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ORIGINAL ARTICLE

Impact of neoadjuvant chemotherapy on short-term complications and survival following radical cystectomy

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Abstract

Objectives To compare perioperative and short-term postoperative complication rates between patients receiving radical cystectomy (RC) after neoadjuvant chemotherapy (NAC) and patients undergoing RC alone. Secondary objectives were to compare overall survival (OS) and cancer-specific survival (CSS).

Materials and methods Clinico-pathological data of all patients who received RC between 1996 and 2015 were retrospectively collected. Only patients with RC for muscle-invasive bladder cancer were included in the final analysis. Short-term (30-day) postoperative complications were assessed by registering the Clavien–Dindo classification (CDC) and dividing into sub-groups: low-grade (LGC) CDC 1–2 and high-grade (HGC) CDC 3–5. To compare populations with similar age, comorbidities and preoperative creatinine, we used a propensity score-adjusted statistical model. Pre- and perioperative predictors of short-term complications were identified using uni- and multivariable models. Survival was assessed using Kaplan–Meier analysis.

Results A total of 491 patients undergoing RC were included, of whom 102 (20.8%) received NAC. After propensity score covariate adjustment, there was no significant difference in postoperative complications between patients undergoing NAC plus RC and RC alone with an overall complication rate of 69% and 66%, respectively. No significant differences in the 30-day HGC rates (11.76% and 11.83%, respectively) were observed. NAC plus RC patients had worse prognostic factors at baseline; nevertheless, after correction for group differences OS and CSS did not differ from RC only group (5-year OS 61.3% vs. 50.2%, and 5-year CSS 61.8% vs. 57.9% respectively, $p > 0.05$ for all).

Conclusion In appropriately selected patients, exposure to NAC is not associated with increased short-term complications.

Keywords Radical cystectomy · Bladder cancer · Neoadjuvant chemotherapy · Complications · Short term

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Abbreviations

BC	Bladder cancer
NMIBC	Non-muscle-invasive bladder cancer
MIBC	Muscle-invasive bladder cancer
RC	Radical cystectomy
PLND	Pelvic lymph node dissection
UD	Urinary diversion
NAC	Neoadjuvant chemotherapy
OS	Overall survival
BCG	Bacillus Calmette–Guérin
CIS	Carcinoma in situ
CCI	Charlson comorbidity index
ACCI	Age-adjusted Charlson comorbidity index
BMI	Body mass index
TNM	Tumor-node-metastasis
EBL	Estimated blood loss

LoS	Length of stay
CDC	Clavien–Dindo Classification
HGC	High-grade complication
LGC	Low-grade complication
CSS	Cancer-specific survival
SD	Standard deviation
IQR	Interquartile range
CIF	Cumulative incidence function
IPTW	Inverse probability of treatment weighting
OR	Odds ratio
CI	Confidence interval
HR	Hazard ratio
OCS	Other-cause survival
UTI	Urinary tract infection
MVAC	Methotrexate–Vinblastine–Adriamycin–Cisplatin
GC	Gemcitabine–Cisplatin

Introduction

Bladder cancer (BC) is the 9th most common cancer worldwide, with more than 430,000 new cases diagnosed in 2012 [1]. About 75% of BC patients present with non-muscle-invasive BC (NMIBC), with a high recurrence rate of 50–70% [2]. About a fourth of the BC diagnoses comprises muscle-invasive BC (MIBC). In this case, radical cystectomy (RC) with pelvic lymph node dissection (PLND) and urinary diversion (UD) remains the standard of care [2, 3]. However, a considerable number of patients with MIBC have an important risk of developing distant metastases after surgery, despite complete tumor excision, most likely due to micro-metastases already present but not visible with current imaging before surgery with curative intent [4, 5].

