Title

Discerning Patterns and Quality of Neoadjuvant Chemotherapy Use Among Patients with Muscle-invasive Bladder Cancer

Journal

European Urology Oncology, 2(5)

ISSN

2588-9311

Authors

Huo, Jinhai
Ray-Zack, Mohamed D
Shan, Yong
et al.

Publication Date

2019-09-01

DOI

10.1016/j.euo.2018.07.009

Peer reviewed

HHS Public Access

Author manuscript

Eur Urol Oncol. Author manuscript; available in PMC 2021 August 13.

Published in final edited form as:

Eur Urol Oncol. 2019 September ; 2(5): 497–504. doi:10.1016/j.euo.2018.07.009.

Discerning Patterns and Quality of Neoadjuvant Chemotherapy Use Among Patients with Muscle-invasive Bladder Cancer

Jinhai Huo[a], **Mohamed D. Ray-Zack**[b], **Yong Shan**[b], **Karim Chamie**[c], **Stephen A. Boorjian**[d], **Preston Kerr**[b], **Bagi Jana**[e], **Stephen J. Freedland**[f], **Ashish M. Kamat**[g], **Hemalkumar B. Mehta**[b], **Stephen B. Williams**[b]

[a]Department of Health Services Research, Management and Policy, The University of Florida, Gainesville, FL, USA

[b]Department of Surgery, Division of Urology, The University of Texas Medical Branch, Galveston, TX, USA

[c]Department of Urology, University of California Los Angeles, Los Angeles, CA, USA

[d]Department of Urology, Mayo Clinic, Rochester, MN, USA

[e]Department of Hematology and Oncology, The University of Texas Medical Branch, Galveston, TX, USA

[f]Department of Urology, Cedars Sinai Medical Center, Los Angeles, CA, USA

[g]Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

Background: Neoadjuvant chemotherapy is underutilized in bladder cancer patients who undergo radical cystectomy. However, the quality of regimens used in this setting remains largely unknown.

Objective: To determine utilization treatment patterns and survival outcomes according to regimens administered.

[*]Corresponding author. Division of Urology, The University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555, USA. Tel. +1 409 7477333; Fax: +1 409 7720088. stbwilli@utmb.edu (S.B. Williams).

Author contributions: Stephen B. Williams had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Williams, Huo.

Acquisition of data: Williams, Huo.

Analysis and interpretation of data: Huo, Ray-Zack, Shan, Chamie, Boorjian, Kerr, Jana, Freedland, Kamat, Mehta, Williams.

Drafting of the manuscript: Huo, Ray-Zack, Shan, Chamie, Boorjian, Kerr, Jana, Freedland, Kamat, Mehta, Williams.

Critical revision of the manuscript for important intellectual content: Huo, Ray-Zack, Shan, Chamie, Boorjian, Kerr, Jana, Freedland, Kamat, Mehta, Williams.

Statistical analysis: Huo.

Obtaining funding: Williams, Kamat.

Administrative, technical, or material support: Williams, Huo, Kamat.

Supervision: Williams, Kamat.

Other: None.

Design, setting, and patients: We used the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database to identify patients diagnosed with clinical stage TII–IV bladder cancer from January 1, 2001 to December 31, 2011.

Outcome measurements and statistical analysis: Temporal trends were assessed using the Cochran-Armitage test. Multivariable logistic regression models were used to identify predictors for neoadjuvant chemotherapy use. Cox proportional hazards models were used to compare overall survival according to regimens administered.

Results and limitations: Of 2738 patients treated with radical cystectomy, 344 (12.6%) received neoadjuvant chemotherapy. The agents most commonly used were gemcitabine (72.3%), cisplatin (55.2%), and carboplatin (31.1%). The regimens most commonly used were gemcitabine-cisplatin (45.3%), gemcitabine-carboplatin (24.1%), and methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC; 6.7%). Use of neoadjuvant chemotherapy more than tripled during the study period, from 5.7% in 2001 to 17.3% in 2011 ($p < 0.001$). The quality of the regimen administered impacted survival outcomes, as M-VAC use was significantly associated with better overall survival among patients diagnosed with stage II bladder cancer (hazard ratio 0.24, 95% confidence interval 0.07–0.86; $p = 0.030$]. Limitations include the limited ability of retrospective analysis to control for selection bias.

Conclusions: Neoadjuvant chemotherapy was underused, and the quality of neoadjuvant chemotherapy regimens administered for bladder cancer was inconsistent with guideline recommendations. These findings are important when interpreting population-based data on the use of chemotherapy and extrapolating survival outcomes.

Patient summary: In a large population-based study, 12.6% of patients undergoing radical cystectomy for bladder cancer received neoadjuvant chemotherapy, half of whom received guideline-recommended regimens. The quality of the regimen impacted survival outcomes, as use of cisplatin-based chemotherapy was significantly associated with better overall survival among patients diagnosed with stage II bladder cancer. However, <1% of radical cystectomy patients received this regimen.

