Perioperative complications after neoadjuvant chemotherapy and radical cystectomy for bladder cancer

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Introduction: *Few data on the perioperative outcomes of cystectomy after neoadjuvant chemotherapy (NAC) exist. In this study, we evaluated whether patients who had previously received NAC were at higher risk of developing perioperative complications.*

Materials and methods: *The National Surgical Quality Improvement Program (NSQIP) database was searched to identify cystectomies performed between January 1, 2005 and December 31, 2011. Of 1394 patients identified, about one-tenth (n = 122 [8.8%]) received NAC. A propensity-weighted comparative analysis of perioperative morbidity was conducted.*

Results: *In unadjusted comparisons, patients undergoing cystectomy after NAC were more likely to have peripheral nerve deficits (1.6% [2/122] versus 0.2% [3/1272]; p = .01), blood transfusions (37.7% [46/122] versus 27.5% [350/1272]; p = .02), and unplanned readmissions (11.5% [14/122] versus 6.6% [84/1272]; p = .04), but were less likely to require hospitalization longer than 8 days (45.1% [55/122] versus 58.8% [748/1272]; p = .01). Propensity-weighted adjustments showed that cystectomy after NAC produced little increased risk of perioperative surgical complications except for peripheral nerve deficits (3.2% [4/122] versus 0.3% [3/1166]; propensity score–adjusted odds ratio [PS-OR], 13.1; 95% CI, 1.90-90.8; p = .01) and resulted in better rates of wound dehiscence (0.8% [1/122] versus 3.3% [38/1166]; PS-OR, 0.20; 95% CI, 0.04-0.89; p = .04) and sepsis (4.9% [6/122] versus 11.4% [134/1166]; PS-OR, 0.36; 95% CI, 0.17-0.76; p = .01). No differences in 30 day mortality were noted.*

Conclusions: *NAC is not associated with perioperative complications after cystectomy. As expected, there was an increase in peripheral nerve deficits in the neoadjuvant chemotherapy group, but this was likely due to the known neurotoxicity of the cisplatin agents.*

Key Words: bladder cancer, radical cystectomy, neoadjuvant chemotherapy, perioperative outcomes

Introduction

Radical cystectomy is the gold standard for treatment of clinically localized muscle-invasive bladder cancer (MIBC). Despite local therapy, the 5 year survival rate of patients with MIBC is approximately 50%.[1] Disease recurrence is often a result of the presence of micrometastatic disease at presentation. Although adjuvant chemotherapy has been used to delay recurrence and prolong survival in high risk patients with MIBC,[2] the principal disadvantages of this approach include the delay to administration of potentially curative systemic therapy, the lack of in vivo response assessment, and difficulties related to administering chemotherapy after cystectomy. Furthermore, up to 30% of patients may have a postsurgical complication that preempts their eligibility for adjuvant chemotherapy.[3]

As a result, neoadjuvant chemotherapy (NAC) protocols incorporating cisplatin-based regimens have been developed to improve the delivery of systemic treatment to patients with MIBC. Level 1 evidence from randomized clinical trials has suggested that platinum-based combination regimens have led to improved overall and disease-free survival in patients with clinical

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stage T2-T4a MIBC.[4,5] In a randomized trial reported by Grossman et al,[4] patients with T2 bladder cancer treated with NAC had a 105 month median survival compared to a 75 month median survival for patients treated with cystectomy alone. In a subsequent meta-analysis, the absolute improvement in 5 year overall and disease-free survival was 5% and 9%, respectively.[5] This translates into a number needed to treat of 20 patients, which is comparable to, and in some instances better than, the accepted figures for the use of perioperative chemotherapy in the treatment of esophageal,[6] lung,[7] and breast cancers.[8]

Despite the improvement in overall survival with NAC, several reports have indicated that its use in patients with bladder cancer remains low.[9,10] Several factors may account for this variation in practice patterns, but one potential reason relates to concerns that NAC may increase the risk of perioperative morbidity. In light of existing uncertainty regarding whether or not NAC is associated with an increase in the risk of perioperative complications, we sought to study a cohort of patients receiving NAC prior to cystectomy using a national data set. To our knowledge, no other study using administrative data has yet addressed the perioperative risks associated with cystectomy after NAC. In this study, we performed a propensity-weighted, population-based analysis to determine the perioperative morbidity and mortality of patients undergoing cystectomy after NAC.

