Complications after neoadjuvant chemotherapy and radical cystectomy for patients with bladder cancer

A propensity score matched analysis

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ABSTRACT

INTRODUCTION: Neoadjuvant chemotherapy (NAC) in combination with radical cystectomy (RC) is the standard of care for muscle-invasive bladder cancer (MIBC). We investigated the impact of NAC on postoperative complications after RC in patients with bladder cancer (BCa).

METHODS: Using the recently available American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) Targeted Cystectomy database, we identified adult patients (>18 years old), who underwent RC for the treatment of BCa. Patients were then dichotomized based on whether they received NAC. We performed a 1:1 propensity score matched (PSM) analysis based on demographic and perioperative covariates. Postoperative outcomes were then compared between the two matched groups. A multivariable analysis was also performed to identify if NAC was associated with any complication.

RESULTS: We identified 1582 eligible patients: 913 (57.7%) in the group that did not receive NAC and 669 (42.3%) in the group that did receive NAC. Before PSM, patients in the NAC group were younger, had lower American Society of Anesthesiology (ASA) scores, had higher rates of preoperative anemia, and were more likely to undergo continent urinary diversion. Similarly, before PSM patients in the NAC group had significantly higher rates of major complications, sepsis, urinary leak/fistula, and intraoperative/postoperative blood transfusion compared to the group that did not receive NAC; however, after 1:1 PSM, we did not find any significant difference in postoperative complication rates. Multivariable analysis confirmed that NAC was not associated with any complications.

CONCLUSIONS: We demonstrated that NAC does not impact 30-day postoperative complications in patients undergoing RC for BCa.

INTRODUCTION

Bladder cancer (BCa) is the 10th most common cancer in the world, accounting for roughly 3% of all new cancer diagnoses.[1,2] In males, BCa is three times more common with four times the mortality rate seen in females.[1] Urothelial BCa represents around 90% of cases worldwide and is associated with direct urothelial exposure to chemicals or tobacco smoking.[3] Muscle-invasive bladder cancer (MIBC) represents approximately 20% of newly diagnoses of BCa. The gold standard treatment for MIBC is radical cystectomy (RC) with pelvic lymph node dissection;[4] however, occult metastatic disease at the time of diagnosis carries a poor prognosis even after RC. The five-year overall survival (OS) for organ-confined MIBC is around 50%, while the five-year OS decreases to 30% with nodal disease.[5,6]

Urothelial carcinoma of the bladder has been found to be a chemosensitive tumor with a response rate ranging from 50–70% in metastatic disease.[7] This makes chemotherapy an encouraging treatment addition in MIBC. The rationale for neoadjuvant chemotherapy (NAC) is to control disease burden by treating micrometastases present at the time of diagnosis.[8] Cisplatin-based NAC is the gold standard treatment option for patients with MIBC prior to RC due to an improvement in OS, especially in patients with clinically localized disease.[9-11] Despite the significant benefit of NAC prior to RC on OS, most urological oncologists have a safety concern regarding the use of