Keywords

Neoadjuvant chemotherapy; Radical cystectomy; Bladder cancer; Surveillance, Epidemiology and End Results; Medicare; Quality

1. Introduction

There will be an estimated 79 030 new cases and 16 870 deaths from bladder cancer in the USA in 2018 [1]. Radical cystectomy with pelvic lymphadenectomy is recommended for patients with muscle-invasive bladder cancer (MIBC) [2]. Neoadjuvant chemotherapy (NAC) is a guideline-recommended treatment that offers approximately 5% better survival benefit among patients who undergo radical cystectomy [2–4].

Over the past several decades, single chemotherapeutic agents and regimens combining two or more agents have been evaluated in the NAC setting [5–8]. A systematic review and meta-analysis showed that combination therapy with one or more agents with a

cisplatin compound can have a significant survival benefit [9,10]. Therefore, clinical practice guidelines recommend cisplatin-based combination NAC followed by radical cystectomy as the standard treatment for MIBC [4,11–13].

Despite these recommendations, several studies have documented significant underutilization of NAC [14,15]. With insufficient evidence to determine an optimal cisplatin-based chemotherapeutic regimen, the quality of NAC regimens administered has been questioned [16]. The lack of consistent oncologic benefit and the varying patient eligibility criteria (ie, renal insufficiency) for cisplatin-based NAC have complicated the interpretation of survival outcomes [16]. Conflicting data on comorbidity status remain, including the degree of renal insufficiency and the impact on utilization of NAC [17,18]. As seen for other cancers [19], adherence to established guidelines regarding treatment strategies continues to be challenging [20,21]. Moreover, registries for cancer in other disease sites suggest that there is better adherence to guidelines when dedicated resources and personnel consistently evaluate adherence to established guidelines [21,22]. Chemotherapy use and the type of regimen administered are important baseline determinants when assessing robust data sets to determine survival outcomes. In this study, we performed a population-based assessment to determine NAC utilization patterns, quality of NAC used, and survival outcomes according to NAC regimens administered for patients with bladder cancer. We hypothesized that overall use of NAC would be low independent of renal insufficiency; appropriate use of guideline-recommended NAC regimens would also be low; and guideline-recommended NAC would be associated with better survival.

2. Patients and methods

2.1. Study cohort

Using the National Cancer Institute Surveillance, Epidemiology and End Results (SEER)-Medicare linked database [23] we identified patients aged ≥66 yr with a diagnosis of clinical stage II–IVa N0M0 bladder cancer (transitional cell or urothelial carcinoma) and treated with radical cystectomy from January 1, 2001 to December 31, 2011. Patients were excluded for: (1) a cancer diagnosis that was not pathologically confirmed; (2) a cancer diagnosis obtained from a death certificate or autopsy; (3) having other cancers either before or after the bladder cancer diagnosis; or (4) not having full coverage of both Medicare parts A and B for 1 yr before and 1 yr after diagnosis (Fig. 1).

2.2. Identification of NAC

NAC use before radical cystectomy was identified using Current Procedural Terminology (CPT) J codes in SEER-Medicare files (Supplementary Table 1). NAC regimens were identified by the combination of specific agents recommended by organizational guidelines or evaluated in randomized clinical trials [8,13,24,25]. These regimens were defined as follows: M-VAC for J codes for methotrexate, vinblastine, doxorubicin, and cisplatin; GCisp for J codes for gemcitabine and cisplatin; and GCarb for J codes for gemcitabine and carboplatin.

2.3. Radical cystectomy and other key variables

Patients were classified into four groups on the basis of time from initial date of bladder cancer diagnosis to date of radical cystectomy: 0–8, 9–12, 13–16, and >16 wk. Patient demographic data were extracted from the SEER database. We used the Charlson comorbidity index (CCI) to assess patient comorbidities 1 yr before bladder cancer diagnosis [26,27]. We also captured the existence of chronic renal disease as a proxy for renal insufficiency 1 yr before cancer diagnosis using ICD-9 diagnosis codes, since cisplatin-based NAC is not advised for patients with the latter condition.

2.4. Statistical analysis

Descriptive statistics were used to describe NAC use among patients with bladder cancer. We compared bladder cancer patients receiving NAC to those not receiving NAC in association with demographic and clinical variables using Pearson χ^2 tests, and identified temporal trends for NAC use via the Cochran-Armitage trend test. We conducted multivariable logistic regression analysis to identify predictors of NAC use. Kaplan-Meier survival curves were generated to illustrate rates of overall survival by NAC use, and log-rank tests were used to compare survival curves. A Cox proportional hazards regression model was used to assess the association between the timing of radical cystectomy, NAC use, and overall survival after controlling for patient and tumor characteristics. Survival analyses were performed for patients with stage II disease, as data from randomized trials have shown that NAC confers a significant survival benefit, especially among these patients [8]. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using SAS v.9.4 (SAS Institute, Cary, NC, USA). Our study was exempted from review by The University of Texas Medical Branch at Galveston and The University of Texas MD Anderson institutional review boards.

