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Neoadjuvant Chemotherapy for Bladder Cancer Does Not Increase Risk of Perioperative Morbidity

David C. Johnson, MD, MPH[1], **Matthew E. Nielsen, MD, MS**[1,2,3], **Jonathan Matthews, MPH**[1,2], **Michael E. Woods, MD**[1,2], **Eric M. Wallen, MD**[1,2], **Raj S. Pruthi, MD**[1,2], **Matthew I. Milowsky, MD**[1,2,4], and **Angela B. Smith, MD**[1,2]

[1]Department of Urology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[2]Lineberger Comprehensive Cancer Center, Cancer Outcomes Research Group, Multidisciplinary Genitourinary Oncology, Chapel Hill, North Carolina

[3]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[4]Department of Medicine, Division of Hematology/Oncology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Abstract

• To determine whether neoadjuvant chemotherapy (NAC) is a predictor of post-operative complications, length of stay, or operative time after radical cystectomy f stay, or operative time after radical cystectomy (RC) for bladder cancer.

Patients and Methods—• A retrospective review of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database was performed to identify patients receiving NAC prior to RC from 2005–2011.

• Bivariable and multivariable analyses were performed to determine whether NAC was associated with 30-day peri-operative outcomes such as complications, length of stay, and operative time.

Results—• Of the 878 patients who underwent RC for bladder cancer in our study, 78 (8.9%) received NAC. Excluding those patients who were ineligible for NAC due to renal insufficiency, 78/642 (12.1%) received NAC.

• 457 of the 878 patients (52.1%) undergoing RC had at least 1 complication within 30 days, including 43 of 78 patients (55.1%) who received NAC and 414 of 800 patients (51.8%) who did not (p = 0.58).

• On multivariable logistic regression, NAC was not a predictor of complications (p=0.87), reoperation (p=0.16), wound infection (p=0.32), or wound dehiscence(p=0.32).

Corresponding Author & Address: Angela B. Smith, MD University of North Carolina, Department of Urology 170 Manning Drive, 2113 Physicians Office Building, CB#7235 Chapel Hill, NC 27599-7235.

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• Using multiple linear regression, NAC was not a predictor of increased operative time (p=0.24), and patients undergoing NAC had decreased hospital length of stay (p=0.02).

Conclusions—• Our study is the first large multi-institutional analysis specifically comparing complications after RC with and without NAC.

• Using a nationally validated, prospectively maintained database specifically designed to measure perioperative outcomes, we found no increase in perioperative complications or surgical morbidity with NAC.

• In light of these findings and the well-established overall survival benefit over surgery alone, efforts are needed to improve the uptake of NAC.

Introduction

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the standard of care for muscle-invasive bladder cancer as well as select cases of recurrent high-risk non-muscle invasive bladder cancer.[1] Overall 5-year survival after RC with PLND is 50% for organ-confined disease, which decreases to 30% with extravesical extension and lymph node involvement.[2] Disease recurrence after RC is relatively common and occurs with greater frequency at distant sites compared to locoregional (20–50% vs. 5–15%)[2] suggesting that systemic treatment modalities may improve outcomes of advanced bladder cancer. Neoadjuvant chemotherapy (NAC) with platinum-based combination therapy prior to RC with PLND provides a well-established 5% overall 5 year survival benefit compared to surgery alone.[3] Additionally, studies have not demonstrated any increase in complications associated with the use of NAC prior to RC,[4] though a paucity of data exist specifically examining this question.[5]

Clinical guidelines recommend “strongly considering” the use of NAC prior to cystectomy in muscle-invasive bladder cancer based on level 1 evidence for survival benefit, tolerable morbidity and mortality, and the lack of evidence for worse operative outcomes.[1,6] Despite these recommendations, NAC prior to RC remains underutilized, even at tertiary care centers with multidisciplinary cancer programs, with no higher than 16% of patients reportedly receiving NAC.[7,8] Reasons for underuse are unclear. However, one potential explanation is the concern for increased perioperative complications in those patients receiving NAC. Available data on this specific question are sparse, and conclusions have largely been derived from studies not specifically designed to evaluate complications.[4,9,10] The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) is a nationally validated, risk-adjusted, outcomes-based database that prospectively captures and reports data on 135 variables including 30-day morbidity and mortality outcomes for major surgical procedures at over 450 participating institutions, including urban, rural, academic and community centers across the United States. Though limited by the lack of data on surgical pathology and techniques, this database is specifically designed to accurately capture perioperative complications across a range of surgical centers and is a powerful tool for evaluating outcomes.[11] Therefore, the objectives of this study were to use the NSQIP database to investigate whether NAC is associated with worse perioperative outcomes and determine the utilization of NAC prior to RC for bladder cancer.

