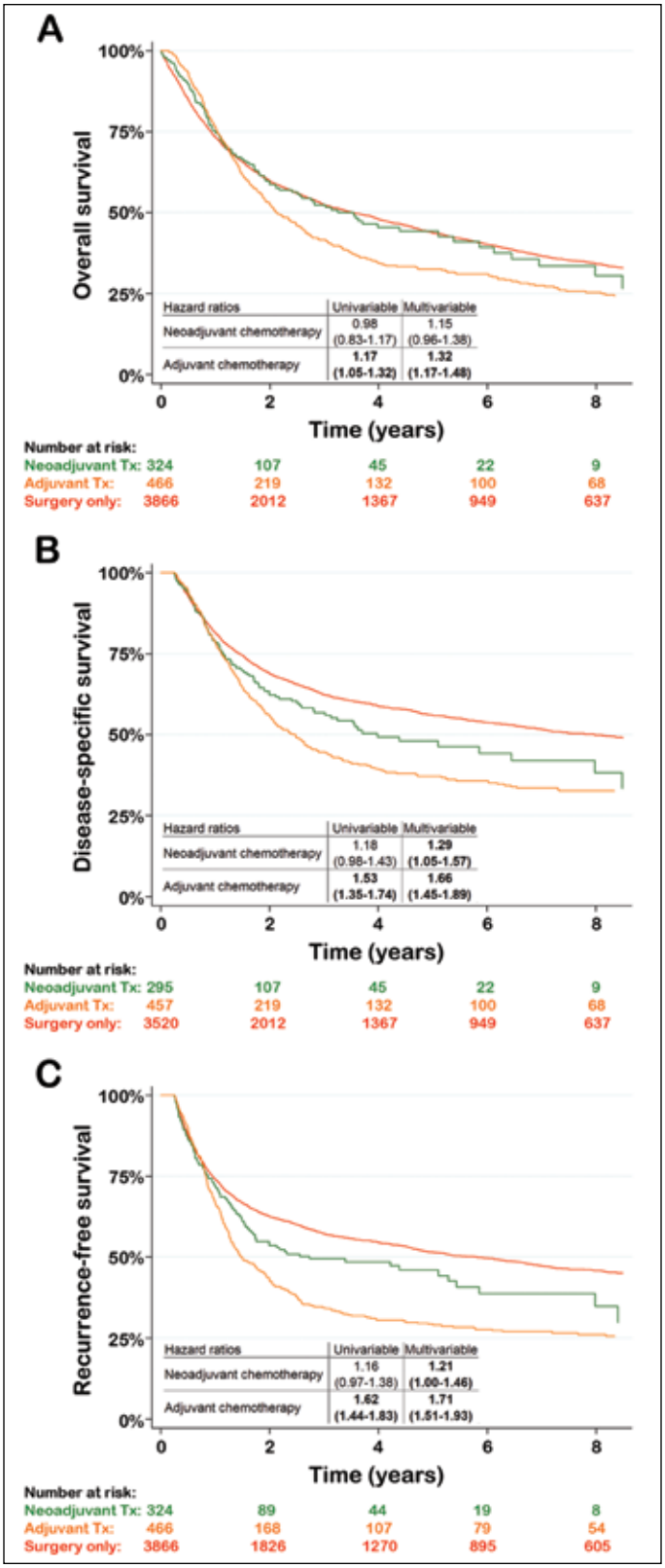

Fig. 2. (A) Overall; ***(B)*** bladder cancer-specific; and ***(C)*** recurrence-free survival. Patients were stratified by (neo)adjuvant chemotherapy use. Covariates in the multivariable model included year of surgery, age, sex, Charlson comorbidity index, region of residence and hospital, distance between residence and hospital, type of hospital, hospital size, and hospital's and surgeons' radical cystectomy volume.

1.47; 95% CI 1.05–2.06), or surgery in an university-affiliated hospital (adjusted HR 1.50; 95% CI 1.16–1.93).