3. Results

3.1. Patient characteristics and NAC utilization

Of 2738 patients treated with radical cystectomy, 344 (12.6%) received NAC. Among those who received NAC, 301 patients (87.5%) underwent radical cystectomy at 16 wk after cancer diagnosis. Patients who received NAC were younger, had fewer comorbidities, and had less advanced disease than patients who did not receive NAC (Table 1). Annual rates of NAC use increased significantly over time from 5.7% in 2001 to 17.3% in 2011 ($p < 0.001$). When stratified according to stage, use of NAC significantly increased during the study period from 9.3% to 20.0% for stage II, from 5.1% to 14.0% for stage III, and from 4.4% to 16.7% for stage disease ($p < 0.001$; Fig. 2). Among patients who received NAC, the agents most commonly used were gemcitabine (72.3%), cisplatin (55.2%), and carboplatin (31.1%). The regimens most commonly used were GCisp (45.3%), GCarb (24.1%), and M-VAC (6.7%). There was no significant difference in NAC use or type according to chronic renal disease status (all $p > 0.05$; Fig. 3).

Multivariable results identifying factors predicting NAC use are shown in Table 2. Patients were more likely to receive NAC if diagnosed during the most recent year of the study period (2011 vs 2001: odds ratio [OR] 3.59, 95% confidence interval [CI] 1.79–7.20; $p <$

0.001). Patients were less likely to receive NAC if they were older (≥80 vs 66–69 yr: OR 0.39, 95% CI 0.26–0.57; $p < 0.001$), had more advanced disease (stage III vs II: OR 0.72, 95% CI 0.54–0.95; $p = 0.022$), and had more comorbidities (CCI ≥3 vs 0: OR 0.41, 95% CI 0.20–0.82; $p = 0.012$).

3.2. Overall survival

In Kaplan-Meier analyses, for patients with stage II disease survival was better among patients who received a combined NAC regimen than those receiving a single agent ($p < 0.001$; Fig. 4). In a multivariable Cox regression model (Table 3), receipt of NAC (vs no NAC) was associated with better overall survival (hazard ratio [HR] 0.74, 95% CI 0.53–1.03; $p = 0.072$). Further sensitivity analyses showed better overall survival among patients who received a combined regimen when compared to those receiving a single agent NAC (HR 0.48, 95% CI 0.24–0.95; $p = 0.036$). M-VAC was the only regimen significantly associated with better overall survival among patients with stage II disease (HR 0.24, 95% CI 0.07–0.86; $p = 0.029$; Supplementary Table 2).

4. Discussion

We examined the patterns and quality of NAC use and the associated impact on survival outcomes among patients with MIBC. Our analysis revealed that NAC use increased significantly over time, and gemcitabine with cisplatin or carboplatin were the principal regimens administered. Of note, chronic renal disease was not associated with use of cisplatin-based NAC. We also found that one specific NAC regimen (M-VAC) was significantly associated with better overall survival. These findings have important implications when interpreting population-based data on chemotherapy use without information on regimen type. The present study revealed that the type of chemotherapy administered (combined and cisplatin-based) had a significant impact on survival outcomes. We observed several important findings. First, a growing trend for NAC utilization for bladder cancer treatment has been reported in several studies [15,18,28–30]. Our results showed that the trend for NAC use increased markedly following publication of the study by Grossman et al in 2003 [8], reaching 23.8% in 2010. We expect NAC use to continually increase following the publication of the 2016 European Association of Urology guidelines on MIBC and metastatic bladder cancer treatment and the 2016 American Society of Clinical Oncology endorsement of the guidelines [3]. While this seems promising, further efforts in advocating the use and quality of guideline-recommended regimens are needed.

Second, the literature recommends administration of cisplatin-based regimens, as these have a proven survival benefit in patients with MIBC [8,10,13]. Since certain cisplatin-based regimens such as M-VAC may be associated with chemotherapy-related toxicities, other regimens with different side-effect profiles such as GCisp, dose-dense M-VAC, and GCarb have been implemented [24,31]. In our investigation, nearly 50% of the patients who received NAC were given GCisp, and M-VAC was used in only 7%. Significantly better survival was associated with M-VAC compared to other regimens, supporting previous results [8,10,13]. Moreover, more than a quarter of patients received a single chemotherapeutic agent in the neoadjuvant setting, which did not impact survival outcomes.

Prior studies attributed low NAC utilization to the NAC side-effect profile, concern regarding a delay to radical cystectomy, and a marginal survival benefit [18,28,29]. Our findings highlight not only underutilization of NAC but also issues related to the quality of regimens administered. Data on the use of chemotherapy need to take into consideration the quality of regimens administered and their impact on survival outcomes. In the present study, <1% of all patients who underwent radical cystectomy received M-VAC, which is the guideline-recommended NAC regimen associated with better survival.

Third, we observed that renal insufficiency did not affect NAC administration in large part. A randomized phase 2/3 trial conducted by the European Organization for Research and Treatment of Cancer investigated the effectiveness of NAC among advanced urothelial cancer patients with impaired renal function and poor performance status [32]. This randomized clinical trial noted that the overall response rate dropped by nearly 40% [32]. In this study, we assigned chronic renal disease as a proxy for renal insufficiency, which may be a contraindication for use of cisplatin-based NAC, depending on the degree of renal insufficiency. We found that the rate of NAC use was independent from chronic renal disease comorbidity. These findings are supported by other studies that noted that the degree of renal insufficiency does not impact NAC use [17] While chronic renal disease is more prevalent in the elderly [33], age alone was not associated with unfavorable clinical outcomes following NAC, and therefore should not preclude a thorough assessment for NAC eligibility [34,35] Nevertheless, utilization should be judicious, given that not all bladder cancer patients are deemed suitable to receive NAC [30].