Materials and methods

Data

Data for this study were obtained from the participant use files of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP). The general methods of NSQIP have previously been described in detail.[11-13] In brief, NSQIP collects clinical data on patients undergoing major surgical procedures at more than 200 hospitals; these data encompass more than 130 variables, including preoperative demographic and comorbidity data, intraoperative and perioperative complications, and mortality outcomes for 30 days after the operation.[14] Trained surgical staff reviewers record the data using standardized definitions. The accuracy of the data is ensured by the use of vigorous quality control measures, including intensive training for data collectors and periodically conducted interrater reliability audits of participating sites.[15]

Study population

Patients were included in the study if they had undergone a radical cystectomy between January 1, 2005 and December 31, 2011 as determined by any of the following Common Procedural Terminology codes listed for the principal operative procedure: 51570, 51575, 51580, 51585, 51590, 51595, 51596, and 51597. Patients undergoing partial cystectomy were excluded. Patients were divided into two groups: those who had received NAC and those who had not received NAC chemotherapy.

Complications

The 30 day outcomes analysis included mortality, wound events (superficial, deep, or organ/space surgical site infection), sepsis, pulmonary events (pneumonia, ventilation > 48 hours), renal failure rates, thromboembolic (deep venous thrombosis or pulmonary embolism), cardiovascular, and neurologic events (stroke with deficit, cardiac arrest, or infarct). Hospital length of stay, rates of return to the operating suite, total operative time, and total blood transfusions were also analyzed. A glossary of definitions for these complications has been previously published.[11]

Statistical analysis

Differences in patient demographics and clinical characteristics were evaluated using the χ^2 or the Fisher exact test for categorical data, whereas continuous variables were evaluated using the t test. Normality assumptions were verified using ladder of powers plots. A 2-sided p value of $< .05$ was considered statistically significant. Because patients who received NAC may differ from those who did not in terms of preoperative clinical and demographic characteristics, we used propensity-weighted comparisons to account for some of these known baseline differences. The propensity score is based on the probability of receiving NAC as a function of patient demographics and clinical characteristics and is obtained using logistic regression assuming common support.[16] Propensity-weighted methods attempt to balance patient characteristics between groups by controlling for factors that might influence group assignment and outcome. Logistic regression models were used to conduct the propensity-weighted adjustments to estimate the propensity of undergoing NAC on the basis of select preoperative clinical and demographic characteristics. The data for each patient were then weighted on the inverse propensity of being in one of the two treatment groups. Variables used for propensity weighting are listed in Table 1. The covariate balance was checked after propensity weighting and all variables were found to be balanced. All statistical calculations were performed using Stata/MP version 12.0 (StataCorp LP, TX, USA).

TABLE 1. **Preoperative clinical and demographic characteristics of 1394 patients undergoing cystectomy who had or did not have neoadjuvant chemotherapy**