Several prospective randomized trials have shown that treatment with neoadjuvant chemotherapy (NAC) is well tolerated and leads to a significant improvement in overall survival (OS) of 5–7% at 5-years after RC [6–13]. Thus, currently, cisplatinum-based chemotherapy regimens are recommended by international guidelines for cT2–T4a node-negative disease [2, 3]. In contrast to these findings, NAC remains underutilized; as only 15–20% of the patients with MIBC are receiving NAC [3, 14–17]. A survey sent out to all active members of the Society for Urologic Oncology in 2012 revealed that age and comorbidities were the most frequently (54%) cited concerns of the clinicians when they recommended NAC to their patients, followed by delay in surgery (35%), marginal benefit (33%), and prolonged diagnosis and referral (22%) [18]. Factors impacting the clinical decision to administer NAC may also include toxicity of chemotherapy and its effects on peri- and postoperative complications [19].

The aim of our study was to explore the impact of NAC on the risk of short-term complications and assess survival in a large cohort of MIBC patients treated with RC in a tertiary referral center.

Materials and methods

After approval by the local ethical committee, the data of all patients who underwent RCs in our department between December 1996 and August 2015 were collected from the hospital's electronic database and were analyzed retrospectively in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The confidentiality of patient data was guaranteed and informed consent was waived.

A total of 924 patients undergoing open RC were reviewed. Exclusion criteria were: RCs for symptom control (palliative care, metastasized patients, salvage cystectomies), non-oncological indications or other tumors than transitional cell carcinoma ($n = 285$), RCs for BCG-resistant CI*n*S or T1 Grade 3/high-grade ($n = 125$), and complete urinary tract extirpation patients ($= 23$). Patients undergoing unilateral nephro-ureterectomy in addition to cystectomy were included.

The following characteristics were identified for each individual (Table 1): age, gender, Charlson comorbidity index (CCI), age-factored CCI (ACCI), body-mass index (BMI), previous abdominal surgery/pelvic radiotherapy, smoking status, clinical stage according to tumor-node-metastasis (TNM) staging, NAC, type of NAC, time to surgery (time between NAC start and surgery), type of surgery (cysto-prostatectomy vs. cysto-prostato-urethrectomy vs. female cystectomy + anterior exenteration), type of UD, duration of surgery, estimated blood loss (EBL), perioperative complications (small bowel/colon/rectal or major vascular injury), adhesiolysis, pathological T- and N-stage, length of stay (LoS), short-term complications, readmission rate within 30 days and time to last follow-up and/or death.

The primary endpoint was the proportion of overall short-term (within 30 days) complications after RC. Moreover, wound, lymphatic, gastrointestinal, hematological, pulmonary, cardiovascular and genitourinary complications were compared using a dichotomization of the Clavien–Dindo classification (CDC). First, we compared no complication (CDC 0) versus any complication (CDC 1–5) and second, we compared high-grade complications (HGC) (CDC 3–5) versus low-grade complications (LGC) (CDC 1–2) between groups. Secondary endpoints were identification of other possible predictors of postoperative complications, OS and cancer-specific survival (CSS). A large number of statistical tests were performed without correction for multiple testing. Hence, the analysis should be considered explorative and