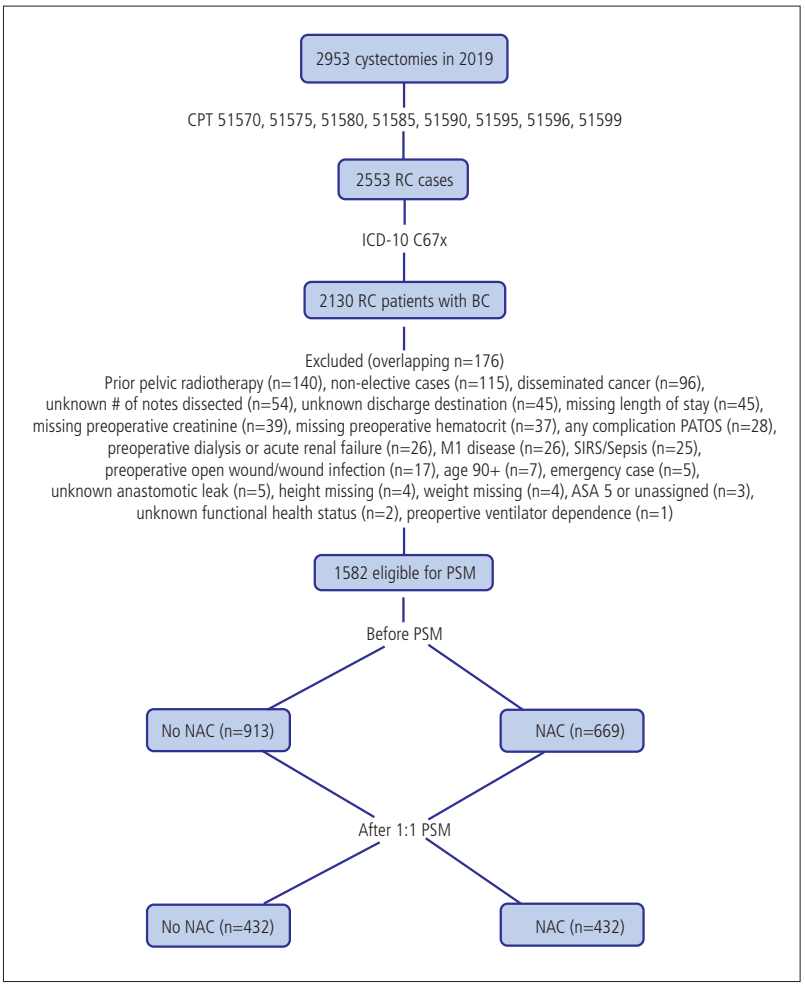

Figure 1. Study flowchart. ASA: American Society of Anesthesiology; BC: bladder cancer; NAC: neoadjuvant chemotherapy; PSM: propensity score-matched; RC: radical cystectomy; SIRS: systemic inflammatory response syndrome.

NAC, especially in frail and elderly patients, which has limited its use to approximately 20–30% of patients.[12]

Among the possible causes of NAC underuse is concern for increased perioperative complications.[12,13] Researchers have previously investigated the impact of NAC on postoperative complications after RC in patients with MIBC using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) Participant Use Data Files (PUFs) from 2005 and 2011; however, because of limitations inherent in the Ggeneral NSQIP PUFs, both studies used NAC administration limited to 30 days prior to surgery,[14,15] and did not have data on cystectomy-specific variables available in the new Urologic Procedure-Targeted PUFs.[16] Using the 2019 ACS-NSQIP Cystectomy-Targeted PUF, we sought to evaluate the impact of NAC (received within 90 days prior to surgery) on 30-day complications after RC in patients with BCa.

METHODS

Data acquisition

After obtaining exemption status from our institutional review board, access to the 2019 ACS-NSQIP Cystectomy-Targeted PUF database was requested. The ACS-NSQIP is a comprehensive outcomes database that has been nationally validated, with a high success rate of capturing 30-day surgical outcomes across hundreds of hospitals. The recently available ACS-NSQIP Procedure-Targeted PUFs for urology are part of an initiative that began in 2019. The PUF for cystectomy contains data from 107 participating hospitals. The database includes individual datapoints collected on specific surgical procedures performed, including numerous preoperative patient characteristics, intraoperative details, and postoperative outcomes up to 30 days.[17] At participating hospitals, data collection is performed per a standard protocol, with rigorous quality checks, and is then submitted for inclusion in the national registry. To make full use of the Procedure-Targeted PUF, the data must be merged with the General PUF of the corresponding year using the 'Case ID' matching variable.

Inclusion and exclusion criteria

We queried the NSQIP Cystectomy-Targeted database for patients who underwent RC for the treatment of BCs. Cases of RC were identified based on the following Current Procedural Terminology (CPT) codes: 51570, 51575, 51580, 51585, 51590, 51595, 51596, and 51999. Similarly, patients with a postoperative diagnosis of malignant neoplasm of the bladder were identified using the International Classification of Disease 10th Revision (ICD-10: C67.x). Patients were excluded if they had a history of prior pelvic radiotherapy, preoperative renal failure or dialysis, disseminated cancer, sepsis, open/infected wounds, or any complication already present at the time of surgery. We also excluded individuals with age greater than 90, patients with missing or unassigned values (preoperative hematocrit or creatinine, height, weight, length of stay [LOS], American Society of Anesthesiology [ASA] score, functional health status or discharge destination, number of nodes evaluated at the time of RC with lymph node dissection [LND], presence of anastomotic leak), as well as patients classified as ASA 5 or who were ventilator-dependent at the time of surgery, those