	Before propensity-weighting No. (%)			After propensity-weighting No. (%)[a]		
	Chemo (n = 122)	No chemo (n = 1272)	p value	Chemo (n = 122)	No chemo (n = 1166)	p value
Characteristic						
Race			.52			.64
White	95 (77.9)[b]	1006 (79.1)[c]		94 (77.0)	941 (80.7)	
Black	8 (6.6)[b]	66 (5.2)[c]		7 (5.7)	59 (5.1)	
Hispanic	5 (4.1)[b]	29 (2.3)[c]		4 (3.3)	24 (2.1)	
Other/unknown	14 (11.5)[b]	170 (13.4)[c]		17 (13.9)	142 (12.2)	
Age, mean (SD), y	63.7 (11.2)[b]	66.3 (12.1)	.02	66.4 (10.8)	66.2 (11.8)	.90
Male sex	92 (75.4)	912 (71.7)	.32	87 (71.3)	843 (72.3)	.68
Year of surgery			< .001			.24
2005-2006	3 (2.5)	45 (3.5)		9 (7.4)	36 (3.1)	
2007	6 (4.9)	63 (5.0)		17 (13.9)	55 (4.7)	
2008	8 (6.6)	101 (7.9)		16 (13.1)	89 (7.6)	
2009	7 (5.7)	264 (20.8)		6 (4.9)	238 (20.4)	
2010	22 (18.0)	327 (25.7)		15 (12.3)	295 (25.3)	
2011	76 (62.3)	472 (37.1)		59 (48.4)	452 (38.8)	
ASA classification			.36			.34
I	0 (0)	17 (1.3)		0 (0)	10 (0.9)	
II	32 (26.2)	314 (24.7)		24 (19.7)	284 (24.4)	
III	87 (71.3)	865 (68.0)		92 (75.4)	802 (68.8)	
IV	3 (2.5)	75 (5.9)		6 (4.9)	69 (5.9)	
V	0 (0)	1 (0.1)		0 (0)	1 (0.1)	
Body mass index, mean (SD)	28.5 (5.1)	28.0 (5.9)	.35	27.9 (5.5)	28.0 (6.0)	.85
Diabetes mellitus			.01			.71
Insulin dependent	2 (1.6)	82 (6.4)		2 (1.6)	77 (6.6)	
Non-insulin dependent	9 (7.4)	167 (13.1)		15 (12.3)	140 (12.0)	
Current smoker	30 (24.6)	317 (24.9)	.94	34 (27.9)	295 (25.3)	.63
Current alcoholic	5 (4.1)	43 (3.4)	.68	3 (2.5)	42 (3.6)	.42
History of COPD	6 (4.9)	89 (7.0)	.38	14 (11.5)	78 (6.7)	.44
History of CAD	15 (12.3)	201 (15.8)	.31	24 (19.7)	190 (16.3)	.68
Hypertension	65 (53.3)	695 (54.6)	.79	65 53.3	644 (55.2)	.77
History of CVA/TIA	2 (1.6)	93 (7.3)	.02	12 (9.8)	79 (6.8)	.70
Disseminated cancer	20 (16.4)	108 (8.5)	.004	11 (9.0)	108 (9.3)	.95
Chronic corticosteroids	6 (4.9)	41 (3.2)	.32	3 (2.5)	38 (3.3)	.55
Preoperative lab values, mean (SD)						
White blood cell count, $x10^9$	7.3 (3.5)	7.9 (3.3)	.09	8.1 (3.8)	7.8 (3.2)	.53
Hematocrit, %	35.6 (4.3)	37.7 (5.5)	<.001	36.8 (4.6)	37.5 (5.7)	.36
Platelets, $\times10^9$	260.3 (125.4)	260.2 (102.4)	.99	281.1 (137.6)	260.7 (103.6)	.25
Creatinine, mg/dL	1.10 (0.34)	1.17 (0.83)	.42	1.18 (0.33)	1.16 (0.83)	.80
Albumin, g/L	3.9 (0.59)	3.8 (0.65)	.23	3.9 (0.48)	3.8 (0.65)	.31

ASA = American Society of Anesthesiology; CAD = coronary artery disease; chemo = chemotherapy; COPD = chronic obstructive pulmonary disease; CVA/TIA = cardiovascular accident/transient ischemic attack; lab = laboratory [a]total numbers in the chemo group and in the no chemo group after propensity weighting are estimations based on the propensity weighting. Values generally differ by a few patients; thus, numbers may total more or less than the overall number and percentages may total more or less than 100%. [b]percentages for race in chemo group before propensity weighting total > 100% due to rounding; [c]numbers for race in the no chemo group before propensity weighting equal 1271 versus 1272 because race was not available for one patient.