Methods

We performed a retrospective review of the NSQIP database from 2005–2011. Cases of RC performed for bladder cancer were extracted from the database using ICD-9 codes for neoplasm of the bladder (188 and 188.x) and Current Procedural Terminology codes for radical cystectomy (51570, 51575, 51580, 51585, 51590, 51595, 51596, and 51597). Patients were identified as having received NAC using the pre-operative code for chemotherapy within 30 days of RC. Despite this description in the data dictionary, the time period of 30 days was not a strict cutoff as confirmed by the NSQIP Division of Research and Optimal Patient Care (Kristopher Huffman, NSQIP statistician, personal communication). NSQIP data collectors included patients who received chemotherapy administered within 30 days as well as those administered prior to 30 days if there was intention for cystectomy (i.e. NAC). A sensitivity analysis was performed by recalculating the proportion of patients receiving NAC after excluding those patients with a pre-operative diagnosis of renal insufficiency. According to the National Kidney Foundation's definition for renal insufficiency, patients with an estimated glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 (as defined by the Cockcroft-Gault equation) were deemed ineligible for NAC.[12]

Univariable analyses were performed to determine the distributions of pre-operative variables. Bivariable analyses were then performed to compare 30-day complication and readmission rates between patients who did and did not receive NAC and describe the patient population in terms of demographic, prognostic, and treatment factors. These factors included age, sex, race, body mass index (BMI), medical comorbidities, smoking and alcohol history, history of pre-operative surgery or blood transfusion, year of operation, presence and training level of resident in operating room, prior radiation therapy, pre-operative acute renal failure (defined as a rising Cr > 3 mg/dL within 24 hours prior to surgery), pre-operative chronic steroid use, and American Society of Anesthesia (ASA) classification. Imputation of missing data was not performed. The Chi-square test was used to compare categorical variables. The Mann-Whitney U-test was used to compare non-normal distributions of continuous variables (age and operative time).

Multivariable logistic regression analyses were performed to determine whether NAC was an independent predictor for the following outcomes: 1) at least one post-operative complication, 2) re-operation, 3) wound/organ space infection, and 4) wound dehiscence. Generalized linear models were used to evaluate continuous outcomes including operative time and length of hospital stay. Initial models included the influential predictors from bivariable analysis (defined as those with a p-value less than 0.2). The final models were selected using backwards elimination of non-significant variables (at the 5% level of significance) so that final models included only the necessary variables affecting the relationship between NAC and the outcome of that model. All statistical analyses were performed using SAS v.9.3 (SAS Institute Inc., Cary NC, USA). The University of North Carolina Institutional Review Board exempted this study from review as the NSQIP database contains deidentified data.

Results

A total of 1,095 patients underwent RC from 2005–2011 at participating NSQIP institutions. Of these, 217 were excluded through use of ICD-9 codes with the following diagnoses: carcinoma in situ (CIS) of the bladder (3.6% of total cases, 18% of excluded cases), rectal cancer (1.6% of total cases, 7.8% of excluded cases), prostate cancer (1.4% of total cases, 6.9% of excluded cases), neurogenic bladder (1.9% of total cases, 9.7% of excluded cases), other neoplasms (4.6% of total cases, 23% of excluded cases), and a variety of miscellaneous diagnoses (6.8% of total cases, 35% of excluded cases). In total, 878 patients underwent RC for non-CIS bladder cancer from 2005–2011 at participating institutions, and 78 (8.9%) received NAC prior to surgery. Pre-operative serum creatinine was available for 749/800 (94.9%) patients who did not receive NAC, of whom 236 patients (29.5%) had a GFR < 60 and were therefore considered ineligible for NAC. Therefore, a total of 642 patients (878 − 236 = 642) were eligible for NAC based on creatinine clearance, assuming that all patients with missing creatinine (n=41) had a CrCl ≥ 60. Therefore, 78/642 (12.1%) of eligible patients received NAC. As a sensitivity analysis, we also calculated utilization under the assumption that all patients with a missing creatinine had a CrCl < 60 and were therefore ineligible. In this scenario, the denominator changes to 642 – 41 = 601, and 78/601 (13.0%) of eligible patients received NAC. Therefore, utilization ranged from 12.1% to 13.0% in this dataset.

Patient characteristics were different between those who did and did not receive NAC in several categories, such as age, BMI, year of operation, and others (Table 1). On average, those who received NAC were younger by approximately 5 years (p=0.001), more likely to be overweight or obese (compared to underweight) (p=0.02), and were less likely to be diabetic (p<0.01). Those who received cystectomy in earlier years (2009 and earlier) were less likely to receive NAC in comparison to those undergoing surgery in 2010 and 2011 (p<0.001). Those who received NAC appeared to have longer operative times by approximately 45 minutes (p<0.01). Finally, while creatinine clearance was higher among those who received NAC, this did not reach statistical significance. Multivariable analysis of NAC as a risk factor for peri-operative progressive renal insufficiency or renal failure was not performed due to the small number of patients with this complication who had received NAC (n = 2).