Table 1. Patient and procedure characteristics

Factor	Before propensity matching				After propensity matching			
	No NAC (n=913)	NAC (n=669)	p	ASD	No NAC (n=432)	NAC (n=432)	p	ASD
Preoperative profile								
Age (years)	72 (65–77)	67 (60–73)	<0.001	0.44	70 (62–76)	70 (63–75)	0.583	0.041
Female sex	176 (19.3%)	124 (18.5%)	0.746	0.019	87 (20.1%)	85 (19.7%)	0.932	0.012
Race			0.088	0.129			0.816	0.067
Caucasian	687 (75.2%)	515 (77.0%)			326 (75.5%)	334 (77.3%)		
African American	34 (3.7%)	27 (4.0%)			15 (3.5%)	15 (3.5%)		
Other	11 (1.2%)	17 (2.5%)			7 (1.6%)	9 (2.1%)		
Unknown	181 (19.8%)	110 (16.4%)			89 (19.4%)	74 (17.1%)		
Hispanic ethnicity			0.066	0.119			0.8	0.046
Yes	18 (2.0%)	19 (2.8%)			11 (2.5%)	10 (2.3%)		
No	717 (78.5%)	547 (81.8%)			342 (79.2%)	350 (81.0%)		
Unknown	178 (19.5%)	103 (15.4%)			79 (18.3%)	72 (16.7%)		
ASA			0.179	0.069			1	0.006
≤2	192 (21.0%)	160 (23.9%)			90 (20.8%)	89 (20.6%)		
>2	721 (79.0%)	509 (76.1%)			342 (79.2%)	343 (79.4%)		
BMI (kg/m²)	27.76 (24.75–31.24)	28.08 (24.84–31.92)	0.21	0.068	27.65 (24.85–31.61)	27.61 (24.58– 31.79)	0.969	0.007
Smoker	193 (21.1%)	176 (26.3%)	0.019	0.122	100 (23.1%)	103 (23.8%)	0.873	0.016
Dyspnea	61 (6.7%)	58 (8.7%)	0.148	0.075	39 (9.0%)	36 (8.3%)	0.809	0.025
m-FI-5 (%)			0.081	0.115			0.974	0.019
0	301 (33.0%)	252 (37.7%)			146 (33.8%)	148 (34.3%)		
1	435 (47.6%)	310 (46.3%)			209 (48.4%)	210 (48.6%)		
≥2	177 (19.4%)	107 (16.0%)			77 (17.8%)	74 (17.1%)		
Bleeding disorder	13 (1.4%)	23 (3.4%)	0.01	0.131	11 (2.5%)	13 (3.0%)	0.837	0.028
Steroid/immunosuppresant for a chronic condition	26 (2.8%)	20 (3.0%)	0.881	0.008	13 (3.0%)	11 (2.5%)	0.837	0.028
Prior pelvic surgery	446 (48.8%)	296 (44.2%)	0.074	0.092	191 (44.2%)	191 (44.2%)	1	<0.001
>10% loss of body weight	20 (2.2%)	25 (3.7%)	0.091	0.091	13 (3.0%)	8 (1.9%)	0.377	0.075
Preoperative creatinine (mg/dL)	1.05 (0.89–1.35)	1.11 (0.91–1.32)	0.208	0.1	1.04 (0.88–1.37)	1.12 (0.93–1.33)	0.145	0.037
Preoperative anemia	343 (37.6%)	513 (76.7%)	<0.001	0.86	283 (65.5%)	278 (64.4%)	0.776	0.024
Preoperative transfusion	2 (0.2%)	5 (0.7%)	0.141	0.076	2 (0.5%)	0 (0.0%)	0.499	0.096

Continuous variables given as median (interquartile range), categorical variables given as frequencies (percentages). ASD: absolute standardized difference; ASA: American Society of Anesthesia; BMI: body mass index; m-FI-5: modified 5-item frailty index; NAC: neoadjuvant chemotherapy; UD: urinary diversion.

Table 1 (cont'd). Patient and procedure characteristics

Factor	Before propensity matching				After propensity matching			
	No NAC (n=913)	NAC (n=669)	p	ASD	No NAC (n=432)	NAC (n=432)	p	ASD
Procedure characteristics								
Urinary diversion type			0.002	0.178			0.479	0.082
Ileal conduit	756 (82.8%)	511 (76.4%)			349 (80.8%)	349 (80.8%)		
Continent UD	118 (12.9%)	130 (19.4%)			65 (15.0%)	71 (16.4%)		
Unknown	39 (4.3%)	28 (4.2%)			18 (4.2%)	12 (2.8%)		
Operative approach			0.078	0.115			0.988	0.01
Open (planned)	645 (70.6%)	438 (65.5%)			305 (70.6%)	303 (70.1%)		
Robotic	157 (17.2%)	141 (21.1%)			74 (17.1%)	75 (17.4%)		
Other	111 (12.2%)	90 (13.5%)			53 (12.3%)	54 (12.5%)		
Wound classification			0.957	0.028			0.927	0.056
I - Clean	13 (1.4%)	8 (1.2%)			7 (1.6%)	5 (1.2%)		
II - Clean/contaminated	844 (92.4%)	617 (92.2%)			398 (92.1%)	398 (92.1%)		
III - Contaminated	53 (5.8%)	42 (6.3%)			26 (6.0%)	27 (6.2%)		
IV - Dirty/infected	3 (0.3%)	2 (0.3%)			1 (0.2%)	2 (0.5%)		
Drain placement	863 (94.5%)	650 (97.2%)	0.012	0.132	418 (96.8%)	415 (96.1%)	0.715	0.037
Use of stents	791 (86.6%)	611 (91.3%)	0.004	0.15	386 (89.4%)	387 (89.6%)	1	0.008
Number of nodes evaluated	16 (10–24)	18 (11–26)	<0.001	0.19	17 (10–25)	17 (11–26)	0.499	0.048
Operative time (minutes)	303 (234–391)	343.00 (272–421)	<0.001	0.304	317 (244–414)	328 (256– 403)	0.596	0.003