Table 1 Patient, tumor and perioperative characteristics by group

Variable	Statistic	RC only ($N=389$)	NAC + RC ($N=102$)	P value
Patient characteristics				
Age (year)	Mean	68.5	62.5	**< 0.001**
	SD	9.71	10.02	
Gender (male)	*n* (%)	318 (81.75)	87 (85.29)	
Obesity (BMI > 30)	*n* (%)	48 (12.34)	13 (12.75)	
Smoker (history/current)	*n* (%)	222 (57.07)	68 (66.67)	
Charlson comorbidity index				**0.002**
0	*n* (%)	177 (45.5)	62 (60.8)	
1	*n* (%)	86 (22.1)	22 (21.6)	
2	*n* (%)	68 (17.5)	10 (9.8)	
3	*n* (%)	29 (7.5)	3 (2.9)	
> 3	*n* (%)	29 (7.5)	5 (4.9)	
Baseline creatinine (mg/dL)	Mean	1.2	1.1	**0.016**
	SD	0.44	0.29	
Baseline hemoglobin (g/dL)	Median	13.7	12.6	**< 0.001**
	IQR	12.1–14.75	11.3–13.35	
Baseline platelet count ($\times 10^3/mm^3$)	Median	222.5	248	**< 0.001**
	IQR	164–264	206.5–298.5	
Tumor characteristics				
Clinical T-stage				
0	*n* (%)	0 (0.00)	9* (9.18)	**< 0.001**
a-1-Cis	*n* (%)	31 (7.97)	13 (13.27)	
2	*n* (%)	285 (73.26)	48 (48.98)	
3–4	*n* (%)	73 (18.77)	28 (28.57)	
Clinical N-stage				
0	*n* (%)	368 (94.60)	73* (74.49)	**< 0.001**
+	*n* (%)	21 (5.40)	25 (25.51)	
Pathologic T-stage				
0	*n* (%)	51 (13.11)	28 (27.45)	**< 0.001**
a-1-Cis	*n* (%)	55 (14.14)	25 (24.51)	
2	*n* (%)	82 (21.08)	17 (16.67)	
3–4	*n* (%)	201 (51.67)	32 (31.37)	
Pathologic N-stage				
0	*n* (%)	285/369 (77.24)	82 (80.39)	0.074
+	*n* (%)	84/369 (22.76)	20 (19.61)	
Perioperative characteristics				
Type of procedure				0.22
Cysto-prostatectomy	*n* (%)	186 (47.81)	60 (58.82)	
Cysto-prostato-urethrectomy	*n* (%)	108 (27.76)	24 (23.53)	
Female cystectomy + anterior exenteration	*n* (%)	81 (20.82)	16 (15.69)	
Additional nephro-ureterectomy	*n* (%)	14 (3.61)	2 (1.96)	
Type of reconstruction				0.61
Bricker ileo-cutaneostomy	*n* (%)	288 (74.04)	66 (64.71)	
Orthotopic neobladder	*n* (%)	92 (23.65)	33 (32.35)	
Mainz	*n* (%)	9 (2.31)	3 (2.94)	
Pelvic lymph node dissection				**< 0.001**
None	*n* (%)	37 (9.51)	2 (1.96)	
Limited	*n* (%)	194 (49.87)	38 (37.25)	
Extended	*n* (%)	143 (36.76)	62 (60.78)	
Surgery duration (min.)				**0.002**

Table 1 (continued)

Variable	Statistic	RC only ($N=389$)	NAC + RC ($N=102$)	P value
	Median	210	217.5	
	IQR	180–240	180–270	
Estimated blood loss (mL)				0.058
	Median	1000	1200	
	IQR	700–1500	800–1700	
Intra-operative adhesiolysis (yes)	*n* (%)	83 (21.34)	26 (25.49)	0.3974
Length of stay	Median	19	18	0.08
	IQR	16–24	16–23	
ICU (yes)	*n* (%)	22 (5.67)	5 (4.90)	0.76
Rehospitalization before first planned visit	*n* (%)	28 (7.25)	6 (5.94)	0.29

RC radical cystectomy, *NAC* neoadjuvant chemotherapy, *SD* Standard deviation, *IQR* Interquartile range, *BMI* body-mass index, *Cis* Carcinoma in situ, *ICU* intensive care unit

*Data missing due to diagnosis and staging outside UZ Leuven and not traceable. Pre-NAC staging not available

hypothesis-generating. Data regarding chemotherapeutic regimens, dosage, and timing with respect to cystectomy are provided in Supplementary Table 1 (data for 97 out of 102 patients could be retrieved).

Patient and tumor characteristics were described as mean ± standard deviation (SD) or median [interquartile range (IQR)] for continuous variables and as proportions with percentages for categorical variables. Comparison of the two treatment groups on patient characteristics was performed using the Mann–Whitney *U* test. OS was estimated using the Kaplan–Meier method, and CSS by means of the cumulative incidence function (CIF), with death of other causes considered as competing event. Differences between treatment groups were analyzed using logistic regression models for binary outcomes, linear models for continuous outcomes, or Cox proportional hazards models for time-to-event outcomes. Correction for group differences was performed by propensity score covariate adjustment [20]. Propensity scores (or group membership probabilities) were estimated by logistic regression including age, comorbidity and kidney function. The analyses are then applied with both treatment group and the propensity score as explanatory variables (Propensity score correction was chosen instead of correction by including the separate confounders in a multivariable model to keep the number of variables in the analysis low, provided that some of the binary outcome variables showed moderate numbers of events). Based on the above-mentioned preoperative features, the propensity score model estimates the probability for a patient of being assigned to either treatment group. The C-index is a quantification of the discriminative ability of the preoperative features for predicting group membership (Supplementary Fig. 1). A high discrimination (C-index close to 1) would indicate that there is no overlap between the groups and, hence, a comparison between the groups is suspect. A low discrimination (C-index close to 0.5) would indicate that the groups are largely comparable, and correction for group differences will then have a small impact. A sensitivity analysis for correction of group differences was performed by inverse probability of treatment weighting (IPTW) based on the propensity scores [21]. All tests were two sided and a 5% significance level was assumed for all tests. Analyses have been performed using SAS software (version 9.4 of the SAS System for Windows).

