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Bladder Cancer

The Effect of Neoadjuvant Chemotherapy on Perioperative Outcomes in Patients Who Have Bladder Cancer Treated with Radical Cystectomy: A Population-based Study

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Abstract

Background: Although therapeutic guidelines recommend the use of neoadjuvant chemotherapy before radical cystectomy (RC) in patients who have muscle-invasive bladder cancer (MIBC), this approach remains largely underused. One of the main reasons for this phenomenon might reside in concerns regarding the risk of morbidity and mortality associated with neoadjuvant chemotherapy.
Objective: To compare perioperative outcomes between patients receiving neoadjuvant chemotherapy and those treated with RC alone.
Design, setting, and participants: Relying on the Surveillance Epidemiology and End Results–Medicare-linked database, 3760 patients diagnosed with MIBC between 2000 and 2009 were evaluated.
Intervention: RC alone or RC plus neoadjuvant chemotherapy.
Outcome measurements and statistical analysis: Complications occurred within 30 and 90 d after surgery. Heterologous blood transfusions (HBTs), length of stay (LoS), readmission, and perioperative mortality were compared. To decrease the effect of unmeasured confounders associated with treatment selection, propensity score–matched analyses were performed.
Results and limitations: Overall, 416 (11.1%) of patients received neoadjuvant chemotherapy. Following propensity score matching, 416 (20%) and 1664 (80%) patients treated with RC plus neoadjuvant chemotherapy and RC alone remained, respectively. The 30-d complication, readmission, and mortality rates were 66.0%, 32.2%, and 5.3%, respectively. The 90-d complication, readmission, and mortality rates were 72.5%, 46.6%, and 8.2%, respectively. When patients were stratified according to neoadjuvant chemotherapy status, no significant differences were observed in the rates of complications, HBT, prolonged LoS, readmission, and mortality between the two groups (all $p \geq 0.1$). These results were confirmed in multivariate analyses, where the use of neoadjuvant chemotherapy was not associated with higher risk of 30- and 90-d complications, HBT, prolonged LoS, readmission, and mortality (all $p \geq 0.1$). Our study is limited by its retrospective nature.

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Conclusions: The use of neoadjuvant chemotherapy is not associated with higher perioperative morbidity or mortality. These results should encourage wider use of neoadjuvant chemotherapy when clinically indicated.
Patient summary: Chemotherapy before radical cystectomy in patients with muscle-invasive bladder cancer does not increase the risk of complications or death. The use of chemotherapy should be strongly encouraged, as recommended by clinical guidelines, given its benefits.

1. Introduction

Bladder cancer (BCa) represents the fourth most common cancer in the United States [1]. Radical cystectomy (RC) represents the standard of care for patients who have muscle-invasive BCa (MIBC) [2]. Although this surgical approach leads to complete tumour excision in a substantial proportion of patients, individuals who have MIBC are at significant risk of distant recurrence after surgery [3,4]. Previous studies showed that the administration of neoadjuvant chemotherapy leads to a significant improvement in overall survival (OS) at 5 yr after RC [5–8]. Accordingly, international guidelines recommend the administration of neoadjuvant cisplatin-based chemotherapy in patients who have cT2–T4a node-negative disease [2,9].

Despite these recommendations, this approach remains largely underutilised [3,4,10–13], with only 15% of MIBC patients receiving neoadjuvant chemotherapy in recent years [12,14]. Many attributed this phenomenon to multiple baseline comorbidities, such as cardiac and renal dysfunction, and advanced age at disease presentation [3,15]. Others hypothesised that patient and physician concerns regarding the increased risk of perioperative morbidity and mortality associated with neoadjuvant chemotherapy might at least contribute to its low utilisation [16,17]. In this context, we aimed at examining the impact of neoadjuvant chemotherapy on the risk of detrimental perioperative outcomes in a large contemporary cohort of patients treated with RC. Particularly, we focused on the 30- and 90-d perioperative complications, length of hospitalisation, readmission, and mortality.

2. Materials and methods

2.1. Population source

The current study relied on the most recent version of the Surveillance Epidemiology and End Results (SEER)–Medicare insurance program linked database, which is 98% complete for case ascertainment. The SEER registries covered approximately 28% of the US population with Medicare administrative data. Medicare insurance includes approximately 97% of Americans ≥65 yr of age.