Our findings must be interpreted within the context of the study design. First, Medicare claims that the SEER database does not allow assessment of patient performance status, a factor that influences their eligibility for NAC. We used the Charlson comorbidity index as a measure for comorbidity. However, this, like other comorbidity indices, is not disease-specific and may not take into account other performance predictors such as frailty, which is important to account for in this patient population [36]. Second, the SEER database does not contain data on glomerular filtration rate and urine creatinine clearance, both of which are used to assess renal function. We considered chronic renal disease to be a proxy for renal function, but it has limited capacity to capture renal dysfunction. Chronic renal disease encompasses variable degrees of renal insufficiency with which some patients may still be candidates for NAC. Third, these results are derived from patients aged ≥66 yr and the findings might not applicable to younger patients. However, given that bladder cancer more commonly occurs after the sixth decade of life, our results are generalizable to a majority of bladder cancer patients. Fourth, the retrospective cohort design does not allow control for inherent selection bias in determining treatment. Fifth, most patients in our study cohort underwent radical cystectomy at 16 wk after cancer diagnosis, so we were unable to determine the effect of NAC among patients who underwent radical cystectomy at a shorter interval than 16 wk. Sixth, even though the SEER-Medicare database is a large national representative data source for examining the utilization of NAC, data from randomized clinical trials are still the gold standard for evaluating the survival benefits of NAC. The SWOG Coxen trial on predicting chemotherapy response in patients with bladder cancer will provide more detailed guidance on the oncological benefits of NAC [37]. Lastly, we were

unable to assess the course of NAC administered, the number of cycles received, and the duration (including dose-dense regimens), all of which may have affected our findings.

5. Conclusions

We observed remarkable underutilization of NAC before radical cystectomy for patients with stage II MIBC. In addition, the quality of the regimens administered was inconsistent with guideline recommendations. In the present study, <1% of all patients who underwent radical cystectomy received M-VAC, a guideline-recommended NAC regimen that has been associated with better patient survival. These findings are important when interpreting population-based data on the use of NAC, and should be taken into consideration when extrapolating survival outcomes. Further research on interventions aimed at improving the utilization and quality of NAC regimens administered for bladder cancer patients is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

This study used the SEER-Medicare linked database. The data interpretation and reporting are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, National Cancer Institute; the Office of Research, Development and Information, CMS; Information Management Services, Inc.; and the SEER program tumor registries for the creation of the SEER database.

Financial disclosures:

Stephen B. Williams certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor:

This study was supported by a Department of Defense Peer Reviewed Cancer Research Program Career Development Award (W81XWH1710576) and the Herzog Foundation (S.B.W.); Center for Translational Science Awards by the NIH (TL1TR001440 and UL1TR001439; M.R.Z.); and the NIH Bladder SPORE (5P50CA091846-03; A.M.K.). The sponsors played no direct role in the study.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin2017;67:7–30. [PubMed: 28055103]
2. Clark PE, Agarwal N, Biagioli MC, et al.Bladder cancer. J Natl Compr Cancer Netw2013;11:446–75.
3. Witjes JA, Lebret T, Comperat EM, et al.Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. Eur Urol2017;71:462–75. [PubMed: 27375033]
4. Chang SS, Bochner BH, Chou R, et al.Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline. J Urol2017;198:552–9. [PubMed: 28456635]
5. International Collaboration of Trialists. 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 Oncol2011;29:2171–7. [PubMed: 21502557]
6. Shipley WU, Winter KA, Kaufman DS, et al.Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation

therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89–03. J Clin Oncol1998;16:3576–83. [PubMed: 9817278]