Results

A total of 491 patients were included in this study of which 102 (20.8%) patients received NAC plus RC and 389 (79.2%) patients RC alone. Mean age at surgery was 68.5 years (SD: 9.71) for RC alone and 62.5 years (SD: 10.02) for the NAC plus RC cohort ($p<0.001$). Patients who underwent NAC plus RC were on average 5 years younger and had fewer comorbidities (according to CCI), better renal function, lower preoperative hemoglobin, and higher platelet count. Data regarding chemotherapeutic regimens, dosage, and timing with respect to cystectomy are provided in Supplementary Table 1. A larger proportion of patients receiving NAC had locally advanced disease (cT3–T4) and/or clinically positive lymph nodes, received a more extensive PLND and thus had a longer duration of surgery ($p<0.05$) (Table 1).

No significant differences were noted between groups regarding prior abdominal/pelvic surgery or irradiation, smoking status, type of UD, EBL, pre- and perioperative complications, per-operative adhesiolysis and need for rehospitalization before planned follow-up. No significant differences were observed in the median LoS between patients treated with RC alone and NAC plus RC (19 days vs. 18 days, respectively; $p=0.08$) (Table 1).

We used propensity score covariate adjustment to account for differences in the populations regarding age, comorbidity and preoperative creatinine. We observed a moderate discrimination (C-index = 0.685) and a rather high but not complete overlap of distributions, justifying the approach of correction for group differences by propensity scores (Supplementary Fig. 1).

Concerning our primary endpoint, for the patients who underwent RC alone and RC plus NAC, the 30-day total complication rates (CDC 1–5) were 66% and 68%, and the 30-day HGC rates 12% and 12%, respectively. The most common 30-day complications were gastrointestinal (38% vs. 33%), genitourinary (16.5% vs. 22.6%) and wound-related (15.8% vs. 13.7%) for patients treated with RC and RC plus NAC, respectively. No significant differences in overall complication rate or proportion of HGC were observed between the two groups after covariate adjustment {Odds Ratio (OR): 0.697 [95% Confidence Interval (CI) 0.425–1.143] and 1.176 (95% CI 0.583–2.376), respectively} ($p > 0.05$) (Tables 2, 3). Additionally, we specified the most prevalent complications for each subdivision (Table 2). After IPTW analysis, only a slight increase in hematologic adverse events after NAC plus RC seemed to occur [OR: 0.541 (95% CI: 0.308–0.952)].

The 5-year OS was 50.2 months (95% CI 44.82–55.29) for patients receiving RC alone and 61.3 months (95% CI 49.58–71.07) for NAC plus RC patients (Table 4, Supplementary Fig. 2a). Uncorrected analysis revealed a hazard ratio (HR) of 1.37 (95% CI 0.98–1.93) ($p = 0.068$). After covariate adjustment, the HR for OS was 1.05 (95% CI 0.74–1.50) ($p = 0.77$) (Table 5). The 5-year CSS for RC alone was 57.9 months (95% CI 52.82–63.06) and was 61.8 (51.23–72.36) for NAC plus RC patients (Table 6, Supplementary Fig. 2b). Uncorrected analysis showed an HR of 1.07 (95% CI 0.72–1.55) ($p = 0.71$) and after adjustment the HR was 0.89 (95% CI 0.61–1.30) ($p = 0.53$) (Table 5). No significant difference could be withheld for the OS and CSS. It should be noted, however, that a significantly higher proportion of patients receiving NAC had a pathological staging pT0 (13% vs. 27%, respectively) (Table 1).