Considering the relative difference in clinical outcome in patients treated with NAC and surgery in 2000–2012 and those treated in 2013–2016, we evaluated which variables independently predicted NAC use in the more recent cohort (Table 4). Baseline and surgery characteristics of this cohort are reported in Supplementary Table 3. In a multivariable analysis, NAC use was higher in patients who were treated more recently (adjusted OR 1.34; 95% CI 1.14–1.58 per one-year increment), younger patients (adjusted OR 0.71; 95% CI 0.64–0.80 per five-year increment), patients living closer to the hospital of surgery (adjusted OR 0.88; 95% CI 0.77–0.99 per 50 km increment), and patients treated in university-affiliated hospitals (adjusted OR 1.86; 95% CI 1.06–3.29). Of all patients undergoing RC in university-affiliated hospitals in 2013–2016, 18.7% (126/673) received NAC, compared to 14.7% (75/509) in non-academic hospitals. In 2015–2016, these percentages had increased to 23.0% (75/326) and 16.3% (38/233), respectively, indicating a continuing trend towards increased NAC use in both hospital types.

Discussion

This is the first study that evaluated the use of POC in bladder cancer patients undergoing RC in Quebec. POC use, particularly NAC, has increased since 2000. As AC is only recommended for patients who did not receive NAC, the increase in NAC use resulted in a decrease in AC use, 2012 being the first year that NAC surpassed AC use. In 2015, POC use was 28.6%, with 20.7% of the patients receiving NAC and 7.9% of patients receiving AC. Although POC use is increasing, aforementioned percentages are lower than generally reported in other countries.[11,12]

Similar to other recent studies, chemotherapy use was similar in men and women, but we observed a lower use of POC, both for neoadjuvant and AC, in older patients and those with a higher Charlson comorbidity index.[12] This likely reflects decreased eligibility for POC in these subgroups.[1] Interestingly, a longer distance between a patient's residence and the hospital of surgery independently predicted decreased chemotherapy use, both for POC use in the whole cohort and for NAC use in patients treated in 2013–2016. As such, we are the first Canadian study to identify distance to the hospital as a predictor for NAC and POC use. While we do not have staging information available, it is unlikely that patients residing further from the hospital would have less advanced tumors at RC. It is more probable that reduced accessibility to care resulted in the observed difference. One study from the United States also observed that increased travel distance was negatively associated with POC use.[21] This is a concern for sparsely populated countries such as Canada, and may

Table 3. Hazard ratios for death in patients receiving neoadjuvant chemotherapy, by subgroups

	OS		DSS	
	Univariable	**Multivariable**	**Univariable**	**Multivariable**
Age ≥70 years	0.98 (0.71–1.35)	1.08 (0.78–1.50)	1.09 (0.75–1.58)	1.16 (0.80–1.70)
Age <70 years	1.18 (0.96–1.45)	1.19 (0.96–1.48)	**1.39 (1.11–1.74)**	**1.38 (1.09–1.75)**
Men	0.95 (0.78–1.16)	1.14 (0.93–1.41)	1.16 (0.93–1.45)	**1.28 (1.02–1.61)**
Women	1.07 (0.77–1.50)	1.18 (0.83–1.68)	1.24 (0.85–1.79)	1.32 (0.89–1.97)
CCI ≥7	1.12 (0.83–1.51)	1.21 (0.89–1.64)	**1.41 (1.02–1.96)**	**1.47 (1.05–2.06)**
CCI <7	0.92 (0.75–1.14)	1.18 (0.95–1.48)	1.06 (0.84–1.34)	1.29 (1.01–1.66)
Year of surgery 2013–2016	**0.73 (0.55–0.97)**	0.78 (0.58–1.06)	0.87 (0.64–1.19)	0.87 (0.62–1.21)
Year of surgery 2000–2012	1.20 (0.96–1.49)	**1.41 (1.13–1.76)**	**1.44 (1.13–1.83)**	**1.59 (1.24–2.03)**
Surgery in hospital not affiliated with a university	0.84 (0.64–1.11)	1.00 (0.76–1.33)	1.00 (0.74–1.36)	1.10 (0.80–1.51)
Surgery in hospital affiliated with a university	1.11 (0.89–1.38)	**1.31 (1.04–1.65)**	**1.33 (1.04–1.69)**	**1.50 (1.16–1.93)**