Results

Patient demographics and clinical characteristics

A total of 1394 patients who underwent cystectomy between 2005 and 2011 are included in the NSQIP database. Of this total, 122 (8.8%) had received NAC, whereas 1272 (91.2%) had not. Table 1 summarizes the demographic and clinical characteristics of the cohort. In general, patients who had received NAC were younger (63.7 years versus 66.3 years; p = .02) and were more likely to have been treated in the later years of the study (80.3% [98/122] treated after 2010 versus 62.8% [799/1272] treated earlier; p < .001). The prevalence of insulin-dependent diabetes mellitus (1.6% [2/122] versus 6.5% [83/1272]; p = .01) and non–insulin-dependent diabetes (7.4% [9/122] versus 13.1% [167/1272]; p = .01) was lower among patients who had received NAC, as was the prevalence of patients with a history of cerebrovascular accident/transient ischemic attack (1.6% [2/122] versus 7.3% [93/1272]; p = .02). As expected, patients who had received NAC had higher rates of disseminated cancer (16.4% [20/122] versus 8.5% [108/1272]; p = .004), a modestly lower preoperative serum white blood cell count (7.3 x 10^9 versus 7.9 x 10^9

TABLE 2. **Unadjusted perioperative outcomes of 1394 patients undergoing cystectomy who had or did not have neoadjuvant chemotherapy**

Variable	Chemo (n = 122) No. (%)	No chemo (n = 1272) No. (%)	p value
Wound complications			
Superficial SSI	7 (5.7)	105 (8.3)	.33
Deep SSI	1 (0.8)	32 (2.5)	.24
Organ space SSI	9 (7.4)	69 (5.4)	.37
Dehiscence	2 (1.6)	42 (3.3)	.32
Pulmonary complications			
Pneumonia	3 (2.5)	53 (4.2)	.36
Unplanned reintubation	1 (0.8)	40 (3.1)	.15
Pulmonary embolism	1 (0.8)	39 (3.1)	.16
Failure to wean from ventilator within 48 hrs	2 (1.6)	52 (4.1)	.18
Renal complications			
Renal insufficiency (no dialysis)	3 (2.5)	31 (2.4)	.99
Neurologic complications			
Peripheral nerve deficit	2 (1.6)	3 (0.2)	.01
Cardiovascular complications			
Cardiac arrest requiring requiring CPR	1 (0.8)	10 (0.8)	.97
Myocardial infarction	1 (0.8)	16 (1.3)	.67
Blood transfusions	46 (37.7)	350 (27.5)	.02
Deep venous thrombosis	4 (3.3)	51 (4.0)	.69
Infectious complications			
Sepsis	10 (8.2)	148 (11.6)	.25
Urinary tract infection	11 (9.0)	131 (10.3)	.66
Miscellaneous surgical outcomes			
Hospitalized > 8 days	55 (45.1)	748 (58.8)	.01
Hospitalized > 30 days	1 (0.8)	15 (1.2)	.72
Operative time > 400 min	61 (50.0)	406 (31.9)	<.001
Unplanned readmission	14 (11.5)	84 (6.6)	.04
Unplanned return to OR	4 (3.3)	87 (6.8)	.13
Mortality, 30 day	3 (2.5)	32 (2.5)	.97

Chemo = chemotherapy; CPR = cardiopulmonary resuscitation; min = minutes; OR = operating room; SSI = surgical site infection

[reference range, 4.2-10.2 x 10^9]; p = .09), and a lower preoperative serum hematocrit (35.6% versus 37.7%; p < .001). After propensity-weighted adjustments, each group was balanced with respect to these preoperative clinical and demographic variables with p values > .05.