Continuous variables given as median (interquartile range), categorical variables given as frequencies (percentages). ASD: absolute standardized difference; ASA: American Society of Anesthesia; BMI: body mass index; m-FI-5: modified 5-item frailty index; NAC: neoadjuvant chemotherapy; UD: urinary diversion.

with confirmed metastatic (M1) disease from BCa, or non-elective/emergent RC.

Variables

The preoperative profiles included the following variables: age, sex, race, Hispanic ethnicity, body mass index (BMI), ASA score, smoking history, steroid use for a chronic condition, history of prior pelvic surgery, dyspnea, bleeding disorder (underlying hematological dyscrasia or chronic anticoagulation), hypertension, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease (COPD), >10% loss of body weight in the six months preceding RC, and dependent functional health status. For race, all other races besides Caucasian and African American were combined to make an 'other' category. The variables for race and Hispanic ethnicity were allowed to have an 'unknown' category in order to preserve our sample size. The variables for hypertension, COPD, congestive heart failure, diabetes mellitus, and functional health status were used to calculate the modified five-item frailty index (mFI-5);[18] the three categories for mFI-5 were: 0, 1, and ≥2.

Additionally, we included preoperative serum creatinine, preoperative anemia, and preoperative blood transfusion (within 72 hours prior to RC). Regarding the surgical procedure, we analyzed the type of urinary diversion and surgical approach, operative time, number of nodes evaluated, intra-abdominal drain placement, use of anastomotic stent, and wound class. For urinary diversion type, we used CPT codes 51590 and 51595 for ileal conduit, while CPT code 51596 was used for orthotopic neobladder; others were classified as 'unknown.' Regarding the operative approach, open (planned) and robotic approaches were left unmodified, while 'hybrid,' 'laparoscopic,' any 'unplanned con-

version,' and any minimally invasive approach with 'hand-assist' were combined into an 'other' category. Pathological TNM staging for the matched cohort is also reported.

Endpoints

The main outcomes of interest were 30-day major and minor complications according to the Clavien-Dindo (CD) classification. Major complications (defined as CD 3–5) were the following: death, cardiac arrest requiring cardiopulmonary resuscitation, myocardial infarction, stroke, pulmonary embolism, failure to wean from the ventilator, unplanned intubation, pneumonia, acute renal failure, sepsis, septic shock, wound disruption, deep or organ/space surgical site infection (SSI), reoperation, anastomotic leak treated with interventional means or reoperation, urinary leak/fistula, lymphocele with required intervention/reoperation, rectal injury detected intraoperatively or postoperatively treated with reoperation, ureteral obstruction requiring reintervention, and preoperative ureteral obstruction worsened requiring intervention.

Minor complications (defined as CD 1–2) were the following: progressive renal insufficiency, pneumonia, superficial SSI, blood transfusion, deep venous thrombosis, urinary tract infection, *Clostridium difficile* infection, ileus, anastomotic leak with no treatment intervention documented, anastomotic leak treated with non-interventional/non-operative means, lymphocele with no treatment intervention documented, rectal injury detected postoperatively treated with non-interventional means, and ureteral obstruction treated without intervention. Secondary endpoints of interest were readmission, extended LOS, and non-home discharge. Secondarily, we examined the rates of individual complications previously mentioned. Extended LOS was defined as a total hospital stay ≥75th percentile (i.e., eight days).