2.2. Study population

Overall, 15 080 patients ≥66 yr of age who had nonmetastatic urothelial MIBC (International Classification of Disease for Oncology site code 67.0, histologic code 8120 or 8130) diagnosed between January 1991 and December 2009 were abstracted. Patients not enrolled in Medicare parts A and B for a minimum of 12 mo prior to their first recorded diagnosis and for 6 mo after diagnosis were not considered. Patients who had health maintenance organisation enrolment in the year prior to diagnosis or for any period following diagnosis were also removed. Exclusion criteria consisted T4b or T4 not-otherwise-specified stage (n = 477) and unknown grade (n = 68). For the purpose of our study, we focused exclusively on patients treated with RC within 12 mo from diagnosis between January 2000 and December 2009 (n = 3760).

2.3. Covariates

For each patient, age at diagnosis, gender, year of diagnosis, race, socioeconomic status, marital status, population density, region, tumour stage, and grade were assigned. Patients receiving a continent diversion were identified using International Classification of Disease, Ninth Revision (ICD-9) procedures and Common Procedural Terminology (CPT) codes (Supplemental Table 1). The Charlson Comorbidity Index (CCI) was derived from the Medicare claims 1 yr prior to diagnosis [18]. Patients who had chemotherapy claims ≤6 mo prior to diagnosis and a claim for RC ≤6 mo before the first chemotherapy claim were considered to have been treated with neoadjuvant chemotherapy. Chemotherapeutic agents were identified using the J codes listed in Supplemental Table 1.

2.4. Outcomes

Our analyses focused on 30- and 90-d perioperative outcomes. Seven schemes of complications were assessed using the ICD-9 and CPT codes (Supplemental Table 2). Patients requiring postoperative heterologous blood transfusion (HBT) were also identified. *Prolonged length of stay* (LoS) was defined as a hospitalisation beyond the highest quartile (>12 d) after surgery. In addition, we focused on readmission rates as determined by any hospitalisation within 30 and 90 d of the surgical procedure [19]. Finally, perioperative mortality rates were examined. The cause of death was defined using the SEER cause-of-death recode variable.

2.5. Statistical analyses

Means, medians, and interquartile ranges (IQRs) were reported for continuous variables. Frequencies and proportions were reported for categorical variables. The Student t test, Mann-Whitney test, and χ^2 test were used to compare the statistical significance of differences in means, medians, and proportions, respectively.

Because of inherent differences among patients included in the two treatment groups, adjustment was performed using a 1-to-4 propensity score–matching ratio [20]. Propensity scores were computed by modelling a logistic regression with the dependent variable as the odds of receiving neoadjuvant chemotherapy and the independent variable as age of diagnosis, gender, race, year, CCI, marital status, population density, socioeconomic status, region, tumour stage, nodal stage, and grade. Subsequently, covariate balance between the matched groups were examined [21]. We then compared the rates of 30- and 90-d complications, HBT, LoS, readmission, and perioperative mortality

between patients receiving RC alone and those receiving RC plus neoadjuvant chemotherapy. Multivariable logistic regression models tested the effect of neoadjuvant chemotherapy use on perioperative outcomes in the postpropensity matched cohort. Separate subanalyses were performed to test the effect of the specific type of chemotherapy (gemcitabine, cisplatin, carboplatin, paclitaxel, and other) on perioperative outcomes. Finally, we repeated our analyses exclusively in a subcohort of patients treated with RC and pelvic lymph node dissection (PLND).

All statistical tests were performed using the R software environment for statistical computing and graphics (Vienna, Austria, version 3.0.1). All tests were two-sided, with a significance level set at $p < 0.05$.

3. Results

3.1. Baseline characteristics

Overall, 3760 patients were included in the study (Table 1). Median (IQR) age at diagnosis was 75 yr of age (range: 70–80). Overall, 416 (11.1%) patients received neoadjuvant chemotherapy before RC. The most commonly used chemotherapeutic agents were gemcitabine ($n = 276$ [66.3%]), cisplatin ($n = 211$ [50.7%]), and carboplatin ($n = 159$ [38.2%]). Statistically significant differences were recorded according to age, year of diagnosis, marital status, tumour stage, and region with respect to patients treated with RC alone and RC plus neoadjuvant chemotherapy (all $p \leq 0.01$). Following propensity score matching, 1664 (80%) and 416 (20%) patients treated with RC alone and RC plus neoadjuvant chemotherapy remained, respectively. The mean standardised differences of patient characteristics between the two groups were <10%, indicating a high degree of similarity in the distribution of both populations. All subsequent analyses were based on the postpropensity matched cohort.