Unadjusted comparisons of perioperative outcomes

The unadjusted comparative analysis of perioperative outcomes is presented in Table 2. No differences were noted with respect to wound, pulmonary, renal, or infectious complications. There were no differences with respect to unplanned reoperations, hospitalization longer than 30 days, or 30 day mortality. However, patients who received NAC had significantly higher rates of peripheral nerve deficits (1.6% [2/122] versus 0.2% [3/1272]; p = .01), blood transfusions (37.7% [46/122] versus 27.5% [350/1272]; p = .02), and unplanned readmissions (11.5% [14/122] versus 6.6% [84/1272]; p = .04). Although hospitalization longer than 8 days was less common in the group that had received NAC (45.1% [55/122] versus 58.8% [748/1272]; p = .01), the proportion of patients with an operative time of more than 400 minutes was significantly higher (50.0% [61/122] versus 31.9% [406/1272]; p < .001).

TABLE 3. **Propensity-weighted perioperative outcomes of cystectomy patients who had or did not have neoadjuvant chemotherapy**

Variable	Chemo (n = 122) No. (%)	No chemo (n = 1166) No. (%)	Chemo versus none, OR (95% CI)	p value
Wound complications				
Superficial SSI	5 (4.1)	95 (8.1)	0.50 (0.20-1.24)	.14
Deep SSI	3 (2.5)	29 (2.5)	0.96 (0.13-7.23)	.97
Organ space SSI	4 (3.3)	63 (5.4)	0.54 (0.25-1.17)	.12
Dehiscence	1 (0.8)	38 (3.3)	0.20 (0.04-0.89)	.04
Pulmonary complications				
Pneumonia	3 (2.5)	50 (4.3)	0.63 (0.17-2.29)	.48
Unplanned reintubation	1 (0.8)	35 (3.0)	0.16 (0.02-1.23)	.08
Pulmonary embolism	1 (0.8)	37 (3.2)	0.19 (0.03-1.41)	.10
Failure to wean from Ventilator within 48 hrs	2 (1.6)	46 (3.9)	0.43 (0.08-2.21)	.31
Renal complications				
Renal insufficiency	2 (1.6)	27 (2.3)	0.74 (0.19-2.84)	.66
Neurologic complications				
Peripheral nerve deficit	4 (3.3)	3 (0.3)	13.1 (1.90-90.8)	.01
Cardiovascular complications				
Cardiac arrest requiring CPR	1 (0.8)	9 (0.8)	0.66 (0.08-5.34)	.70
Myocardial infarction	1 (0.8)	15 (1.3)	0.49 (0.06-3.79)	.49
Blood transfusions	30 (24.6)	335 (28.7)	0.77 (0.45-1.31)	.33
Deep venous thrombosis	3 (2.5)	47 (4.0)	0.59 (0.19-1.81)	.36
Infectious complications				
Sepsis	6 (4.9)	134 (11.5)	0.36 (0.17-0.76)	.01
Urinary tract infection	9 (7.4)	117 (10.0)	0.71 (0.29-1.76)	.46
Miscellaneous outcomes				
Hospitalized > 8 days	46 (37.7)	685 (58.7)	0.41 (0.24-0.70)	.001
Hospitalized > 30 days	1 (0.8)	14 (1.2)	0.18 (0.02-1.42)	.11
Operative time > 400 min	56 (45.9)	380 (32.6)	1.65 (0.94-2.93)	.08
Unplanned readmission	11 (9.0)	80 (6.9)	1.33 (0.62-2.81)	.46
Unplanned return to OR	3 (2.5)	82 (7.0)	0.36 (0.10-1.22)	.10
Mortality, 30 day	8 (6.6)	26 (2.2)	3.03 (0.60-15.3)	.18

Chemo = chemotherapy; CPR,= cardiopulmonary resuscitation; min = minutes; OR = operating room; SSI = surgical site infection