Statistical analysis

We compared the preoperative profiles of the two groups: NAC vs. no-NAC, along with the postoperative outcomes. BMI (kg/m^2) was calculated as: 703 × (weight/height^2). Preoperative anemia was computed based on the preoperative hematocrit: <40% in males and <35% in females.[19] Continuous data were reported as median (interquartile range) and analyzed using the Mann-Whitney U test. Categorical variables were expressed as numbers (%), and differences between the two groups were assessed using Chi-squared or Fisher's exact test where appropriate. To control for differences between the two groups, we performed propensity score matching (PSM). A conditional logistic regression model was fitted to having received NAC as the outcome, while the covariates used were age, sex, BMI, ASA score (dichotomized into ≤2 and >2), race, mFI-5, use of steroids for a chronic condition, bleeding disorder, smoking history, dyspnea, >10% weight loss in the six months preceding RC, operative time, preoperative creatinine, preoperative anemia, preoperative blood transfusion, surgical approach, urinary diversion type, intra-abdominal drain placement, history of pelvic surgery, use of intraoperative anastomotic stent, number of nodes evaluated, and wound class. Since Hispanic ethnicity had a variance inflation factor >2.5, it was considered highly multicollinear and was not included in the model.

Table 2. Tumor characteristics

Factor	Before propensity matching			After propensity matching		
	No NAC (n=913)	NAC (n=669)	p	No NAC (n=432)	NAC (n=432)	p
T stage			<0.001			<0.001
Tx	6 (0.7%)	6 (0.9%)		3 (0.7%)	5 (1.2%)	
T0	59 (6.5%)	144 (21.5%)		30 (6.9%)	84 (19.4%)	
Ta	55 (6.0%)	9 (1.3%)		30 (6.9%)	6 (1.4%)	
Tis	94 (10.3%)	74 (11.1%)		35 (8.1%)	48 (11.1%)	
T1	119 (13.0%)	64 (9.6%)		50 (11.6%)	41 (9.5%)	
T2	182 (19.9%)	136 (20.3%)		84 (19.4%)	86 (19.9%)	
T3	273 (29.9%)	149 (22.3%)		134 (31.0%)	103 (23.8%)	
T4	90 (9.9%)	54 (8.1%)		49 (11.3%)	38 (8.8%)	
Unknown	35 (3.8%)	33 (4.9%)		17 (3.9%)	21 (4.9%)	
N stage			0.231			0.07
Nx	29 (3.2%)	11 (1.6%)		12 (2.8%)	10 (2.3%)	
N0	664 (72.7%)	497 (74.3%)		291 (67.4%)	322 (74.5%)	
N1	68 (7.4%)	47 (7.0%)		42 (9.7%)	25 (5.8%)	
N2	98 (10.7%)	65 (9.7%)		62 (14.4%)	41 (9.5%)	
N3	10 (1.1%)	14 (2.1%)		4 (0.9%)	12 (2.8%)	
Unknown	44 (4.8%)	35 (5.2%)		21 (4.9%)	22 (5.1%)	
M stage			0.381			0.214
M0	529 (57.9%)	372 (55.6%)		253 (58.6%)	244 (56.5%)	
Unknown	384 (42.1%)	297 (44.4%)		179 (41.4%)	188 (43.5%)	

Tx: could not be assessed. Continuous variables given as median (interquartile range), categorical variables given as frequencies (percentages). NAC: neoadjuvant chemotherapy.