Additionally, we evaluated the effect of age on CSS and other-cause survival (OCS) after 5 and 10 years using a cumulative incidence curve (competing risk analysis). We found that in our patient cohort, higher age is significantly associated with both increased risk of CSS and OCS ($p < 0.05$ and $p < 0.0001$, respectively) (Table 7, Supplementary Fig. 2c, d).

Discussion

In our study, after propensity score covariate adjustment of patients for age, comorbidities and kidney function, the number of complications was comparable to the available literature. About 66–69% of the patients had at least one complication at 30 days, of which 11.8% was HGC. The most common types of complications were gastrointestinal, genitourinary and wound-related problems. Tables 2 and 3 also list the most prevalent complications for each organ system. For gastrointestinal complications, the most frequent one was ileus (26% vs. 23%, respectively), genitourinary complications mostly involved urinary tract infections (UTI) (e.g., pyelonephritis, pouchitis) (11.6% vs. 14.7%) and wound-related problems were mainly superficial wound dehiscence (9.5% vs. 7.8%). NAC did not appear to be associated with a more significant risk of complications. The increased amount of hematologic adverse events (mainly blood transfusions) in the NAC plus RC group is most likely attributable to patients having lower hemoglobin concentrations preoperatively (Table 1).

Additionally, there was a substantial difference in the clinical tumor staging between RC alone and NAC plus RC groups. Remarkably, the NAC group had significantly more clinical T3–T4 (29% vs. 19%) and clinical nodal disease (26% vs. 5%). Moreover, even though NAC patients were worse off regarding clinical tumor stage, the OS and CSS did not differ significantly. However, these results should be interpreted with some caution, since the current study was insufficiently powered to detect such differences. Nonetheless, this could suggest a potential survival benefit in our cohort of patients receiving NAC. Additionally, a significantly higher proportion of patients receiving NAC was pT0 (13% vs. 27%, respectively). A pT0 status is associated with significantly higher OS. Our findings suggest that, when indicated, physicians should strongly consider administering NAC to improve the OS rates of MIBC. However, it is important to note that patient selection is essential to optimize the trade-off between benefits and risks (e.g., toxicity, non-response, and delay in RC). Individuals with extensive comorbidities and/or impaired renal function should be excluded; similar barriers include advanced age and decreased performance status [3]. If cisplatin-based NAC is not possible due to renal dysfunction, cardiac dysfunction, substantial hearing loss, grade 2 (or higher) polyneuropathy, immediate surgery should be recommended, since regimens with carboplatinum are inferior. Comorbidities and advanced age also predispose the patient to a higher occurrence of postoperative morbidity.

MIBC is an aggressive disease with a high risk of recurrence due to micro-metastases already present at diagnosis [22]. NAC can eradicate early (micro-metastatic) systemic disease, which is impossible by RC alone [6]. Multiple landmark studies and meta-analyses have already demonstrated an improved 5-year OS of about 5–7% for platinum-based NAC in patients with MIBC [6–13]. However, establishing the use of NAC into standard urological practice has proven to be a difficult feat.