Propensity-weighted comparisons of perioperative outcomes

We then repeated our analysis after applying the propensity weights using logistic regression, Table 3. Results showed that patients who received NAC were slightly less likely to develop wound dehiscence (0.8% [1/122] versus 3.2% [38/1166]; propensity score–adjusted odds ratio [PS-OR], 0.20; 95% CI, 0.04-0.89; p = .04); were less likely to develop sepsis (4.9% [6/122] versus 11.4% [134/1,166]; PS-OR, 0.36; 95% CI, 0.17-0.76; p = .01); and were more likely to have a peripheral nerve deficit (3.3% [4/122] versus 0.3% [3/1166]; PS-OR, 13.1; 95% CI, 1.90-90.8; p = .01). However, there were no other differences in major perioperative complications. The difference in blood transfusion rates noted on the unadjusted analysis was no longer evident on the propensity-weighted analysis (24.6% [30/122] versus 28.7% [335/1166]; PS-OR, 0.77; 95% CI, 0.45-1.31; p = .33). There were no differences in 30 day mortality, unplanned readmissions, unplanned reoperations, operative time, or hospitalization longer than 30 days.

Discussion

Level 1 evidence from randomized clinical trials supports the use of NAC in patients with MIBC, yet only a small percentage of these patients are receiving this therapy.[4,5] One impediment to the use of multimodal therapy has been a concern that NAC increases a patient's perioperative risk of a complication. We therefore undertook the sentinel analysis of perioperative morbidity in patients undergoing cystectomy after NAC using a population-based data set with propensity-weighted outcome measures.

The most notable finding from the current study was that there were no major differences between groups in terms of major perioperative surgical complications or 30 day mortality. There were slight decreases in the rates of wound dehiscence and episodes of sepsis in the NAC group, but these differences were modest. The increased incidence of peripheral neuropathy is consistent with the expected side effect profile of cisplatin-based chemotherapy in the NAC cohort. Despite the potential for nephrotoxicity of cisplatin, no differences were found in preoperative and postoperative rates of renal insufficiency. Altogether, these data demonstrate that these patients at least did no worse than the controls in terms of perioperative surgical complications.

These data are surprising in the sense that one would expect that hospital length of stay, rates of nephrotoxicity, and bleeding complications would be greater in the neoadjuvant chemotherapy group. After propensity weighting, we demonstrated no such differences which indicate that, at least in terms of perioperative morbidity, there is no downside to the receipt of neoadjuvant chemotherapy prior to cystectomy. The rates of peripheral nerve deficits are modestly higher in the NAC cohort which is an expected side effect of platinum based agents, and not really thought to represent neurapraxias due to positioning.

Another strength associated with this paper is that the data are of high quality because NSQIP imposes standardized data collection procedures at each site with strict variable definitions and annual quality checks. The database has been validated for accuracy and reproducibility and has a greater than 95% 30 day outcome follow up rate.[17] The advantage of this methodological approach is three-fold. First, it reduces reporting bias. Second, it is generalizable since NSQIP captures a wide variety of hospital types and regions across the United States. And third, the sheer size of population-based datasets allow for multivariable statistics with sufficient power to detect small differences.

Despite these findings, these data should be considered in the context of certain limitations of the study design. First, this is a retrospective study and, although it is the first analysis of cystectomy after NAC using a population-based instrument, the data are observational and inherently inadequate to allow for firm conclusions to be drawn. Second, the short time frame (30 days) provided by NSQIP makes it impossible to ascertain whether these results are durable over longer term follow up. Furthermore, there are no data regarding cancer-specific or overall survival. Third, because of the American College of Surgeons policy on maintenance of confidentiality of data-reporting institutions, we cannot account for differences in surgeon and hospital volume, which could possibly influence surgical results through the volume–outcome relationship.[18,19] Fourth, because self-selected institutions contribute patient data, the surgical population captured by NSQIP may not be fully representative of the United States cystectomy population. However, the data are collected prospectively from several different types of hospital systems, for a large and diverse sample size that roughly parallels the race and sex distributions of patients in the United States.[20]

Conclusion

Cystectomy after NAC is associated with peripheral nerve deficits but is not otherwise associated with increased perioperative morbidity in the NSQIP data set from 2005-2011. □

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