7. International Collaboration of Trialists. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. Lancet1999;354:533–40. [PubMed: 10470696]
8. Grossman HB, Natale RB, Tangen CM, et al.Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med2003;349:859–66. [PubMed: 12944571]
9. Vale CNeoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet2003;361:1927–34. [PubMed: 12801735]
10. Vale CL. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data: Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol2005;48:202–6. [PubMed: 15939524]
11. Milowsky MI, Rumble RB, Booth CM, et al.Guideline on muscle-invasive and metastatic bladder cancer (European Association of Urology guideline): American Society of Clinical Oncology Clinical practice guideline endorsement. J Clin Oncol2016;34:1945–52. [PubMed: 27001593]
12. Witjes JA, Compérat E, Cowan NC, De Santis M, Gakis G, Lebret T, et al.EAU Guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. Eur Urol2014;65:778–92. [PubMed: 24373477]
13. National Comprehensive Cancer Network. Bladder cancer practice guidelines version 2.2016. Williston Park, NY: NCCN; 2016.
14. 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 Urol2007;178:451–4. [PubMed: 17561135]
15. Schiffmann J, Sun M, Gandaglia G, et al.Suboptimal use of neoadjuvant chemotherapy in radical cystectomy patients: a population-based study. Can Urol Assoc J2016;10:E82–6. [PubMed: 27330584]
16. Chou R, Selph SS, Buckley DI, et al.Treatment of muscle-invasive bladder cancer: a systematic review. Cancer2016;122:842–51. [PubMed: 26773572]
17. Krabbe LM, Westerman ME, Margulis V, et al.Changing trends in utilization of neoadjuvant chemotherapy in muscle-invasive bladder cancer. Can J Urol2015;22:7865–75. [PubMed: 26267024]
18. Reardon ZD, Patel SG, Zaid HB, et al.Trends in the use of perioperative chemotherapy for localized and locally advanced muscle-invasive bladder cancer: a sign of changing tides. Eur Urol2015;67:165–70. [PubMed: 24472710]
19. Chamie K, Saigal CS, Lai J, et al.Quality of care in patients with bladder cancer: a case report? Cancer2012;118:1412–21. [PubMed: 21823107]
20. Simonato A, Varca V, Gacci M, et al.Adherence to guidelines among Italian urologists on imaging preoperative staging of low-risk prostate cancer: results from the MIRROR (Multicenter Italian Report on Radical Prostatectomy Outcomes and Research) study. Adv Urol2012;2012:651061. [PubMed: 22666241]
21. Hernes E, Kyrdalen A, Kvale R, et al.Initial management of prostate cancer: first year experience with the Norwegian National Prostate Cancer Registry. BJU Int2010;105:805–11. [PubMed: 19735258]
22. Chamie K, Williams SB, Hershman DL, Wright JD, Nguyen PL, Hu JC. Population-based assessment of determining predictors for quality of prostate cancer surveillance. Cancer2015;121:4150–7. [PubMed: 26307939]
23. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care2002;40:IV3–18.
24. von der Maase H, Hansen SW, Roberts JT, et al.Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol2000;18:3068–77. [PubMed: 11001674]

25. Sternberg CN, de Mulder P, Schornagel JH, et al.Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer2006;42:50–4. [PubMed: 16330205]

26. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. J Clin Epidemiol2000;53:1258–67. [PubMed: 11146273]

27. Charlson ME, Sax FL, MacKenzie CR, Fields SD, Braham RL, Douglas RG. Assessing illness severity: does clinical judgment work?J Chronic Dis1986;39:439–52. [PubMed: 3086355]

28. Porter MP, Kerrigan MC, Donato BMK, Ramsey SD. Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. Urol Oncol2011;29:252–8. [PubMed: 19450992]

29. Zaid HB, Patel SG, Stimson CJ, et al.Trends in the utilization of neoadjuvant chemotherapy in muscle-invasive bladder cancer: results from the National Cancer Database. Urology2014;83:75–80. [PubMed: 24231210]

30. Keegan KA, Zaid HB, Patel SG, Chang SS. Increasing utilization of neoadjuvant chemotherapy for muscle-invasive bladder cancer in the United States. Curr Urol Rep2014;15:394. [PubMed: 24566815]

31. Plimack ER, Hoffman-Censits JH, Viterbo R, et al.Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. J Clin Oncol2014;32:1895–901. [PubMed: 24821881]

32. De Santis M, Bellmunt J, Mead G, et al.Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II—results of EORTC study 30986. J Clin Oncol2009;27:5634–9. [PubMed: 19786668]

33. Hill NR, Fatoba ST, Oke JL, et al.Global prevalence of chronic kidney disease—a systematic review and meta-analysis. PLoS One2016;11:e0158765. [PubMed: 27383068]

34. Jiang DM, Raissouni S, Mercer J, et al.Clinical outcomes of elderly patients receiving neoadjuvant chemoradiation for locally advanced rectal cancer. Ann Oncol2015;26:2102–6. [PubMed: 26232491]

35. Bellmunt J, Mottet N, De Santis M. Urothelial carcinoma management in elderly or unfit patients. Eur J Cancer Suppl2016;14:1–20.

36. Chappidi MR, Kates M, Patel HD, et al.Frailty as a marker of adverse outcomes in patients with bladder cancer undergoing radical cystectomy. Urol Oncol2016;34:256.e1–6.

37. Dinney CP, Hansel D, McConkey D, et al.Novel neoadjuvant therapy paradigms for bladder cancer: results from the National Cancer Center Institute Forum. Urol Oncol2014;32:1108–15. [PubMed: 25443274]

Neoadjuvant chemotherapy was underused, and the quality of neoadjuvant chemotherapy regimens administered for bladder cancer patients was inconsistent with guideline recommendations. Only 12.6% of radical cystectomy patients received neoadjuvant chemotherapy, half of whom received guideline-recommended regimens. The quality of regimen impacted survival outcomes, as use of cisplatin-based chemotherapy was significantly associated with better overall survival among patients diagnosed with stage II bladder cancer. However, <1% of all radical cystectomy patients received this regimen.