In multivariable analyses, we adjusted for year of surgery, age, sex, Charlson comorbidity index, region of residence and hospital, distance between residence and hospital, type of hospital, hospital size, and hospital's and surgeons' radical cystectomy volume. CCI: Charlson comorbidity index; DSS: disease-specific survival; OS: overall survival.

be an important explanation as to why POC use in both Quebec and Ontario[14] is lower than in most other countries. In a previously published manuscript in which we used the same database as in the current manuscript, we reported that patients residing further from the hospital of surgery had worse overall and bladder cancer-specific survival.[15] The reduced use of POC in patients living further away from the hospital of surgery might contribute to the worse long-term outcome of these patients. While future studies will need to confirm such a correlation, based on our data, we think it is important for policymakers to ensure appropriate accessibility to POC for patients living in remote areas.

In our cohort, NAC use was significantly higher in university-affiliated hospitals, both in the whole cohort and in the patients treated in 2013–2016. This may indicate slower adaptation to the new guidelines in non-academic hospitals. Alternatively, various authors, including Raphael and Booth,[22] have suggested that POC use would increase with increased referrals of patients to medical oncologists and multidisciplinary teams. Perhaps the access to medical oncologists and/or the availability of multidisciplinary teams is lower in non-academic hospitals, and/or physicians in non-academic hospitals referred suitable candidates for POC to academic hospitals.

Several considerations need to be made when interpreting our findings. The Quebec administrative databases do not contain information on pathological or clinical staging of tumors, and due to privacy legislation, we are unable to link these data to pathology reports in hospitals. This lack of information is crucial for interpretation of our analyses. For example, patients who received AC consistently had a worse clinical outcome. However, since adjuvant therapy is only recommended for patients with more advanced bladder cancer, this difference is likely caused by selection bias. Similarly, although OS was improved in patients treated with NAC in 2013–2016, in other survival curves patients who received NAC had similar or even worse clinical outcome than those who did not receive POC. Previous studies have reported that NAC use is relatively higher in patients with more advanced bladder cancer.[12] Since NAC is increasingly administered in our cohort, it is plausible that more recently, patients with less advanced bladder cancer increasingly received NAC, resulting in the relative improved survival rates for NAC. This hypothesis is supported by the fact that patients treated with NAC in 2013–2016 had better survival rates than those treated before 2013. Also, misclassification may have occurred. For example, the Charlson comorbidity index would have been incorrect if medical staff incorrectly filed diagnostic codes, or physicians may have incorrectly filed or forgot to file administration of chemotherapy. We were unable to determine the exact chemotherapy regimen administered to patients. Due to database limitations, we had to assume that patients who recurred received treatment for their recurrence or died within a short period of time, thereby overestimating the time to recurrence. Similarly, we may have underestimated the time to recurrence if patients initiated adjuvant therapy more than three months after post-operative discharge. Finally, in the subgroup analyses, some