3.2. Perioperative outcomes

The 30- and 90-d complication rates were 66.0% and 72.5%, respectively. The most common 30- and 90-d complications were respiratory (39.9% and 44.1%, respectively) and genitourinary (33.3% and 39.4%, respectively). No significant differences were observed in the overall complication rates between patients treated with RC alone and RC plus neoadjuvant chemotherapy (all $p \geq 0.5$). This held true when the specific types of complication were considered (Table 2; all $p \geq 0.1$). The 30- and 90-d HBT rates were 30.4% and 33.6%, respectively. No significant differences were observed in the HBT rates between patients treated with RC alone and RC plus neoadjuvant chemotherapy (all $p \geq 0.3$).

Median (IQR) LoS was 9 d (range: 7–12). No significant differences were observed in the median LoS between patients treated with RC alone and RC plus neoadjuvant chemotherapy (9 d vs 9 d, respectively; $p = 0.1$). No significant differences were observed in the rates of prolonged LoS between patients treated with RC alone and RC plus neoadjuvant chemotherapy (25.8% vs 20.9%, respectively; $p = 0.1$). The 30- and 90-d readmission rates were 32.2% and 46.6%, respectively. When patients were stratified according to the receipt of neoadjuvant chemotherapy, no statistically significant differences were observed in the readmission rates between individuals treated with RC alone and with RC plus neoadjuvant chemotherapy (all $p \geq 0.3$). Finally, the 30- and 90-d perioperative mortality rates were 3.8% and 8.2%, respectively. No significant differences were observed in perioperative mortality rates between patients treated with RC alone and RC and neoadjuvant chemotherapy (all $p \geq 0.7$). The most common cause of 90-d mortality was represented by "urinary bladder" (63.9% vs 82.1% for patients treated with RC vs RC plus neoadjuvant chemotherapy, respectively; $p = 0.1$). In multivariate logistic regression analyses, neoadjuvant chemotherapy use was not associated with higher odds of complications, prolonged LoS, HBT, readmission, or perioperative mortality after adjusting for confounders (all $p \geq 0.1$).

3.3. Sensitivity analyses

The type of chemotherapy was not associated with 30- and 90-d complications, HBT, prolonged LoS, readmission, or mortality after adjusting for confounders (all $p \geq 0.07$). In analyses focusing exclusively on patients treated with RC and PLND ($n = 3224$), the 90-d overall complications, HBT, readmission, and perioperative mortality rates were 73.4%, 29.5%, 47.9%, and 10.1%, respectively. Following propensity score matching, 1440 (80%) and 360 (20%) patients treated with RC alone and RC plus neoadjuvant chemotherapy remained, respectively. No significant differences were observed in complications, HBT, prolonged LoS, readmission, and mortality rates between patients treated with RC alone and their counterparts receiving RC plus neoadjuvant chemotherapy (all $p \geq 0.3$). These results were confirmed in multivariate analyses, where neoadjuvant chemotherapy was not associated with a higher risk of complications, HBT, prolonged LoS, readmission, or mortality (all $p \geq 0.1$).

4. Discussion

The administration of neoadjuvant chemotherapy has been shown to be associated with an improvement in OS in patients who have MIBC [2–8,22,23]. Consequently, this therapeutic approach is currently recommended by international guidelines [2,9,24], although several studies reported worrisomely low utilisation rates for this treatment modality, where only 15% of patients treated with RC received neoadjuvant chemotherapy [3,4,10–12,15].