Table 3. 30-day postoperative complications

Factor	Before propensity matching			After propensity matching		
	No NAC (n=913)	NAC (n=669)	p	No NAC (n=432)	NAC (n=432)	p
Acute renal failure	10 (1.1%)	7 (1.0%)	1	7 (1.6%)	5 (1.2%)	0.773
Anastomotic leak	15 (1.6%)	21 (3.1%)	0.06	10 (2.3%)	11 (2.5%)	1
Cardiac arrest requiring CPR	9 (1.0%)	1 (0.1%)	0.051	7 (1.6%)	1 (0.2%)	0.069
Clostridium difficile infection	16 (1.8%)	14 (2.1%)	0.71	3 (0.7%)	9 (2.1%)	0.143
Deep incisional SSI	5 (0.5%)	1 (0.1%)	0.411	3 (0.7%)	1 (0.2%)	0.624
DVT requiring therapy	12 (1.3%)	8 (1.2%)	1	10 (2.3%)	6 (1.4%)	0.45
Extended length of stay (≥8 days)	265 (29.0%)	185 (27.7%)	0.573	130 (30.1%)	125 (28.9%)	0.765
Failure to wean from ventilator	4 (0.4%)	3 (0.4%)	1	3 (0.7%)	2 (0.5%)	1
Ileus	151 (16.5%)	92 (13.8%)	0.138	70 (16.2%)	60 (13.9%)	0.392
Intraop/postop transfusion	203 (22.2%)	207 (30.9%)	<0.001	133 (30.8%)	138 (31.9%)	0.769
Lymphocele	43 (4.7%)	43 (6.4%)	0.145	19 (4.4%)	31 (7.2%)	0.108
Major complications	171 (18.7%)	164 (24.5%)	0.006	87 (20.1%)	106 (24.5%)	0.141
Minor complications	425 (46.5%)	333 (49.8%)	0.222	229 (53.0%)	224 (51.9%)	0.785
Mortality	13 (1.4%)	6 (0.9%)	0.484	7 (1.6%)	4 (0.9%)	0.546
Myocardial infarction	9 (1.0%)	6 (0.9%)	1	3 (0.7%)	2 (0.5%)	1
Non-home discharge	98 (10.7%)	53 (7.9%)	0.069	48 (11.1%)	35 (8.1%)	0.166
Organ/space SSI	54 (5.9%)	40 (6.0%)	1	27 (6.2%)	28 (6.5%)	1
Pneumonia	18 (2.0%)	6 (0.9%)	0.097	9 (2.1%)	6 (1.4%)	0.604
Progressive renal insufficiency	17 (1.9%)	19 (2.8%)	0.233	11 (2.5%)	10 (2.3%)	1
Pulmonary embolism	11 (1.2%)	5 (0.7%)	0.452	5 (1.2%)	3 (0.7%)	0.725
Readmission	194 (21.2%)	146 (21.8%)	0.804	102 (23.6%)	93 (21.5%)	0.515
Rectal injury	7 (0.8%)	9 (1.3%)	0.312	3 (0.7%)	6 (1.4%)	0.506
Reoperation	30 (3.3%)	32 (4.8%)	0.149	13 (3.0%)	18 (4.2%)	0.465
Sepsis	51 (5.6%)	56 (8.4%)	0.033	27 (6.2%)	36 (8.3%)	0.295
Septic shock	15 (1.6%)	9 (1.3%)	0.683	8 (1.9%)	5 (1.2%)	0.578
Stroke	4 (0.4%)	1 (0.1%)	0.404	2 (0.5%)	1 (0.2%)	1
Superficial incisional SSI	48 (5.3%)	19 (2.8%)	0.022	24 (5.6%)	13 (3.0%)	0.092
Unplanned intubation	12 (1.3%)	8 (1.2%)	1	8 (1.9%)	8 (1.9%)	1
Ureteral obstruction	48 (5.3%)	31 (4.6%)	0.641	24 (5.6%)	20 (4.6%)	0.643
Urinary leak/fistula	21 (2.3%)	32 (4.8%)	0.010	13 (3.0%)	25 (5.8%)	0.067
Urinary tract infection	60 (6.6%)	54 (8.1%)	0.279	29 (6.7%)	38 (8.8%)	0.309
Wound disruption	14 (1.5%)	15 (2.2%)	0.344	6 (1.4%)	10 (2.3%)	0.45

Categorical variables given as percentages. CPR: cardiopulmonary resuscitation; DVT: deep venous thrombosis; NAC: neoadjuvant chemotherapy; SSI: surgical site infection.

After obtaining a propensity score, we performed 1:1 matching using the nearest-neighbor method, with a caliper size of 0.2 to identify the impact of NAC on 30-day complication rates after RC. The absolute standardized difference (ASD) was measured to determine the balance between the two groups before and after propensity score matching. An ASD value <0.1 was used as the cutoff for sufficient balance between the two groups. After 1:1 PSM, categorical variables were compared using Chi-squared or Fisher's exact test where appropriate, while continuous variables were compared using the Mann-Whitney U test. We conducted a sensitivity analysis by repeating the PSM after listwise deletion (complete case analysis). A subgroup analysis for patients >75 years old was also performed, given that increasing age has been associated with decreased use of NAC.[12] All statistical analyses were conducted using the RCommander package with the EZR plugin for R version 4.1.0,[20] with significance defined as two-tailed p<0.05 for all tests