Evaluating overall complications, 457 of the 878 patients (52.1%) undergoing RC experienced at least 1 complication within 30 days, including 43 of 78 patients (55.1%) who received NAC and 414 of 800 patients (51.8%) who did not. (Table 2) This difference was not statistically significant on bivariable analysis (p = 0.58). Compared to those patients who were not administered NAC, those receiving NAC experienced less reoperations (1.3% vs. 6.0%), less wound infection (9.0% vs. 12.9%), and less wound dehiscence (0% vs. 3.0%), although all did not reach statistical significance. On bivariable analysis, patients receiving NAC had a higher rate of bleeding requiring transfusion than those who had not received NAC (38% vs. 28%, p = 0.043). However, this difference was no longer statistically significant after adjusting for significant factors on multivariable analysis (p = 0.97). No other specific complications, including urinary tract infection (9% vs. 9%), sepsis (5% vs. 11%) or septic shock (0% vs 4%), respiratory (3% vs. 7%), thrombotic (3% vs. 6%),

cardiovascular (3% vs. 2%), or neurologic (0% vs. 0.6%) complications, were significantly different between those who were administered NAC and those who were not. Readmission rates in 2011, the only year that this data are available, were examined. No difference was noted between those patients who received NAC (9/45, 20%) and those who did not (66/300, 22%) (p = 0.76).

Multivariable logistic regression showed that NAC was not a predictor of postoperative complications, re-operation, wound/organ-space infection or wound dehiscence when adjusting for all significant variables (Table 3). Overall complications were evaluated in Model 1. On bivariable analysis, age (p=0.02), year of operation (p<0.0001), operative time (p=0.03), and prior surgery within 30 days (p=0.02) were found to be possible influential predictors. When adjusting for these variables in the multivariable model, NAC was not found to be a predictor of overall outcomes (p=0.87).

Models 2–4 evaluated specific complications pertinent to NAC and wound healing. Model 2 evaluated re-operation as an outcome. On bivariable analysis, >2 alcoholic drinks per day in the 2 weeks prior to surgery (p=0.02), pre-operative acute renal failure (p=0.04), and year of operation (p=0.02) were potential significant variables. When adjusting for these factors, NAC was not a predictor of re-operation (p=0.16). Model 3, which evaluated wound/organ space infections had no significant predictors, and NAC was not associated with a significant difference in infection rate (p=0.32). In Model 4, wound dehiscence was evaluated as an outcome, and NAC was not found to be a predictor of wound dehiscence (p=0.32) when adjusting for all significant factors, including male sex (p=0.04), pre-operative pulmonary complications (p=0.004), and ASA score (p=0.008).

Additionally, NAC was not shown to be a predictor of longer operative time (363 (NAC) vs. 345 minutes (no NAC); p=0.24) when adjusting for significant predictors (age, BMI, and resident presence in the OR). However, NAC was found to independently predict a shorter length of hospital stay (9.3 (NAC) vs. 11.3 days (no NAC); p=0.02) compared to those who did not receive NAC after adjusting for age, race, functional status, year of operation and operative time (Table 4).

Discussion

Our analysis of the NSQIP database suggests that NAC does not increase complications in patients undergoing RC for bladder cancer and to our knowledge, is the first study to specifically address this question using a robust dataset with standardized and validation methods for collection and reporting complications. Importantly, complications are recorded and maintained by trained NSQIP clinical nurses at each site in a prospective manner using detailed complication definitions. This standardized methodology leads to extremely accurate ascertainment of complications with a discordance rate between institutions of only 1.56%.[13] Additionally, multivariable analysis revealed that NAC was not an independent predictor of complication rate, re-operation, wound infection, operative time, or length of hospital stay. In fact, patients receiving NAC in our study had a shorter length of stay, though this can likely be attributed to selection bias. Patients who underwent NAC may have been healthier at baseline than those who did not receive NAC.

The utilization of NAC has been potentially hindered by physicians' concern for increased post-operative complications after RC in patients with muscle invasive bladder cancer. A paucity of prior data exists to confirm or refute this presumption. Grossman *et al*[4] reported no difference in incidence or severity of complications in a randomized trial of patients who did or did not receive NAC prior to RC. However, assessment of postoperative complications was not an objective of the trial, and therefore, the method for capturing and reporting complications was non-standardized. With regard to additional trials involving NAC, neither the Nordic Cystectomy I and II randomized trials[14,15] nor the International Collaboration of Trialists[10] analyzed or reported post-operative complications.