One of the main reasons for this phenomenon might reside in concerns regarding the possibility of detrimental perioperative outcomes associated with neoadjuvant chemotherapy [16,17]. For example, at least one-third of patients treated with cisplatin-based chemotherapy before RC experience severe haematologic or gastrointestinal side-effects [5]. Consequently, some authors have hypothesised that the toxicity associated with the systemic administration of chemotherapy 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. However, only a few studies addressed the impact of neoadjuvant chemotherapy

Table 1 – Descriptive statistics of 3760 patients treated with radical cystectomy for muscle-invasive bladder cancer between 2000 and 2009 within the Surveillance Epidemiology and End Results database, stratified according to the use of neoadjuvant chemotherapy

	Before propensity score matching				After propensity score matching			
	Total (*n* = 3760)	RC alone (*n* = 3344 [88.9%])	RC + NC (*n* = 416 [11.1%])	*Standardized difference*	Total (*n* = 2080)	RC alone (*n* = 1664 [80%])	RC + NC (*n* = 416 [20%])	*Standardized difference*
Age at diagnosis								
Median	75	75	73	−27.2	73	73	73	−2.2
IQR	70–80	71–80	69–78		69–78	69–78	69–78	
Year of diagnosis								
Median	2004	2004	2006	42.3	2006	2006	2006	6.6
IQR	2002–2007	2002–2007	2003–2008		2003–2008	2003–2008	2003–2008	
Gender, no. (%)								
Female	1061 (28.2)	948 (28.3)	113 (27.2)	2.6	576 (27.7)	463 (27.8)	113 (27.2)	1.5
Male	2699 (71.8)	2396 (71.7)	303 (72.8)		1594 (72.3)	1201 (72.2)	303 (72.8)	
Race, no. (%)								
White	3407 (90.6)	3021 (90.3)	386 (92.8)	−9.4	1940 (93.3)	1554 (93.4)	386 (92.8)	2.3
Other*	353 (9.4)	323 (9.7)	30 (7.2)		140 (6.7)	110 (6.6)	30 (7.2)	
Marital status, no. (%)								
Married	2400 (63.8)	2107 (63.0)	293 (70.4)	−16.2	1450 (69.7)	1157 (69.5)	293 (70.4)	−1.9
Other**	1360 (36.2)	1237 (37.0)	123 (29.6)		630 (30.3)	507 (30.5)	123 (29.6)	
Population density, no. (%)								
Metropolitan	3384 (90.0)	3008 (90.0)	376 (90.4)	−1.4	1875 (90.1)	1499 (90.1)	376 (90.4)	−1.0
Non-metropolitan	376 (10.0)	336 (10.0)	40 (9.6)		205 (9.9)	165 (9.9)	40 (9.6)	
Socioeconomic status, no. (%)								
Low	2534 (67.4)	2260 (67.6)	274 (65.9)	3.6	1391 (66.9)	1117 (67.1)	274 (65.9)	2.6
High	1226 (32.6)	1084 (32.4)	142 (34.1)		689 (33.1)	547 (32.9)	142 (34.1)	
CCI, no. (%)								
0	1426 (37.9)	1262 (37.7)	164 (39.4)	−5.8	852 (41.0)	688 (41.3)	164 (39.4)	1.4
1	570 (15.2)	502 (15.0)	68 (16.3)		310 (14.9)	242 (14.5)	68 (16.3)	
2	762 (20.3)	680 (20.3)	82 (19.7)		402 (19.3)	320 (19.2)	82 (19.7)	
≥3	1002 (26.6)	900 (26.9)	102 (24.5)		516 (24.8)	414 (24.9)	102 (24.5)	
Type of urinary diversion, no. (%)								
Incontinent	3111 (82.7)	2770 (82.8)	341 (82.0)	N/A	1693 (81.4)	1352 (81.3)	341 (82.0)	N/A
Continent	649 (17.3)	574 (17.2)	75 (18.0)		387 (18.6)	312 (18.7)	75 (18.0)	
Tumour grade, no. (%)								
Low	188 (5.0)	173 (5.2)	15 (3.6)	8.4	84 (4.0)	69 (4.1)	15 (3.6)	2.9
High	3572 (95.0)	3171 (94.8)	401 (96.4)		1996 (96.0)	1595 (95.9)	401 (96.4)	
Tumour stage, no. (%)								
T2	1869 (49.7)	1617 (48.5)	252 (60.6)	−19.6	1185 (57.0)	933 (56.1)	252 (60.6)	−2.2
T3	1266 (33.7)	1163 (34.8)	103 (24.8)		638 (30.7)	535 (32.2)	103 (24.8)	
T4a	625 (16.6)	564 (16.9)	61 (14.6)		257 (12.3)	196 (11.7)	61 (14.6)	
Nodal stage, no. (%)								
Nx	536 (14.3)	480 (14.4)	56 (13.5)	2.6	295 (13.7)	229 (13.8)	56 (13.5)	−0.1
N0	2486 (66.1)	2205 (65.9)	281 (67.5)		1405 (67.5)	1124 (67.5)	281 (67.5)	
N1	738 (19.6)	659 (19.7)	79 (19.0)		390 (18.8)	311 (18.7)	79 (19.0)	
Region, no. (%)								
East	1738 (46.2)	1535 (45.9)	203 (48.8)	13.6	1019 (49.0)	816 (49.0)	203 (48.8)	4.7
Pacific Coast	1396 (37.1)	1265 (37.8)	131 (31.5)		679 (32.6)	548 (32.9)	131 (31.5)	
Northern Plains	470 (12.5)	402 (12.0)	68 (16.3)		311 (15.0)	243 (14.6)	68 (16.3)	
Southwest	156 (4.1)	142 (4.2)	14 (3.4)		71 (3.4)	57 (3.5)	14 (3.4)	
Chemotherapeutic agent, no. (%)								
Gemcitabine	276 (7.5)	–	276 (66.3)	N/A	276 (13.3)	–	276 (66.3)	N/A
Cisplatin	211 (5.7)		211 (50.7)		211 (10.1)		211 (50.7)	
Carboplatin	159 (4.3)		159 (38.2)		159 (7.6)		159 (38.2)	
Paclitaxel	99 (2.7)		99 (23.8)		99 (4.7)		99 (23.8)	
Doxorubicin	53 (1.4)		53 (12.7)		53 (2.5)		53 (12.7)	
Vinblastine	46 (1.2)		46 (11.1)		46 (2.2)		46 (11.1)	
Methotrexate	28 (0.8)		28 (6.7)		28 (1.3)		28 (6.7)	
Other***	41 (1.1)		41 (9.9)		41 (1.9)		41 (9.9)	