RESULTS

A total of 1582 patients met inclusion criteria: 913 in the no-NAC group and 669 in the NAC group (Figure 1). Before PSM, patients receiving NAC were younger (67 vs. 72, p<0.001), had higher rates of preoperative anemia (76.7% vs. 37.6%, p<0.001), more likely to have a bleeding disorder (3.4% vs. 1.4%, p<0.01), more likely to be smokers (26.3% vs. 21.1%, p=0.019), more likely to undergo continent urinary diversion (19.4% vs. 12.9%, p=0.002), had a higher number of lymph nodes evaluated (18 vs. 16, p<0.001), and experienced greater operative times (343 vs. 303 minutes, p<0.001) (Table 1). Pathology results indicated a higher rate of complete response (pT0: 19.7% vs. 6.5%) among patients in the NAC group compared to their counterparts (Table 2). Likewise, before PSM, patients in the NAC group had higher rates of 30-day major complications (CD 3–5) (24.5% vs. 18.7%, p=0.006), urinary leak/fistula (4.8% vs. 2.3%, p<0.05), intraoperative/postoperative blood transfusion (30.9% vs. 22.2%, p<0.001), and lower rates of superficial incisional SSI (2.8% vs. 5.3%, p <0.05) (Table 3).

After 1:1 PSM, 864 patients remained, with 432 well-balanced pairs (Table 1). We did not find any significant difference in rates of major or minor 30-day complications or any other endpoint of interest (Table 3). In the sensitivity analysis, we generated a total of 178 matched pairs and found no significant difference in rates of 30-day complications. In our subgroup analysis of patients >75 years old (n=386), we were able to balance 85 pairs. We

Table 4. Multivariable analysis of factors associated with any 30-day complication

Factor	OR	95% CI	p
Age (per unit increase)	1.02	1.01–1.04	0.001
Anastomotic stent placement	0.62	0.44–0.88	0.01
ASA score			
<2	1	Reference	
≥2	1.16	0.89–1.51	0.277
Bleeding disorder	0.65	0.32–1.31	0.23
BMI (per unit increase)	1.02	1.00–1.04	0.030
Chronic steroid use	2.98	1.46–6.10	0.003
Drain placement	1.05	0.62–1.77	0.87
Dyspnea	0.80	0.54–1.20	0.29
Female sex	1.69	1.27–2.25	<0.001
mFI-5			
0	1	Reference	
1	1.24	0.97–1.58	0.088
≥2	1.45	1.05–2.02	0.025
Neoadjuvant chemotherapy	1.06	0.83–1.35	0.635
Number of nodes evaluated	1.00	0.99–1.01	0.532
Operative approach			
Open (planned)	1	Reference	
Robotic	0.38	0.28–0.51	<0.001
Other	0.35	0.25–0.49	<0.001
Operative time (per unit increase)	1.00	1.00–1.00	0.002
Preoperative creatinine (per unit increase)	1.15	0.92–1.44	0.22
Preoperative transfusion	0.88	0.17–4.57	0.880
Race			
Caucasian	1	Reference	
African American	1.80	0.99–3.29	0.06
Other	1.39	0.60–3.19	0.44
Unknown	0.83	0.63–1.11	0.21
Urinary diversion type			
Ileal conduit	1	Reference	
Continent urinary diversion	1.98	1.44–2.72	<0.001
Unknown	0.84	0.49–1.43	0.525

ASA: American Society of Anesthesia; BMI: body mass index; CI: confidence interval; mFI-5: modified 5-item frailty index; OR: odds ratio.

Table 4 (cont'd). Multivariable analysis of factors associated with any 30-day complication

Factor	OR	95% CI	p
Wound classification			
I - Clean	1	Reference	
II - Clean/contaminated	1.13	0.46–2.77	0.80
III - Contaminated	1.26	0.46–3.43	0.65
IV - Dirty/infected	1.99	0.18–22.10	0.58
>10% loss of body weight	1.18	0.61–2.27	0.62

ASA: American Society of Anesthesia; BMI: body mass index; CI: confidence interval; mFI-5: modified 5-item frailty index; OR: odds ratio.

failed to demonstrate differences in adjusted complication rates between the groups after PSM. A multivariable analysis of key preoperative factors associated with any 30-day complication in the entire cohort was performed. Patients with a mFI-5 ≥2 had 1.5x higher odds of any complication (p=0.025); female patients had 1.7x higher odds of any complication (p<0.001); chronic steroid use had 3x higher odds of any complication (p=0.003). Increasing age and BMI were also associated with higher odds of any 30-day complication (Table 4).