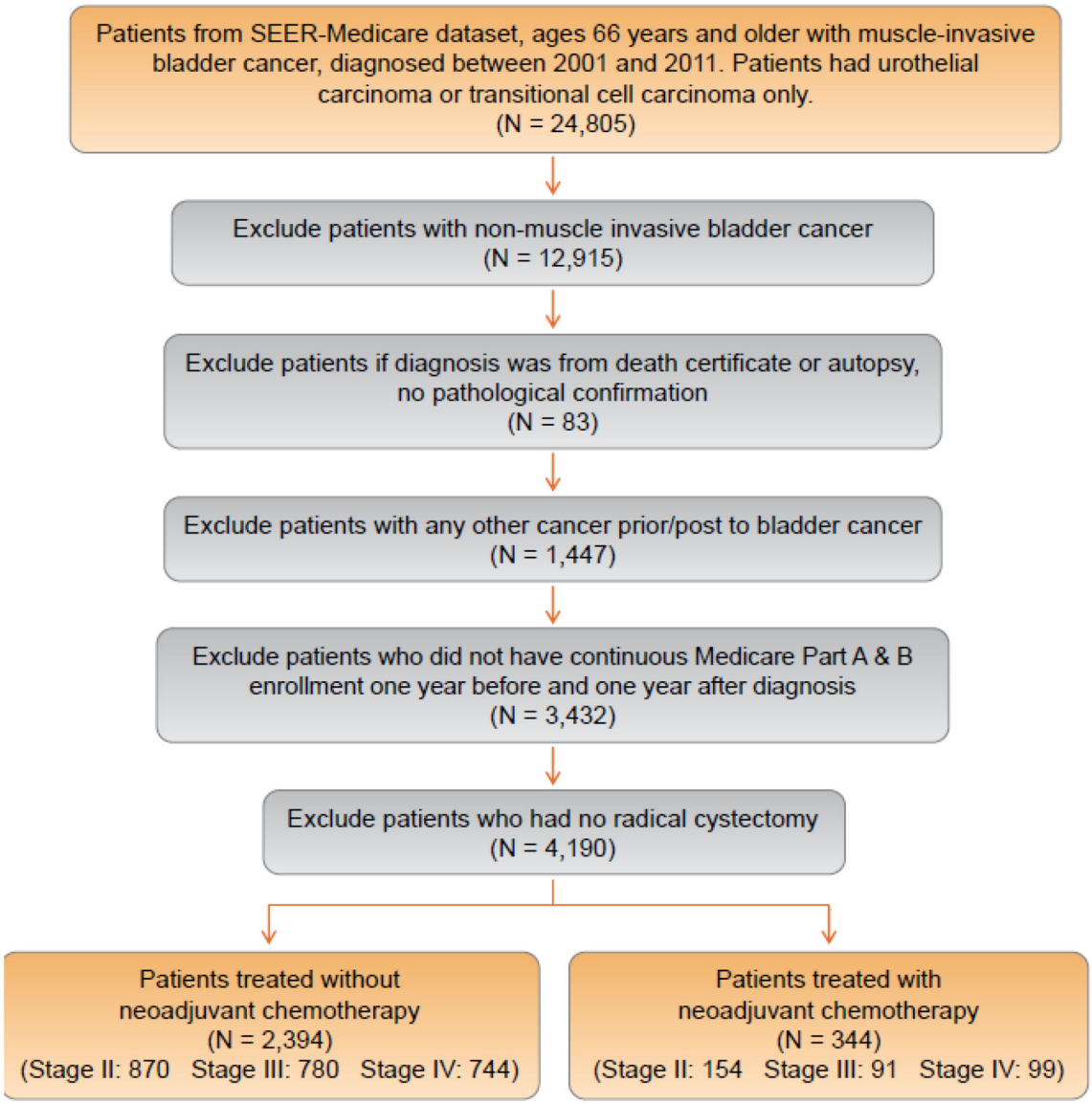

Fig. 1 –.
Derivation of the cohort size. SEER = Surveillance, Epidemiology and End Results.