One multi-institutional study demonstrated increased complication rates with NAC. A recently published report on complications of 939 robotic cystectomies from the International Robotic Cystectomy Consortium (IRCC) database reported that receipt of NAC prior to robotic RC is an independent predictor of both any complication and high-grade complications.[8] 16% of patients in this population received NAC. The overall complication rate was comparable to the complication rate in our study with 41% experiencing at least 1 complication at 30 days and 48% at 90 days. However, this study differs from ours in several ways. First, while NSQIP does not include data on whether RC was performed robotically or open, the majority of RC in the US is performed using an open approach whereas the IRCC study reports exclusively on robotic procedures. Second, the IRCC study does not systematically track complications prospectively, leading to possible bias in reporting. Furthermore, the study tracked complications for 90 days, suggesting that complications related to NAC may occur with increased frequency between 30–90 days. Finally, the gastrointestinal tract was the most common site of complication in the IRCC study (27%). These gastrointestinal complications, including ileus, partial small bowel obstruction and small bowel obstruction, are not collected by NSQIP, therefore introducing the possibility of underreporting of complications that are particularly relevant to RC.

The question of post-operative complications aside, pre-operative administration of systemic therapy offers numerous advantages.[1,5] First, the high complication rate after RC with PLND may preclude administration of adjuvant systemic therapy in up to 30% of patients.[16] Patients receiving pre-operative chemotherapy are often better able to tolerate higher doses and a greater number of cycles than post-operatively.[17] Second, tumor response to NAC serves as *in vivo* drug sensitivity testing, to help elucidate tumor biology, and potentially provide prognostic information.[18] Third, NAC may reduce tumor volume to theoretically reduce operative morbidity or convert unresectable disease to an operable tumor burden.[19] Finally, responsiveness to NAC may help guide the adjuvant treatment strategy by identifying ineffective agents that should be avoided post-operatively.[5]

Despite these advantages, numerous barriers to widespread utilization of NAC exist, including concerns about patient age and comorbidities, the potential toxicity of NAC, presumed lack of benefit in organ-confined disease, patient or physician preference, lack of referral or access to medical oncologists, and concern about treatment delay.[20,21] The low utilization rate may be potentiated by the perception of both patients and physicians that the 5–6% overall survival benefit and 16% relative disease-specific mortality risk reduction over 10 years is not substantial enough to warrant systemic therapy. However, the survival

benefit of NAC for bladder cancer compares favorably to the survival benefit of other standard of care perioperative systemic therapies in breast and colon cancer, both of which confer a 7% survival benefit.[22]

The morbidity and mortality of the traditional combination NAC regimen, methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), is acceptable yet not unsubstantial and warrants proper patient selection.[6] Up to 56% of patients receiving MVAC experience granulocytopenia (33% classified as severe), and 17% suffer from grade 3 gastrointestinal toxicity.[4] These side effects were self-limiting and have not been shown to decrease patients' chance of undergoing RC.[4] Reports of mortality from NAC range from <1%[4,10] to as high as 3–4%.[23] Gemcitabine and cisplatin (GC) combination therapy has emerged as an alternative to MVAC, with a superior toxicity profile resulting in improved patient tolerability, compliance and decreased time to cystectomy.[24] Despite encouraging retrospective data, direct head-to-head prospective trials are needed to confirm equivalent oncologic outcomes between GC and MVAC.[25]

NAC is not indicated in patients with renal insufficiency, but exclusion of these patients only partially accounts for low utilization. Three single-institution reports from large, tertiary care cancer centers suggest that up to 30–40% of patients undergoing RC are ineligible for NAC on the basis of their renal function.[26] Consistent with these reports, 30% of patients were not eligible for NAC based on a GFR < 60 mL/min/1.73 m^2 in our study. However, limited population-based data exist on the proportion of patients who are ineligible for NAC based on renal insufficiency, an area that requires future study.[27]

Our analysis of a large, prospectively maintained national database demonstrates that the utilization of NAC prior to RC for MIBC in the United States remains low and is consistent with prior studies.[28]Previously reported national utilization rates suggest that uptake of NAC is slowly increasing, from 1.2% in 1998–2003[7] to 6% in 2003 and 13% in 2007.[28] A single tertiary referral center reported a utilization rate of 14% in 2012,[29] and a 2013 report of 939 robotic cystectomy patients from >20 predominantly tertiary care international institutions reported that 16% received NAC.[8] Our study's utilization rates of 12–13% are in line with these data, suggesting that pre-operative systemic chemotherapy remains underutilized in MIBC in a national cross-section of clinical sites.