RC = radical cystectomy; NC = neoadjuvant chemotherapy; IQR = interquartile range; CCI = Charlson Comorbidity Index; N/A = not applicable.
* Including black, Asian, Hispanic, North American Native, and unknown.
** Including single, separated, divorced, widowed, and unknown.
*** Including cyclophosphamide, ifosfamide, and docetaxel.

Table 2 – Comparison of 90-d postoperative complications, heterologous blood transfusions, readmission rates, and mortality between patients treated with radical cystectomy (RC) alone or RC and neoadjuvant cystectomy for muscle-invasive bladder cancer after propensity score matching

	After propensity score matching				RC alone vs RC + NC	
	Overall (*n* = 2080)	RC alone (*n* = 1664 [80%])	RC + NC (*n* = 416 [20%])	*p value*	OR (95% CI)*	*p value*
Postoperative complication, no. (%):						
Overall	1508 (72.5)	1209 (72.7)	299 (71.9)	0.7	0.96 (0.75–1.22)	0.7
Cardiac	117 (5.6)	95 (5.7)	22 (5.3)	0.8	0.93 (0.57–1.51)	0.7
Respiratory	917 (44.1)	741 (44.5)	176 (42.3)	0.4	0.91 (0.73–1.14)	0.4
Genitourinary	819 (39.4)	652 (39.2)	167 (40.1)	0.7	1.04 (0.83–1.30)	0.7
Vascular	289 (13.9)	221 (13.3)	68 (16.3)	0.1	1.28 (0.95–1.73)	0.1
Gastrointestinal	255 (12.3)	210 (12.6)	45 (10.8)	0.3	0.82 (0.58–1.16)	0.3
Miscellaneous medical	528 (25.4)	425 (25.5)	103 (24.8)	0.8	0.94 (0.72–1.21)	0.6
Wound	84 (4.0)	67 (4.0)	17 (4.1)	0.9	1.02 (0.59–1.76)	0.9
HBT, no. (%)	699 (33.6)	562 (33.8)	137 (32.9)	0.7	0.96 (0.76–1.21)	0.7
Readmission, no. (%)**	850 (46.6)	717 (47.1)	131 (43.8)	0.3	0.88 (0.69–1.14)	0.3
Perioperative mortality, no. (%)***	160 (8.2)	132 (8.3)	28 (7.7)	0.7	0.96 (0.62–1.48)	0.8

CCI = Charlson Comorbidity Index; CI = confidence interval; HBT = heterologous blood transfusion; NC = neoadjuvant chemotherapy; OR = odds ratio; RC = radical cystectomy.