Table 2 Comparison of 30-day complication rates of the groups

Variable	Statistic	RC only ($N=389$)	NAC + RC ($N=102$)
All complications			
CDC			
CDC 0	*n* (%)	132 (33.93)	32 (31.37)
CDC 1–5	*n* (%)	257 (66.07)	70 (68.63)
CDC			
CDC 0–2	*n* (%)	343 (88.17)	90 (88.24)
CDC 3–5	*n* (%)	46 (11.83)	12 (11.76)
Specific complications (no vs. any)			
Gastrointestinal			
Need for re-intervention	*n* (%)	21 (5.40)	4 (3.92)
Post-op intestinal anastomotic leakage	*n* (%)	16 (4.11)	3 (2.94)
Re-opening/-placing nasogastric tube	*n* (%)	61 (15.68)	19 (18.63)
Ileus and/or 5-day with no signs of transit	*n* (%)	101 (25.96)	23 (22.55)
CDC 0	*n* (%)	240 (61.86)	68 (66.67)
CDC 1–5	*n* (%)	148 (38.14)	34 (33.33)
Lymphatic			
Lymphedema	*n* (%)	2 (0.52)	0
Lymphocele	*n* (%)	3 (0.77)	2 (1.96)
CDC 0	*n* (%)	384 (99.48)	100 (98.04)
CDC 1–5	*n* (%)	2 (0.52)	2 (1.96)
Wound-related			
Infection	*n* (%)	20 (5.14)	5 (4.90)
Superficial dehiscence or need for re-opening wound	*n* (%)	37 (9.51)	8 (7.84)
Evisceration or eventration	*n* (%)	9 (2.33)	2 (1.96)
CDC 0	*n* (%)	326 (84.24)	88 (86.27)
CDC 1–5	*n* (%)	61 (15.76)	14 (13.73)
Hematologic			
Erythrocyte transfusion	*n* (%)	45 (11.57)	18 (17.65)
Fresh frozen plasma transfusion	*n* (%)	4 (1.03)	1 (0.98)
Embolism	*n* (%)	5 (1.29)	3 (2.94)
Deep venous thrombosis	*n* (%)	2 (0.52)	2 (1.96)
CDC 0	*n* (%)	338 (87.11)	83 (81.37)
CDC 1–5	*n* (%)	50 (12.89)	19 (18.63)
Pulmonary			
Infection	*n* (%)	29 (7.46)	8 (7.84)
Other	*n* (%)	12 (3.08)	4 (3.92)
CDC 0	*n* (%)	351 (90.46)	90 (88.24)
CDC 1–5	*n* (%)	37 (9.54)	12 (11.76)
Cardiovascular			
Infarction	*n* (%)	1 (0.26)	0
New onset atrial fibrillation	*n* (%)	10 (2.57)	0
Cerebrovascular accident	*n* (%)	3 (0.77)	1 (0.98)
CDC 0	*n* (%)	376 (96.91)	101 (99.02)
CDC 1–5	*n* (%)	12 (3.09)	1 (0.98)
Genitourinary			
Fistula	*n* (%)	5 (1.29)	1 (0.98)
Obstruction of NB with need for CIC	*n* (%)	3 (0.77)	4 (3.92)
Need for re-surgery	*n* (%)	6 (1.54)	3 (2.94)
Urosepsis	*n* (%)	25 (6.43)	5 (4.90)
UTI (pyelonephritis, pouchitis…)	*n* (%)	45 (11.57)	15 (14.71)

Table 2 (continued)

Variable	Statistic	RC only ($N=389$)	NAC + RC ($N=102$)
CDC 0	*n* (%)	323 (83.46)	79 (77.45)
CDC 1–5	*n* (%)	64 (16.54)	23 (22.55)
Specific complications (minor vs. major)			
Gastrointestinal			
CDC 0–2	*n* (%)	370 (95.36)	99 (97.06)
CDC 3–5	*n* (%)	18 (4.64)	3 (2.94)
Wound healing			
CDC 0–2	*n* (%)	373 (96.38)	100 (98.04)
CDC 3–5	*n* (%)	14 (3.62)	2 (1.96)
Pulmonary			
CDC 0–2	*n* (%)	378 (97.67)	99 (97.06)
CDC 3–5	*n* (%)	9 (2.33)	3 (2.94)
Genitourinary			
CDC 0–2	*n* (%)	377 (97.42)	99 (97.06)
CDC 3–5	*n* (%)	10 (2.58)	3 (2.94)

Table 3 Comparison of short-term complications of the groups, uncorrected and corrected (propensity score covariate adjustment)