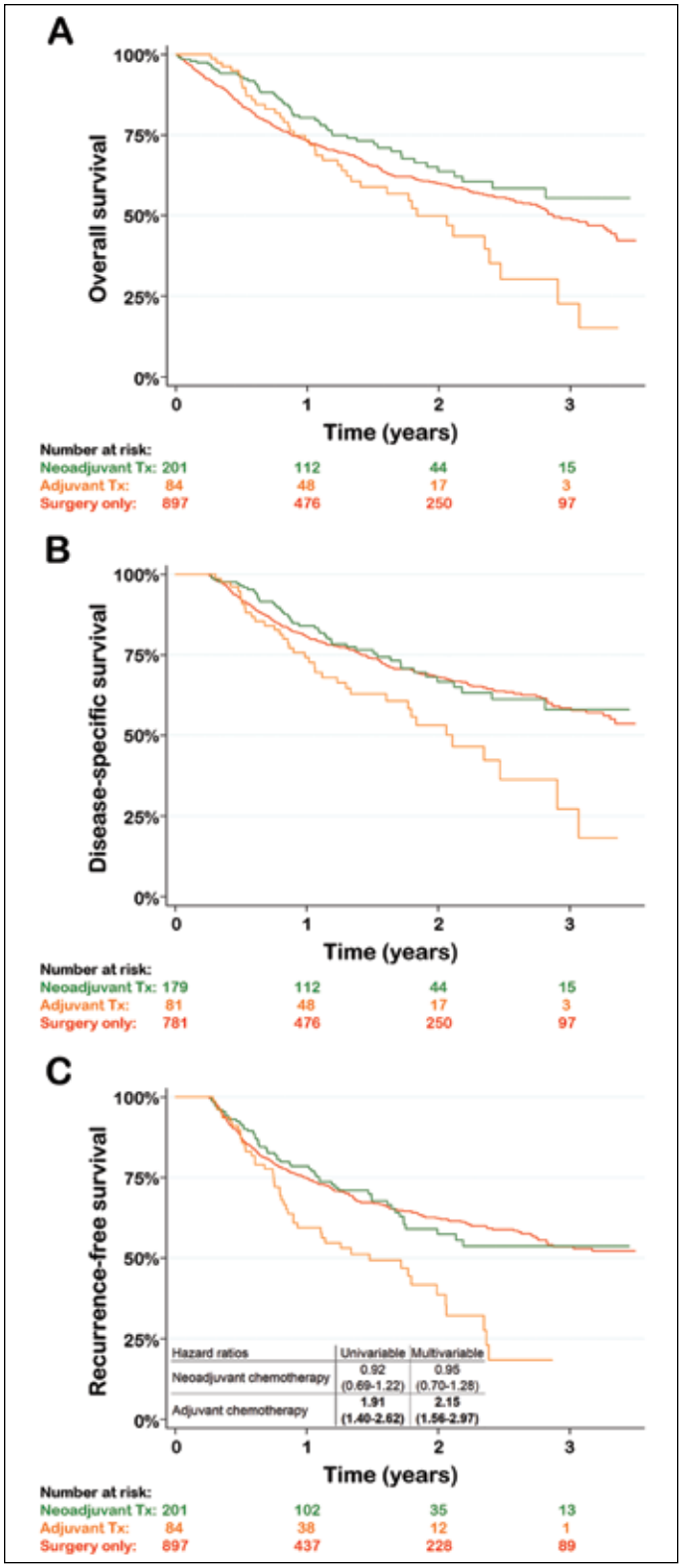

Fig. 3. (A) Overall; ***(B)*** bladder cancer-specific; and ***(C)*** recurrence-free survival of patients treated from 2013–2016. Patients were stratified by (neo)adjuvant chemotherapy use. Covariates in the multivariable model included year of surgery, age, sex, Charlson comorbidity index, region of residence and hospital, distance between residence and hospital, type of hospital, hospital size, and hospital's and surgeons' radical cystectomy volume.

Table 4. Predictors for neoadjuvant chemotherapy use in patients undergoing radical cystectomy in 2013–2016

	Univariable	Multivariable[1]
Year of surgery (per 1-year increment)	**1.24 (1.07–1.44)**	**1.34 (1.14–1.58)**
Age (per 5-year increment)	**0.71 (0.66–0.77)**	**0.71 (0.64–0.80)**
Sex (female; ref.: male)	1.04 (0.72–1.49)	1.06 (0.72–1.55)
Charlson comorbidity index, per-point increment	0.78 (0.72–0.85)	0.98 (0.89–1.09)
Region of residence (ref.: regions with cities with >400 000 inhabitants)		
Regions with cities with 100 000–400 000 inhabitants	0.97 (0.69–1.34)	0.87 (0.55–1.38)
Rural regions (largest city in region <100 000 inhabitants)	**0.43 (0.19–0.97)**	1.35 (0.35–5.22)
Region of hospital of surgery (ref.: regions with cities with >400 000 inhabitants)		
Regions with cities with 100 000–400 000 inhabitants	0.98 (0.72–1.33)	1.23 (0.73–2.07)
Distance between residence and hospital (per 50 km increase)	**0.91 (0.84–0.97)**	**0.88 (0.77–0.99)**
Type of hospital, university-affiliated	**1.33 (0.98–1.82)**	**1.86 (1.06–3.29)**
Hospital size (ref.: ≥500 beds)		
250–499 beds	**0.64 (0.47–0.88)**	0.93 (0.61–1.42)
<250 beds	0.52 (0.25–1.08)	0.62 (0.27–1.45)
Hospital's radical cystectomy volume (per 5/active year increment)	0.97 (0.92–1.02)	0.91 (0.81–1.01)
Surgeon's radical cystectomy volume (per 5/active year increment)	0.98 (0.86–1.12)	1.12 (0.85–1.46)