* Model adjusted for age at diagnosis, CCI, race, gender, year of diagnosis, socioeconomic status, marital status, population density, urinary diversion, tumour stage, nodal stage, and tumour grade.

** Available for 1824 patients.

*** Available for 1946 patients.

on perioperative outcomes after RC, reporting conflicting results [5,16,17,25–29]. Of note, the generalizability of these findings is limited by the inclusion of highly select patients enrolled in clinical trials [5] or exclusively treated at high-volume centres [16,17,25–29]. Observations obtained in these settings might not be applicable to the general patient population treated with RC.

In the face of such a paucity of data, we aimed at reassessing the impact of neoadjuvant chemotherapy on perioperative morbidity and mortality in a large contemporary cohort of patients treated with RC for MIBC. To reduce to a minimum the potential effect of selection bias related to the receipt of neoadjuvant chemotherapy, baseline characteristics of individuals treated with RC alone or RC plus neoadjuvant chemotherapy were matched using a propensity score methodology.

First, we show that the utilisation rate of neoadjuvant chemotherapy in our large contemporary cohort of patients with MIBC was only 11%. This rate is comparable to previous reports focusing on institutional series or academic centres [3,4,10–13,15]. This finding raises serious concerns regarding the important underutilisation of neoadjuvant chemotherapy in patients who have MIBC. Indeed, according to international guidelines, the vast majority of the patients included in our cohort should have received neoadjuvant chemotherapy [2,24]. Consequently, these observations suggest that substantial efforts should be made to improve guideline adherence with regard to the use of neoadjuvant chemotherapy before RC [2–4].

Second, our findings clearly show that the administration of neoadjuvant chemotherapy is not associated with detrimental perioperative outcomes in the overall population and when considering exclusively patients treated with RC and PLND. Indeed, the rates of 30- and 90-d perioperative complications, LoS, readmission, and mortality were comparable between patients treated with RC alone and those receiving RC plus neoadjuvant chemotherapy. This held true even when considering the specific types of complications. Particularly, although concerns have been raised regarding gastrointestinal toxicity related to the administration of cisplatin-based chemotherapy in the neoadjuvant setting, our investigation failed to show significant differences in the rates of gastrointestinal complications between patients treated with RC alone and RC plus neoadjuvant chemotherapy. These results are in line with what Grossman et al. reported [5]. In their landmark study, the authors evaluated a cohort of 317 patients enrolled in a prospective randomised trial and reported no significant differences in the rates or severity of postoperative complications between individuals receiving RC alone and NC plus neoadjuvant chemotherapy [5]. Since then, other, smaller-scale retrospective studies have confirmed these observations [25–29]. However, Johar et al. [16] recently reported that the administration of neoadjuvant chemotherapy represents an independent predictor of any and of high-grade complication after surgery. Several considerations should be factored in when comparing their results to ours. First, they included a cohort of patients treated with robot-assisted RC. Because of the better perioperative outcomes associated with the adoption of minimally invasive approaches, these findings might not be applicable to patients treated with an open approach [30]. Second, they evaluated a cohort of patients treated at high-volume referral centres. Findings obtained in this context are usually not comparable to general population data. Finally, their analyses were not restricted to patients who had MIBC. The inclusion of patients who have lower-stage and grade disease might have resulted in a favourable selection bias towards individuals not receiving neoadjuvant chemotherapy.

From a clinical standpoint, our observations suggest that, when clinically indicated, clinicians should strongly consider neoadjuvant chemotherapy to improve the OS rates of patients who have MIBC. Nonetheless, it is important to note that careful patient selection is necessary to optimise the trade-off between neoadjuvant chemotherapy benefits and toxicities. For example, baseline comorbidities and in particular impaired renal function might preclude the use of chemotherapy [15]. Similarly, suboptimal performance status (PS) and advanced age represent barriers to neoadjuvant chemotherapy use. These characteristics also predispose patients to a higher risk of complications after RC [16,17,25]. Consequently, the combination of neoadjuvant chemotherapy and RC may result in an exponential increase in detrimental outcomes or even death. It is also worthwhile to mention that as many as two out of three patients treated with RC will experience one or more complications within 90 d of surgery. In addition, one out of two RC patients will require readmission within 90 d. Finally, at 90 d after RC, approximately 1 out of 10 patients will die as a direct or indirect consequence of the surgery. These sobering facts and figures should be used for judicious patients selection.