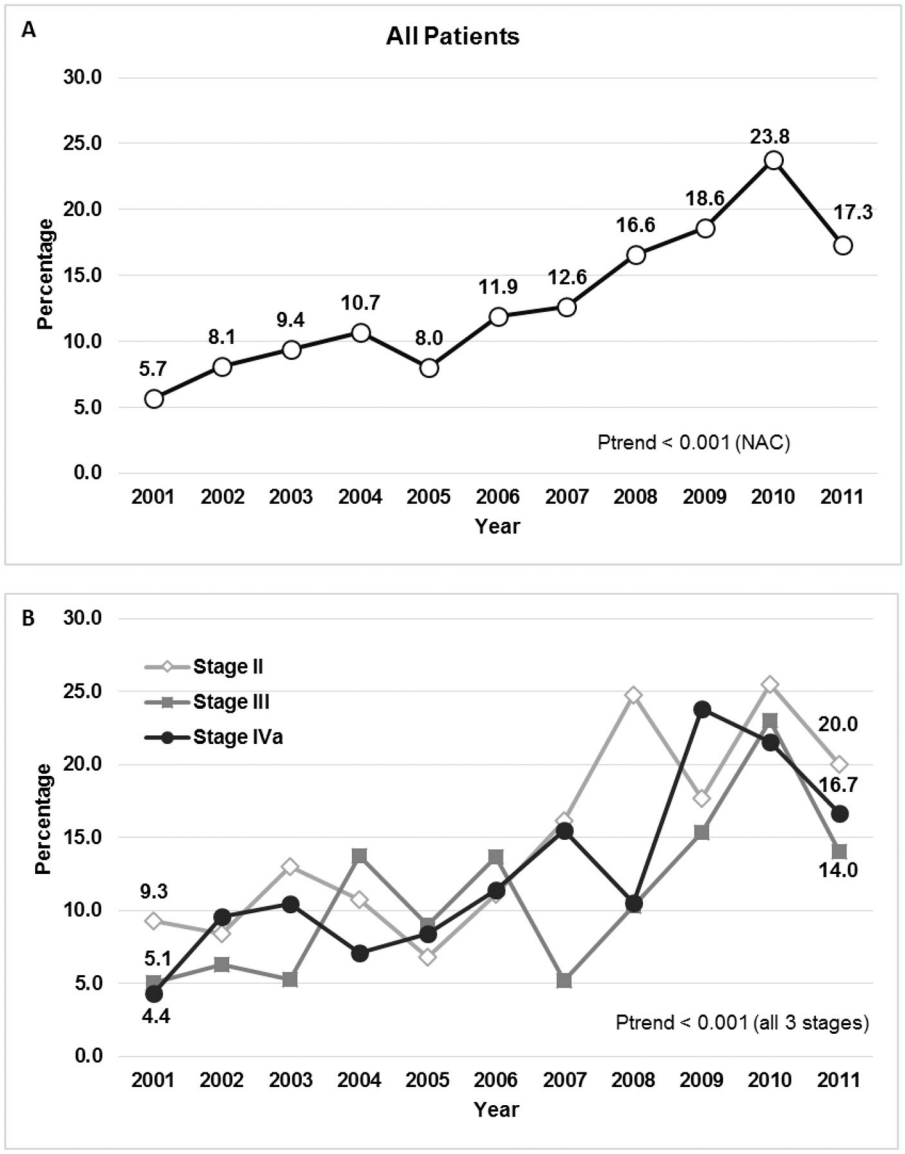

Fig. 2 –.

Neoadjuvant chemotherapy (NAC) use for (A) the overall cohort and (B) stratified by clinical stage.

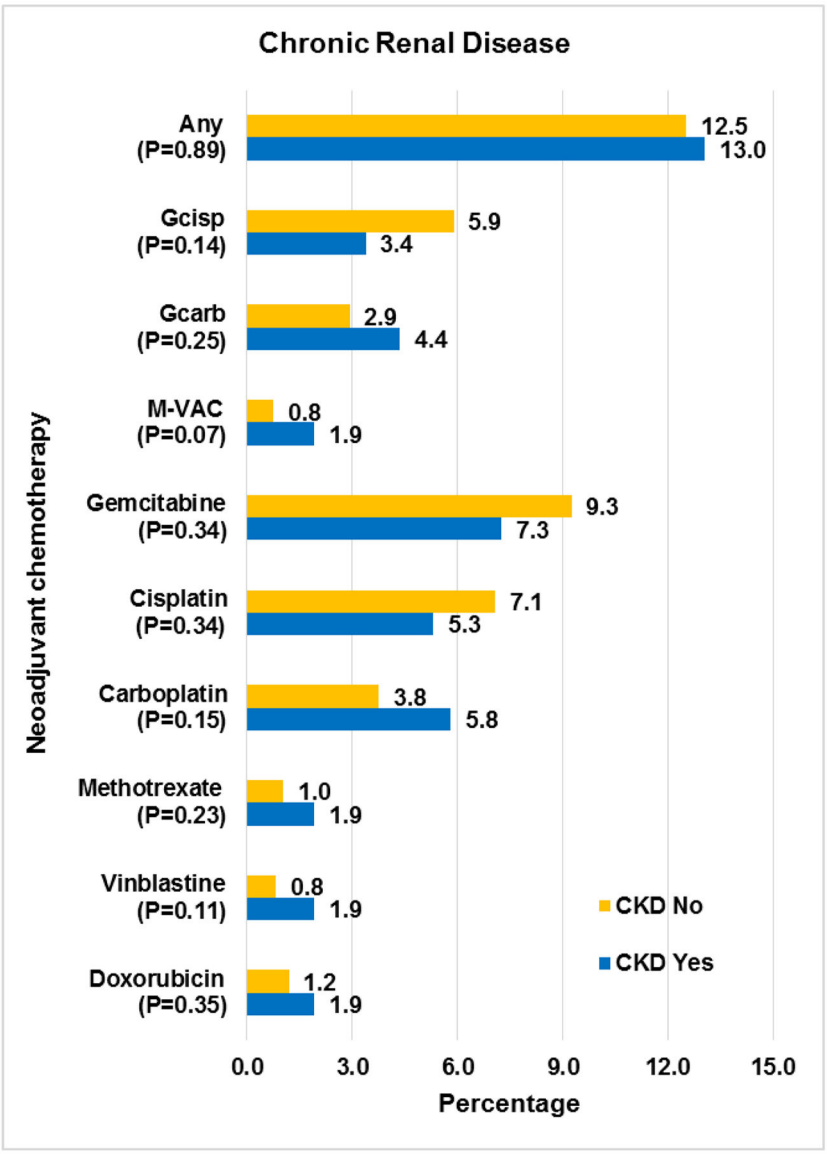

Fig. 3 –.