Our study is limited by several notable factors. The NSQIP dataset lacks pathologic data making it impossible to account for the effect of disease extent of disease on complications or exclude patients who underwent RC for non-muscle invasive disease other than CIS, for which NAC is not indicated. The latter could therefore result in an underestimation of the true utilization of NAC. Other limitations are those inherent to the NSQIP dataset. Data on surgical technique (open vs laparoscopic), whether a lymph node dissection or removal of adjacent organs was performed, or type of urinary diversion is not included in the NSQIP dataset. Chemotherapeutic regimen or number of cycles completed is unknown, which could certainly affect outcomes. Furthermore, there are no data regarding when treatment began and ended. While overall survival does not appear to be affected by the timing of cystectomy after termination of NAC if surgery is performed between 4 and 12 weeks[30], anecdotal evidence and consensus opinion support the notion that complications are

increased if cystectomy is performed <4 weeks from chemotherapy cessation. Additionally, gastrointestinal complications that are particularly relevant to RC, including ileus, partial small bowel obstruction, and small bowel obstruction, are not included in the ACS NSQIP dataset. As a result, this study was unable to confirm or refute the findings of Milliken *et al* that demonstrated a higher rate of post-operative ileus in the NAC arm.[17] The validity of our results would certainly be augmented by inclusion of these variables in the future. Finally, this dataset does not take into account patient and provider preferences, which could affect utilization rates.

Despite these limitations, our study provides strong evidence that post-operative complications, operative time, and length of stay are not increased in patients that receive NAC prior to RC for bladder cancer, contradicting a widely held belief that likely hinders appropriate utilization of multimodal therapy. These findings, combined with well-accepted Level 1 evidence for overall survival benefit for NAC over surgery alone, further validate existing national and international guidelines that recommend the strong consideration of NAC prior to RC for muscle invasive bladder cancer. Further efforts are needed to improve physician and patient awareness of the benefits and tolerability of NAC in order to increase utilization of this multi-modal therapy and improve treatment outcomes for MIBC.

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References

1. Stenzl A, Cowan NC, De Santis M, et al. Treatment of muscle-invasive and metastatic bladder cancer: Update of the EAU guidelines. Eur Urol. 2011; 59(6):1009–1018. doi: 10.1016/j.eururo.2011.03.023; 10.1016/j.eururo.2011.03.023. [PubMed: 21454009]
2. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1,054 patients. J Clin Oncol. 2001; 19(3):666–675. [PubMed: 11157016]
3. Winquist E, Kirchner TS, Segal R, Chin J, Lukka H, Genitourinary Cancer Disease Site Group; Cancer Care Ontario Program in Evidence-based Care Practice Guidelines Initiative. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: A systematic review and meta-analysis. J Urol. 2004; 171(2 Pt 1):561–569. doi: 10.1097/01.ju.0000090967.08622.33. [PubMed: 14713760]
4. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003; 349(9):859–866. doi: 10.1056/NEJMoa022148. [PubMed: 12944571]
5. Milowsky MI, Stadler WM, Bajorin DF. Integration of neoadjuvant and adjuvant chemotherapy and cystectomy in the treatment of muscle-invasive bladder cancer. BJU Int. 2008; 102(9 Pt B):1339–1344. doi: 10.1111/j.1464-410X.2008.07980.x; 10.1111/j.1464-410X.2008.07980.x. [PubMed: 19035902]
6. Sternberg CN, Bellmunt J, Sonpavde G, et al. ICUD-EAU international consultation on bladder cancer 2012: Chemotherapy for urothelial carcinoma-neoadjuvant and adjuvant settings. Eur Urol. 2013; 63(1):58–66. doi: 10.1016/j.eururo.2012.08.010; 10.1016/j.eururo.2012.08.010. [PubMed: 22917984]
7. David KA, Milowsky MI, Ritchey J, Carroll PR, Nanus DM. Low incidence of perioperative chemotherapy for stage III bladder cancer 1998 to 2003: A report from the national cancer data base. J Urol. 2007; 178(2):451–454. doi: 10.1016/j.juro.2007.03.101. [PubMed: 17561135]