Outcome	Uncorrected		Corrected			
			Covariate adjustment		IPTW	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
CDC 0 vs. CDC 1–5	0.890 (0.557;1.421)	0.6256	0.697 (0.425;1.143)	0.1530	0.702 (0.432;1.141)	0.1532
CDC 1–2 vs. CDC 3–5	0.994 (0.506;1.955)	0.9866	1.176 (0.583;2.376)	0.6504	0.962 (0.477;1.940)	0.9136
Gastrointestinal (CDC 0 vs. 1–5)	1.233 (0.779;1.953)	0.3714	1.076 (0.668;1.734)	0.7637	1.022 (0.649;1.610)	0.9252
Wound healing (CDC 0 vs. 1–5)	1.176 (0.628;2.201)	0.6119	1.022 (0.534;1.955)	0.9476	1.043 (0.562;1.934)	0.8941
Hematologic (CDC 0 vs. 1–5)	0.646 (0.362;1.154)	0.1402	0.581 (0.317;1.065)	0.0793	0.541 (0.308;0.952)	0.0333
Pulmonary (CDC 0 vs. 1–5)	0.791 (0.396;1.578)	0.5050	0.643 (0.312;1.325)	0.2308	0.704 (0.354;1.397)	0.3152
Cardiovascular (CDC 0 vs. 1–5)	3.223 (0.414;25.084)	0.2635	2.444 (0.303;19.712)	0.4015	4.021 (0.378;42.740)	0.2486
Genitourinary (CDC 0 vs. 1–5)	0.680 (0.398;1.163)	0.1593	0.667 (0.383;1.164)	0.1542	0.632 (0.372;1.073)	0.0894

OR > 1 means higher probability of adverse outcome for RC only. OR < 1 means higher probability of adverse outcome for NAC + RC

RC radical cystectomy, *NAC* neoadjuvant chemotherapy, *CDC* Clavien–Dindo classification, *NB* neobladder, *CIC* clean intermittent self-catheterization, *UTI* urinary tract infection, *IPTW* inverse probability treatment weights, *CI* Confidence interval, *OR* odds ratio

There is a perception among both patients and physicians that 5–7% absolute OS benefit over 5 years is not enough to warrant the use of NAC with its known toxicity, complications and discomforts. Nevertheless, systemic therapies conferring a 7% survival benefit are widely used in breast and colon cancers [23]. Delay in surgery is particularly feared as well since most of MIBC mortality occurs within 5 years of diagnosis due to rapidly growing and spreading metastases. However, previous studies could not demonstrate a difference in survival when surgery was postponed due to receiving NAC [24–26]. This suggests a false perception among urologists that the risks do not outweigh the benefits. We believe that our study adds to the knowledge that NAC does not predispose patients for higher peri- and postoperative complications in a matched population.

To date, only a small number of studies have addressed the effect of NAC on perioperative complications after RC. Mixed results were reported, which has led to continued concern about increased perioperative complications. There is a paucity of prior data to either confirm or refute this presumption. Neither Grossman et al. [6] nor the randomized Nordic Cystectomy I and II trials [7] and the International Collaboration of Trialists [8] objectively reported postoperative complications. This was addressed in studies by Johnson et al. [27] and Gandaglia et al. [28], who were the first in their attempt to answer this issue. In the former, NAC plus RC versus RC alone did not predict a more significant number of complications, respectively 55.1% and 51.8%. The latter found that NAC did not increase the rate of complications, readmissions or mortality.

Table 4 Frequency of deaths, median and 2-,4-,5-,6-,8- and 10-year overall survival rates of the groups

Variable	Statistic	RC only	NAC + RC
Death			
No	*n* (%)	155 (40.16)	62 (61.39)
Yes	*n* (%)	231 (59.84)	39 (38.61)
% Survival (95% CI)			
Months		RC only	NAC + RC
24		67.08 (62.00;71.63)	67.49 (56.38;76.36)
48		51.20 (45.86;56.28)	63.15 (51.69;72.60)
60		50.18 (44.82;55.29)	61.29 (49.58;71.07)
72		45.33 (39.90;50.59)	61.29 (49.58;71.07)
96		39.85 (34.35;45.29)	58.37 (45.78;69.01)
120		32.09 (26.42;37.88)	45.37 (30.56;59.05)
Median survival (months) (95% CI)			
RC only			NAC + RC
60.1 (37.8;72.5)			106.7 (53.8;.)