[1]All variables were mutually adjusted for each other. Values represent odds ratios with 95% confidence intervals. RC: radical cystectomy.

groups had low patient numbers, decreasing the power of these analyses.

The strengths of our study include the large cohort size, virtually including all cases of RC in Quebec, the relatively long followup, and extensive demographic and administrative information.

Conclusions

The use of POC, and particularly NAC, has increased in bladder cancer patients undergoing RC in Quebec between 2000 and 2016, but is still lower than its use in other developed countries. Distance between a patient's residence and the hospital of surgery was inversely associated with POC receipt, including NAC. Other predictors for increased POC use included a lower age, fewer comorbidities, surgery in academic hospitals, and treatment by higher-volume surgeons.

Competing interests: Dr. Kassouf has received grants/honoraria from Amgen, Astellas, and Janssen. Dr. Tanguay has been an advisory board member for Ipsen, Merck, Roche, and Sanofi; has received grants and/or honoraria from Janssen; and has participated in clinical trials suported by AstraZeneca and Roche. Dr. Aprikian has been an advisory board member for Astellas and Bayer; has received honoraria from Abbvie, Astellas, Bayer, Janssen, and Sanofi; and has participated in clinical trials suported by Astellas. Dr. Wissing reports no competing personal or financial interests related to this work.