DISCUSSION

The use of NAC is strongly recommended in patients with MIBC. NAC can eradicate systemic micrometastases at the time of diagnosis that are impossible to be excise at the time of RC.[9] The tolerability of the chemotherapeutic regimen by the patient is expected to be higher preoperatively compared to after RC. Completion of NAC leads to favorable pathological staging following surgery, reflected by complete response, negative surgical margins, and absent nodal compromise.[4] Multiple studies have shown that NAC leads to a marked improvement in five-year OS following surgery.[21,22] A recent metanalysis of 17 articles by Hamid et al found significant improvement in OS for patients who received NAC compared to RC alone, with a hazard ratio of 0.82 (95% confidence interval 0.71–0.95).[23]

The two most used chemotherapy regimens for BCs are: 1) methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC); and 2) gemcitabine and cisplatin/carboplatin (GC). Yin et al conducted a systematic review and meta-analysis comparing MVAC and GC. The authors found no significant difference in the pathological response between the two regimens; however, GC was associated with a significant reduction in OS.[6] Despite the OS benefits, most urological oncologists have concerns about the use of NAC. The major concerns center around comorbidities, adverse effects, the risk of perioperative morbidity, and delay in definitive treatment. This explains why the use of NAC prior to surgery remains limited despite almost two-thirds of patients being elegible.[24] Nonetheless, there are several advantages of NAC, including favorable pathological response rate, better tolerability and patient compliance, and the determination of tumor chemosensitivity.

A limited number of studies have assessed the effect of NAC on postoperative complications after surgery. In the current study, we did not find any significant difference in rates of 30-day major or minor complications or any other measures of interest in a matched population. This is in agreement with Tyson et al, who reported no differences in major 30-day perioperative surgical complication rates between those who received NAC prior to surgery compared to those who did not receive NAC. In addition, the authors reported that there was no difference in the incidence of preoperative and postoperative renal insufficiency, which is one of the major toxicities of cisplatin-based chemotherapy.[15] Our study found no significant difference in the incidence of renal failure before or after PSM.

Additionally, Johnson et al reported that NAC does not increase rate of complications, including acute renal failure and progressive renal insufficiency, in patients undergoing RC.[14] The incidence of peripheral nerve deficit was higher in the study done by Tyson et al, which was explained as an expected side effect of platinum-based chemotherapy; however, Johnson et al showed there was no difference in the incidence of nerve injury between the two cohorts.[14,15] In our study, we lack data regarding the incidence of peripheral nerve injury following RC, since the collection of that variable was discontinued.

Venous thromboembolism (VTE) is one of the major complications in patients with MIBC. Major practice guidelines from both the American Urological Association and European Association of Urology recommend pharmacological prophylaxis for up to four weeks in patients with high risk for VTE. Our study showed that the incidence of VTE was lower (1.3%) than has been previously reported in the literature, irrespective of the NAC status. Despite the lack of

data on pharmacological prophylaxis in the NSQIP database, it is likely that the prevalence of standard prophylaxis, including mechanical and pharmacological, may contribute to a lower incidence of VTE. Previous studies have similarly shown a significant increase in the incidence of VTE in patients undergoing NAC for BCa, even in the immediate postoperative period.[25] In contrast, our study found no significant difference in the incidence of VTE. Our findings should further strengthen the confidence among clinicians in the use of NAC in patients with MIBC.

We are the first to report on cystectomy-specific complications using a NSQIP Procedure-Targeted PUF, along with PSM. We found no statistically significant difference in the incidence of 30-day urinary leakage/fistulae, urinary tract infection, ureteral obstruction, rectal injury, readmission, and reoperation between the two cohorts. This is in accordance with a retrospective, single-institution analysis by Milenkovic et al, which showed no significant difference in genitourinary complications following surgery between patients who received NAC vs. patients who did not.[26]

Limitations

There are several limitations to our study that are inherent to national registries. Although NSQIP is a robust dataset, we only have followup data of 30 days post-cystectomy. As NSQIP reports retrospective data, we are unable to perform randomization; however, we were able to improve selection bias by using PSM. As with any national database, there is less granularity without possibility of performing detailed queries; thus, there is a lack of information regarding the chemotherapeutic regimen or number of cycles received by patients in the NAC cohort. We were only able to ascertain that NAC was administered within 90 days prior to RC, which is a strength compared to previous NSQIP studies.[14,15] We are also unable to ascertain the differences in OS between the two cohorts in the current study, since long-term data is not available in the NSQIP database. Moreover, we were not able to determine the specific reasons for a patient not receiving NAC. Further research is needed to elucidate potential reasons why patients may not be receiving NAC despite being cisplatin-eligible.

CONCLUSIONS

To the best of our knowledge, this is the first NSQIP study that evaluates chemotherapy received within 90 days prior to surgery along with cystectomy-specific complications, such as rectal injury, lymphocele, anastomotic leak, and urinary fistula, in patients with MIBC. There was no significant difference in 30-day minor or major complications in patients who received NAC prior to RC compared to those who received RC alone.

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