8. Johar RS, Hayn MH, Stegemann AP, et al. Complications after robot-assisted radical cystectomy: Results from the international robotic cystectomy consortium. Eur Urol. 2013; 64(1):52–57. doi: 10.1016/j.eururo.2013.01.010; 10.1016/j.eururo.2013.01.010. [PubMed: 23380164]
9. Meeks JJ, Bellmunt J, Bochner BH, et al. A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol. 2012; 62(3):523–533. doi: 10.1016/j.eururo.2012.05.048; 10.1016/j.eururo.2012.05.048. [PubMed: 22677572]
10. International Collaboration of Trialists, Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group); European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group. et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: Long-term results of the BA06 30894 trial. J Clin Oncol. 2011; 29(16):2171–2177. doi: 10.1200/JCO.2010.32.3139; 10.1200/JCO.2010.32.3139. [PubMed: 21502557]
11. Ingraham AM, Richards KE, Hall BL, Ko CY. Quality improvement in surgery: The american college of surgeons national surgical quality improvement program approach. Adv Surg. 2010; 44:251–267. [PubMed: 20919525]
12. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third national health and nutrition examination survey. Am J Kidney Dis. 2003; 41(1):1–12. doi: 10.1053/ajkd.2003.50007. [PubMed: 12500213]
13. Shiloach M, Frencher SK Jr, Steeger JE, et al. Toward robust information: Data quality and inter-rater reliability in the american college of surgeons national surgical quality improvement program. J Am Coll Surg. 2010; 210(1):6–16. doi: 10.1016/j.jamcollsurg.2009.09.031; 10.1016/j.jamcollsurg.2009.09.031. [PubMed: 20123325]
14. Malmstrom PU, Rintala E, Wahlqvist R, Hellstrom P, Hellsten S, Hannisdal E. Five-year followup of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic cystectomy trial I. the nordic cooperative bladder cancer study group. J Urol. 1996; 155(6):1903–1906. [PubMed: 8618283]
15. Sherif A, Rintala E, Mestad O, et al. Neoadjuvant cisplatin-methotrexate chemotherapy for invasive bladder cancer -- nordic cystectomy trial 2. Scand J Urol Nephrol. 2002; 36(6):419–425. doi: 10.1080/003655902762467567. [PubMed: 12623505]
16. Donat SM, Shabsigh A, Savage C, et al. Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: A high-volume tertiary cancer center experience. Eur Urol. 2009; 55(1):177–185. doi: 10.1016/j.eururo.2008.07.018; 10.1016/j.eururo.2008.07.018. [PubMed: 18640770]
17. Millikan R, Dinney C, Swanson D, et al. Integrated therapy for locally advanced bladder cancer: Final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with both preoperative and postoperative M-VAC. J Clin Oncol. 2001; 19(20):4005–4013. [PubMed: 11600601]
18. Bellmunt J, Albiol S, Suarez C, Albanell J. Optimizing therapeutic strategies in advanced bladder cancer: Update on chemotherapy and the role of targeted agents. Crit Rev Oncol Hematol. 2009; 69(3):211–222. doi: 10.1016/j.critrevonc.2008.06.002; 10.1016/j.critrevonc.2008.06.002. [PubMed: 18640849]
19. Sternberg CN. Neo-adjuvant and adjuvant chemotherapy of bladder cancer: Is there a role? Ann Oncol. 2002; 13(Suppl 4):273–279. [PubMed: 12401701]
20. Sternberg CN. Neoadjuvant and adjuvant chemotherapy in locally advanced bladder cancer. Semin Oncol. 1996; 23(5):621–632. [PubMed: 8893873]
21. Chang SS, Hassan JM, Cookson MS, Wells N, Smith JA Jr. Delaying radical cystectomy for muscle invasive bladder cancer results in worse pathological stage. J Urol. 2003; 170(4 Pt 1): 1085–1087. doi: 10.1097/01.ju.0000086828.26001.ca. [PubMed: 14501697]
22. Apolo AB, Grossman HB, Bajorin D, Steinberg G, Kamat AM. Practical use of perioperative chemotherapy for muscle-invasive bladder cancer: Summary of session at the society of urologic oncology annual meeting. Urol Oncol. 2012; 30(6):772–780. doi: 10.1016/j.urolonc.2012.01.012; 10.1016/j.urolonc.2012.01.012. [PubMed: 23218068]