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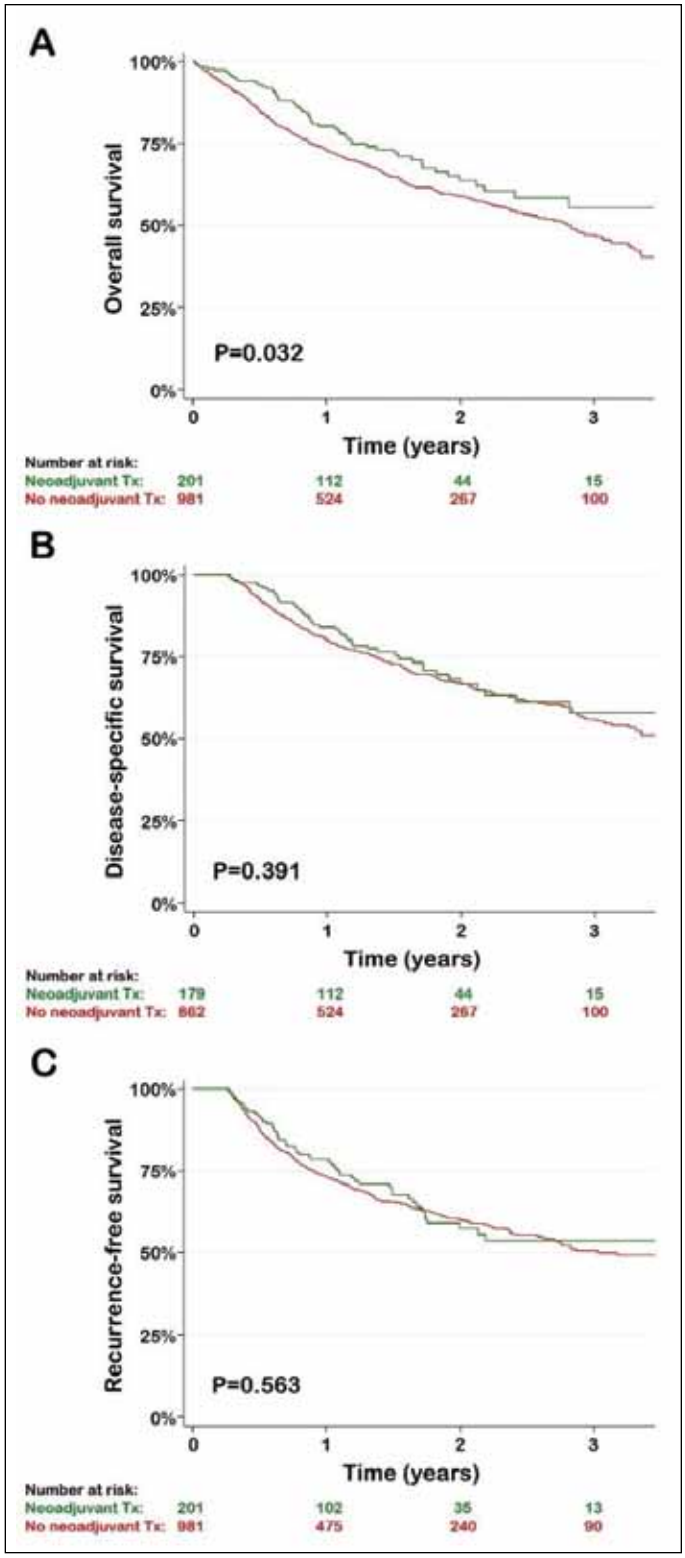
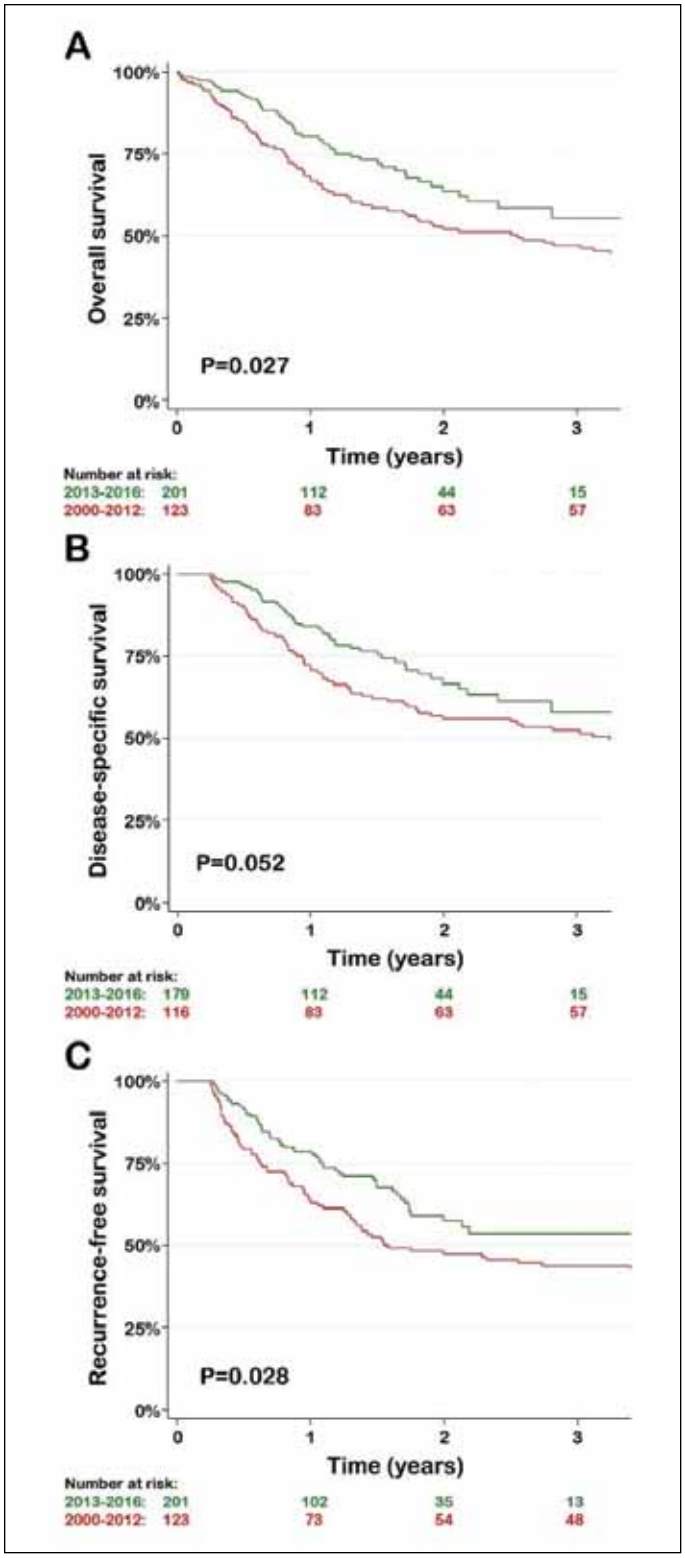