Despite several strengths, our study is not devoid of limitations. First, patients receiving neoadjuvant chemotherapy might represent younger and healthier subjects and thus may be at a lower risk of perioperative morbidity and mortality. To minimise this potential bias, propensity score matching was performed. In addition, the lack of data regarding preoperative body mass index and the use of anticoagulant and antiplatelet medications in part limits our study. Similarly, because of the nature of our database, we could not adjust our analyses for preoperative PS and renal function, which represent determinants of neoadjuvant chemotherapy administration [15]. We attempted to circumvent these limitations by adjusting for CCI, which has been proven a reliable proxy of patient comorbidity status [18].

Second, our findings might not be generalizable to younger individuals, although it should be highlighted that younger patients are more likely to better tolerate systemic chemotherapy [31]. Thus, it is unlikely that neoadjuvant chemotherapy would have led to worse perioperative outcomes if younger and healthier patients were included in our analyses. Third, the SEER–Medicare database does not contain information on the number of neoadjuvant chemotherapy cycles completed nor on the proportion of patients who failed to complete their treatment because of treatment-related toxicity. Previous studies showed that although administration of neoadjuvant chemotherapy resulted in non-negligible toxicity, the majority of patients (87–94%) completed at least one cycle of neoadjuvant chemotherapy [5,7]. Similarly, it was not possible to know whether some patients who experienced complications after neoadjuvant chemotherapy were unable to undergo RC. In previous studies, the number of planned RCs was not affected despite neoadjuvant chemotherapy–related toxicities [5,6,9].

Fourth, the lack of data on surgical and hospital volume prevented us from adjusting our analyses for these important variables, which have been shown to have a significant impact on perioperative outcomes [32,33]. In addition, the SEER–Medicare database is based on claim files, which preclude detailed clinical information (eg, Clavien classification and cause of HBT administration). Consequently, we cannot exclude the possibility that RC plus neoadjuvant chemotherapy patients had more severe complications than their RC-alone counterparts. It is noteworthy that in prospective trials, no statistically significant differences with respect to severity of complications were observed [5]. That said, Medicare claims have a high degree of validity for detecting surgical complications, with roughly 90% of Medicare complications corroborated by medical records [34].

Finally, ascertainment of cause of death was achieved through the SEER-specific cause-of-death recode variable. Specifically, the vast majority of deaths recorded in this cohort were attributed to "urinary bladder" (ie, cancer-specific mortality). This observation reflects the fact that in the context of administrative databases, deaths occurred in the perioperative period are conventionally attributed to the cancer for which the surgery was performed [35]. Hence, some misattribution may have been applicable. That said, previous studies demonstrated that such cause-of-death misattribution results in minimal variations [35].

5. Conclusions

In patients who have MIBC treated with RC, the exposure to neoadjuvant chemotherapy is not associated with increased risk of postoperative morbidity and mortality. Consequently, neoadjuvant chemotherapy should be considered a safe approach in patients who have MIBC. Substantial efforts should be made to improve guideline adherence to the use of neoadjuvant chemotherapy when clinically indicated.

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Study concept and design: Gandaglia, Sun, Abdollah, Popa, Trinh, Briganti, Montorsi, Karakiewicz.
Acquisition of data: Gandaglia, Popa, Schiffmann.
Analysis and interpretation of data: Gandaglia, Sun.
Drafting of the manuscript: Gandaglia, Sun, Trinh, Briganti, Montorsi, Karakiewicz.
Critical revision of the manuscript for important intellectual content: Karakiewicz, Abdollah, Sun, Popa, Shiffmann, Shariat, Trinh, Briganti, Montorsi.
Statistical analysis: Gandaglia, Sun.
Obtaining funding: Karakiewicz, Trinh, Montorsi.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2014.01.014.

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