.: not estimable

RC radical cystectomy, *NAC* neoadjuvant chemotherapy, *CI* Confidence interval

Table 5 Comparison of survival curves of the groups, uncorrected and corrected (propensity score covariate adjustment)

Outcome	Hazard ratio (95% CI)	*P* value
Uncorrected		
Overall survival	1.372 (0.977;1.927)	0.0680
Cancer-specific survival	1.074 (0.742;1.554)	0.7053
Corrected		
Overall survival	1.053 (0.742;1.495)	0.7719
Cancer-specific survival	0.886 (0.605;1.298)	0.5347

Despite the evidence supporting its use in clinical practice, it is estimated that only 15–20% of the patients who undergo RC do receive NAC [14–16]. In this analysis, we showed that utilization rate in our institution (20.8%) was comparable to that of the previous studies, where the relatively low rate can be explained by the retrospective design with historic underutilization. However, 32.6% of the patients who have undergone RC have received NAC over the last 3 years of our analysis, which shows a rising usage in our institution (Supplementary Fig. 3).

Table 6 Frequency of deaths/causes, and 2-,4-,5-,6-,8- and 10-year cancer-specific survival rates of the groups

Variable	Statistic	RC only	NAC + RC
Cancer-specific survival			
Alive	*n* (%)	154 (40.00)	61 (61.00)
Death—cancer	*n* (%)	165 (42.86)	34 (34.00)
Death—other	*n* (%)	66 (17.14)	5 (5.00)
	% Survival (95% CI)		
Months	Months		Months
24		28.08 (23.59;32.73)	32.13 (22.54;42.09)
48		41.45 (36.31;46.51)	36.42 (26.18;46.71)
60		57.89 (52.82;63.06)	61.75 (51.23;72.36)
72		44.70 (39.39;49.86)	38.25 (27.64;48.77)
96		45.08 (39.75;50.26)	41.13 (29.52;52.38)
120		46.64 (41.16;51.93)	41.13 (29.52;52.38)

RC radical cystectomy, *NAC* neoadjuvant chemotherapy, *CI* Confidence interval

Table 7 Effect of age on cancer-specific survival (CSS) and other-cause survival (OCS)

Outcome	Odds ratio (95% CI)	*P* value
Cancer-specific survival	1.014 (1.001;1.028)	0.0415
Other-cause survival	1.058 (1.031;1.086)	**< 0.0001**

There are many hypotheses suggesting that the toxicity induced by NAC before a major surgical procedure, such as RC, might lead to an impairment of the patient's general health status, resulting in a higher risk of postoperative morbidity and mortality. These toxicities are, however, self-limiting in most of the cases and have not been shown to increase perioperative complication risk [29]. Historically, the use of MVAC regimen (methotrexate, vinblastine, doxorubicin [adriamycin] and cisplatin) has been associated with relative toxicity [5, 30]. With the advent of gemcitabine and cisplatin (GC) combination therapy, however, more favorable toxicity profiles have been observed. There were improved patient tolerability, compliance and decreased time to RC [23]. Nonetheless, direct prospective trials that need to be set up to prove the treatments have comparable oncological outcomes.

Our study is not devoid of limitations. First, there are the inherent limitations of the retrospective design of the study leading to incomplete data (risk of underreporting low-grade complications) and selection bias. Moreover, we were not able to record reasons for patients not receiving NAC or not receiving RC after NAC. Second, we did not account for dose reductions in the NAC regimens. Third, we included the patients with positive nodal disease who received induction chemotherapy. Due to partial or complete response, these patients were offered an RC. This could introduce a limited selection bias. Fourth, due to its sample size, the study was insufficiently powered and no correction for multiple testing was performed to detect differences in separate complication categories. Lastly, we evaluated a cohort at a high-volume referral center, usually not comparable to general patient data. Not all pertinent risk factors are likely to have been identified and recorded.

Conclusion

Despite the limitations of our study, we can conclude that, provided a cautious patient selection takes place, exposure to NAC is not associated with increased risk of short-term postoperative morbidity and mortality. Therefore, NAC can be considered a safe approach for MIBC patients. Further efforts are needed to improve physician and patient guideline adherence and to raise awareness of the benefits and tolerability of NAC when clinically indicated.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest related to this manuscript.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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