Supplementary Fig. 1. (A) Overall; ***(B)*** bladder cancer-specific; and ***(C)*** recurrence-free survival of patients treated from 2013–2016. Patients were stratified by neoadjuvant chemotherapy use. P values were calculated using log-rank tests.



Supplementary Fig. 2. Comparison of ***(A)*** overall; ***(B)*** bladder cancer-specific; and ***(C)*** recurrence-free survival in patients treated with neoadjuvant chemotherapy from 2000–2012 to those treated from 2013–2016. P values were calculated using log-rank tests.

Supplementary Table 1. Predictors for neoadjuvant chemotherapy use

	Univariable	Multivariable[1]
Year of surgery (per 1-year increment)	**1.28 (1.24–1.33)**	**1.30 (1.26–1.35)**
Age (per 5-year increment)	**0.78 (0.74–0.83)**	**0.76 (0.71–0.82)**
Sex (female; ref.: male)	1.07 (0.82–1.39)	1.13 (0.85–1.50)
Charlson comorbidity index, per point increment	**0.78 (0.73–0.82)**	0.95 (0.88–1.02)
Region of residence (ref.:regions with cities with >400 000 inhabitants)		
Regions with cities with 100 000–400 000 inhabitants	1.21 (0.95–1.55)	0.99 (0.71–1.38)
Rural regions (largest city in region <100 000 inhabitants)	0.72 (0.41–1.27)	0.92 (0.34–2.50)
Region of hospital (ref.: regions with cities with >400 000 inhabitants)		
Regions with cities with 100 000–400 000 inhabitants	0.97 (0.77–1.23)	1.06 (0.72–1.57)
Distance between residence and hospital (per 50 km increase)	0.99 (0.95–1.03)	0.95 (0.87–1.03)
Type of hospital, university-affiliated	**1.56 (1.24–1.97)**	**1.69 (1.12–2.55)**
Hospital size (ref.: ≥500 beds)		
250–499 beds	0.81 (0.64–1.02)	1.19 (0.89–1.59)
<250 beds	**0.42 (0.23–0.77)**	0.54 (0.28–1.08)
Hospital's radical cystectomy volume (per 5/active year increment)	1.03 (0.99–1.07)	**0.89 (0.82–0.96)**
Surgeon's radical cystectomy volume (per 5/active year increment)	**1.15 (1.05–1.26)**	1.16 (0.95–1.42)

Values represent odds ratios with 95% confidence intervals. [1]All variables were mutually adjusted for each other.

Supplementary Table 2. Predictors for adjuvant chemotherapy use

	Univariable	Multivariable[1]
Year of surgery (per 1-year increment)	**0.95 (0.93–0.97)**	**0.95 (0.93–0.97)**
Age (per 5-year increment)	**0.80 (0.76–0.83)**	**0.87 (0.82–0.92)**
Sex (female; ref.: male)	0.88 (0.70–1.11)	0.83 (0.66–1.05)
Charlson comorbidity index, per point increment	**0.81 (0.77–0.85)**	**0.86 (0.81–0.91)**
Region of residence (ref.:regions with cities with >400 000 inhabitants)		
Regions with cities with 100 000–400 000 inhabitants	0.96 (0.78–1.17)	1.09 (0.82–1.45)
Rural regions (largest city in region <100 000 inhabitants)	0.77 (0.50–1.20)	1.30 (0.58–2.88)
Region of hospital (ref.: regions with cities with >400 000 inhabitants)		
Regions with cities with 100 000–400 000 inhabitants	0.99 (0.81–1.21)	0.82 (0.59–1.13)
Rural regions (largest city in region <100 000 inhabitants)	1.31 (0.55–3.12)	0.98 (0.31–3.07)
Distance between residence and hospital (per 50 km increase)	**0.95 (0.90–0.99)**	**0.90 (0.83–0.97)**
Type of hospital, university-affiliated	0.90 (0.74–1.09)	**0.70 (0.50–1.00)**
Hospital size (ref.: ≥500 beds)		
250–499 beds	**1.75 (1.42–2.16)**	**1.71 (1.34–2.17)**
<250 beds	**1.75 (1.21–2.53)**	1.40 (0.93–2.12)
Hospital's radical cystectomy volume (per 5/active year increment)	1.01 (0.98–1.04)	0.95 (0.89–1.02)
Surgeon's radical cystectomy volume (per 5/active year increment)	**1.09 (1.01–1.18)**	**1.34 (1.14–1.59)**