23. Loehrer PJS, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: A cooperative group study. J Clin Oncol. 1992; 10(7):1066–1073. [PubMed: 1607913]
24. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol. 2005; 23(21):4602–4608. doi: 10.1200/JCO.2005.07.757. [PubMed: 16034041]
25. Yeshchina O, Badalato GM, Wosnitzer MS, et al. Relative efficacy of perioperative gemcitabine and cisplatin versus methotrexate, vinblastine, adriamycin, and cisplatin in the management of locally advanced urothelial carcinoma of the bladder. Urology. 2012; 79(2):384–390. doi: 10.1016/j.urology.2011.10.050; 10.1016/j.urology.2011.10.050. [PubMed: 22196406]
26. Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. 2006; 107(3):506–513. doi: 10.1002/cncr.22031. [PubMed: 16773629]
27. Feifer AH, Taylor JM, Tarin TV, Herr HW. Maximizing cure for muscle-invasive bladder cancer: Integration of surgery and chemotherapy. Eur Urol. 2011; 59(6):978–984. doi: 10.1016/j.eururo.2011.01.014; 10.1016/j.eururo.2011.01.014. [PubMed: 21257257]
28. Fedeli U, Fedewa SA, Ward EM. Treatment of muscle invasive bladder cancer: Evidence from the national cancer database, 2003 to 2007. J Urol. 2011; 185(1):72–78. doi: 10.1016/j.juro.2010.09.015; 10.1016/j.juro.2010.09.015. [PubMed: 21074192]
29. Raj GV, Karavadia S, Schlomer B, et al. Contemporary use of perioperative cisplatin-based chemotherapy in patients with muscle-invasive bladder cancer. Cancer. 2011; 117(2):276–282. doi: 10.1002/cncr.25429; 10.1002/cncr.25429. [PubMed: 20830767]
30. Alva AS, Tallman CT, He C, et al. Efficient delivery of radical cystectomy after neoadjuvant chemotherapy for muscle-invasive bladder cancer: A multidisciplinary approach. Cancer. 2012; 118(1):44–53. doi: 10.1002/cncr.26240; 10.1002/cncr.26240. [PubMed: 21598245]

Table 1

Patient Characteristics and Use of Preoperative Chemotherapy

Patient Characteristic		Preoperative chemotherapy (n=78) n (%) or median (IQR)	No preoperative chemotherapy (n=800) n (%) or median (IQR)	p-value
Sex	Male	57 (74)	609 (76)	0.67
	Female	20 (26)	190 (24)	
Age (years)		65 (58–73)	70 (62–77)	0.001
Body mass index (kg/m^2)	<18.5	1 (1)	29 (4)	0.02
	18.5 to 24.9	12 (15)	243 (30)	
	25 – 29.9	35 (45)	279 (35)	
	≥ 30	30 (38)	249 (31)	
Race	African American	2 (3)	36 (5)	0.55
	Hispanic	3 (4)	16 (2)	
	Other	0 (0)	6 (1)	
	White	67 (93)	650 (92)	
Preoperative creatinine (mg/dL)		1.1 (0.9–1.4)	1.0 (0.9–1.3)	0.13
Creatinine Clearance[a]		76.5 (58.0–95.1)	71.9 (55.6–97.6)	0.44
Resident present in OR	Yes	62 (82)	475 (69)	0.02
	No	14 (18)	217 (31)	
Year of operation	2005, 2006, 2007, 2008, or 2009	11 (14)	266 (33)	<0.001
	2010 or 2011	67 (86)	534 (67)	
Diabetes mellitus treated with oral agents or insulin	Diabetic treated with insulin	1 (1)	45 (6)	0.007
	Diabetic treated with oral agents	5 (6)	119 (15)	
	Not diabetic	72 (92)	636 (80)	
Smoker in past year	Yes	21 (27)	210 (26)	0.90
	No	57 (73)	590 (74)	
More than 2 alcoholic drinks in 2 weeks prior to admission	Yes	4 (5)	32 (4)	0.55
	No	74 (95)	768 (96)	
Functional status	At least partially dependent	1 (1)	20 (3)	1.00
	Independent	77 (99)	780 (98)	
One or more pulmonary comorbidities[b]	Yes	9 (12)	142 (18)	0.17
	No	69 (88)	658 (82)	
One or more cardiac comorbidities[c]	Yes	12 (15)	124 (16)	0.98
	No	66 (85)	676 (85)	
Hypertension requiring medication	Yes	40 (51)	468 (59)	0.22

Patient Characteristic		Preoperative chemotherapy (n=78) n (%) or median (IQR)	No preoperative chemotherapy (n=800) n (%) or median (IQR)	p-value
	No	38 (49)	332 (42)	
Preoperative acute renal failure	Yes	1 (1)	6 (1)	0.48
	No	77 (99)	794 (99)	
Preoperative dialysis	Yes	0 (0)	1 (0.1)	1.00
	No	78 (100)	799 (100)	
One or more vascular comorbidities[d]	Yes	0 (0)	11 (1)	0.61
	No	78 (100)	789 (99)	
One or more neurological comorbidities[e]	Yes	2 (3)	46 (6)	0.30
	No	76 (97)	754 (94)	
Steroid use for chronic condition	Yes	4 (5)	18 (2)	0.12
	No	74 (95)	782 (98)	
Greater than 10% loss in body weight in the last 6 months	Yes	3 (4)	27 (3)	0.74
	No	75 (96)	773 (97)	
Bleeding disorder	Yes	4 (5)	23 (3)	0.29
	No	74 (95)	777 (97)	
Radiotherapy for malignancy in last 90 days	Yes	2 (3)	2 (0.3)	0.04
	No	76 (97)	798 (100)	
Prior operation within 30 days	Yes	4 (5)	50 (6)	1.00
	No	74 (95)	748 (94)	
ASA classification	ASA 1	0 (0)	8 (1)	0.046
	ASA 2	26 (33)	202 (25)	
	ASA 3	52 (67)	543 (68)	
	ASA 4	0 (0)	47 (6)	
Transfused more than 4 units pRBCs in 72 hours prior to surgery	Yes	6 (8)	22 (3)	0.03
	No	72 (92)	778 (97)	
Operative time (min)		366 (277–466)	320 (250–405)	0.007

[a] Cockcroft-Gault method, mL/min

[b] Dyspnea, ventilator dependence, COPD, and/or pneumonia

[c] CHF, MI, angina, PCI, and/or previous cardiac surgery

[d] Revascularization and/or rest pain

[e] Coma, hemiplegia, TIA, CVA with neurological deficit, CVA without neurological deficit, tumor involving CNS, paraplegia, and/or quadriplegia

Table 2

Bivariable analysis of complication rates between patients who did and did not receive NAC

	NAC (n=78)	No NAC (n=800)	p-value
Any Complication	43 (55.1%)	414 (51.8%)	0.57
Re-operation	1 (1.3%)	48 (6.0%)	0.11
Wound Infection	7 (9.0%)	103 (12.9%)	0.26
Wound Dehiscence	0 (0.0%)	24 (3.0%)	0.32
Urinary Tract Infection	7 (9.0%)	72 (9.0%)	0.99
Respiratory (pneumonia, reintubation, intubation > 48 hours)	2 (2.6%)	54 (6.8%)	022
Thrombotic (pulmonary embolism, deep venous thrombosis)	2 (2.6%)	48 (6.0%)	0.30
Renal (progressive insufficiency, acute failure)	2 (2.6%)	28 (3.5%)	1.0
Cardiovascular (myocardial infarction, required cardiopulmonary resuscitation)	2 (2.6%)	13 (1.6%)	0.64
Neurologic (stroke/cerebrovascular accident, coma > 24 hours, peripheral nerve injury)	0 (0%)	4 (0.6%)	1.0
Bleeding requiring transfusion	30 (38.5%)	414 (51.8%)	0.04

Table 3

Multivariable analyses evaluating NAC as a predictor of complications

Outcome	Independent Variable	Multivariable Adjusted OR[1] (95% CI)	p-value
Model 1: Any complication	**NAC (ref: no NAC)**	**0.96 (0.57,1.61)**	**0.87**
	Age (per 10 year increase)	1.20 (1.03, 1.40)	0.0186
	Year of operation (2005–2009, ref: 2010–2011)	0.47 (0.34, 0.65)	<0.0001
	Operative time (per 1 hour increase)	1.09 (1.01, 1.17)	0.0345
	Prior surgery within 30 days (ref: no surgery)	0.47 (0.26, 0.87)	0.016
Model 2: Re-operation	**NAC (ref: no NAC)**	**0.24 (0.03,1.79)**	**0.16**
	Year of operation (2005–2009, ref: 2010–2011)	2.13 (1.15, 4.0)	0.02
	More than 2 alcoholic drink in the 2 weeks prior to admission (ref: < 2 drinks)	3.20 (1.16, 8.85)	0.03
	Pre-operative acute renal failure (ref: no pre-operative acute renal failure)	5.89 (1.04, 33.24)	0.04
Model 3: Wound/organ space infection *	**NAC (ref: no NAC)**	**0.67 (0.30,1.49)**	**0.32**
Model 4: Wound dehiscence	**NAC (ref: no NAC)**	**0.25 (0.02,3.90)**	**0.32**
	Male sex (ref: no NAC)	16.51 (1.13, 241.34)	0.04
	1 or more pulmonary comorbidities (ref: no pulmonary comorbidities)	3.49 (1.50, 8.13)	0.004
	ASA score 4 (ref: 1)	0.01 (<0.001, 0.31)	0.008
	ASA score 3 (ref: 1)	0.06 (0.01, 0.35)	0.002
	ASA score 2 (ref: 1)	0.036 (0.01, 0.25)	0.001

* No significant predictors were noted for this model

Table 4

Adjusted means for operative time and length of stay among those who did and did not receive neoadjuvant chemotherapy.

	NAC Adjusted Mean	No NAC Adjusted Mean	p-value
Operative time[1] (minutes)	363	345	0.24
Length of stay[2] (days)	9.3	11.3	0.02

[1] Adjusted for age, BMI, resident presence in OR

[2] Adjusted for age, sex, year of operation, functional status, operative time