Values represent odds ratios with 95% confidence intervals. [1]All variables were mutually adjusted for each other.

Supplementary Table 3. Baseline characteristics of patients treated from 2013–2016

	No perioperative chemotherapy	Perioperative chemotherapy	Neoadjuvant chemotherapy	Adjuvant chemotherapy
Number of patients	897	285	201	84
Age	71 (64–76)	65 (59–70)	64 (58–69)	67 (61–72)
Sex				
Male	694 (77.4%)	218 (76.5%)	154 (76.6%)	64 (76.2%)
Female	203 (22.6%)	67 (23.5%)	47 (23.4%)	20 (23.8%)
Charlson comorbidity index	6 (5–8)	5 (4–6)	5 (4–6)	5 (4–7)
Index ≥10	78 (8.7%)	6 (2.1%)	4 (2.0%)	2 (2.4%)
Region of residence				
Regions with cities with >400 000 inhabitants	277 (30.9%)	91 (31.9%)	65 (32.3%)	26 (31.0%)
Regions with cities with 100 000–400 000 inhabitants	537 (59.9%)	180 (63.2%)	123 (61.2%)	57 (67.9%)
Rural regions (largest city in region <100 000 inhabitants)	75 (8.4%)	8 (2.8%)	7 (3.5%)	1 (1.2%)
Unknown	8 (0.9%)	6 (2.1%)	6 (3.0%)	0 (0.0%)
Region of hospital of surgery				
Regions with cities with >400 000 inhabitants	530 (59.1%)	159 (55.8%)	118 (58.7%)	41 (48.8%)
Regions with cities with 100 000–250 000 inhabitants	367 (40.9%)	126 (44.2%)	83 (41.3%)	43 (51.2%)
Rural regions (largest city in region <100 000 inhabitants)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Distance (in km) between residence and hospital	28 (10–111)	22 (9–56)	23 (10–56)	18 (7–58)
Type of hospital				
University-affiliated hospital	511 (57.0%)	162 (56.8%)	126 (62.7%)	36 (42.9%)
Other hospital	386 (43.0%)	123 (43.2%)	75 (37.3%)	48 (57.1%)
Hospital size				
<250 beds	51 (5.7%)	25 (8.8%)	9 (4.5%)	16 (19.0%)
250–499 beds	432 (48.2%)	114 (40.0%)	77 (38.3%)	37 (44.0%)
≥500 beds	414 (46.2%)	145 (50.9%)	114 (56.7%)	31 (36.9%)
Unknown	0 (0.0%)	1 (0.4%)	1 (0.5%)	0 (0.0%)
Radical cystectomy volume/active year				
Hospital	16.1 (9.9–32.2)	16.1 (10.9–32.2)	16.1 (12.8–32.2)	13.4 (9.9–23.9)
Surgeon	8.9 (5.7–13.4)	9.3 (5.7–13.4)	10.3 (5.7–13.4)	8.6 (5.0–13.1)
Time (days) from cystoscopy/TURB to surgery	56 (33–85)	106 (50–155)	133 (95–167)	52 (33–83)

Continuous variables are displayed as the median (interquartile range). Categorical variables are displayed as patient number (percentage). TURB: transurethral resection of the bladder.