Neoadjuvant chemotherapy use and type of chemotherapy for patients with muscle-invasive bladder cancer stratified by chronic renal disease. There was no significant difference in neoadjuvant chemotherapy use between patients with and without chronic kidney disease (CKD). M-VAC = methotrexate, vinblastine, doxorubicin, and cisplatin; Gcisp = gemcitabine and cisplatin; Gcarb = gemcitabine and carboplatin.

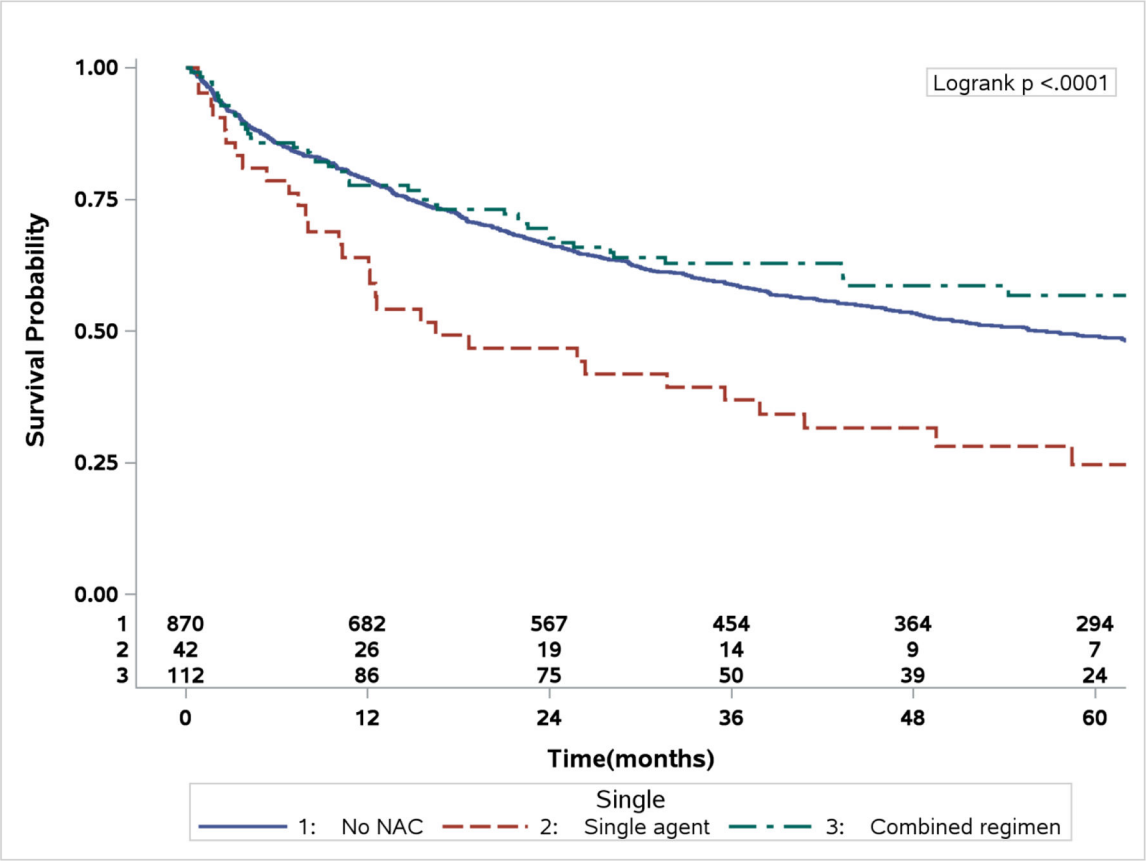

Fig. 4 –.

Kaplan-Meier curves for overall survival among patients with stage II muscle-invasive bladder cancer, stratified by use of neoadjuvant chemotherapy (NAC).

Table 1 –

Baseline characteristics of the cohort by neoadjuvant chemotherapy use

Characteristic	Patients (*n*)	Patients, *n* (%)		*p* value
		NAC	No NAC	
Age group				<0.001
66–69 yr	563	96 (17.1)	467 (82.9)	
70–74 yr	757	116 (15.3)	641 (84.7)	
75–79 yr	757	86 (11.4)	671 (88.6)	
≥80 yr	661	46 (7.0)	615 (93.0)	
Sex				0.944
Male	1700	213 (12.5)	1487 (87.5)	
Female	1038	131 (12.6)	907 (87.4)	
Race				0.483
Non-Hispanic White	2379	303 (12.7)	2076 (87.3)	
Other	359	41 (11.4)	318 (88.6)	
Marital status				
Single	385	59 (15.3)	326 (84.7)	
Married	1666	222 (13.3)	1444 (86.7)	
Unknown	687	63 (9.2)	624 (90.8)	
Census region				0.523
West	1140	1009 (88.5)	131 (11.5)	
Northeast	621	540 (87)	81 (13)	
Midwest	316	275 (87)	41 (13)	
South	661	570 (86.2)	91 (13.8)	
Median household income				0.676
1st quartile	719	87 (12.1)	632 (87.9)	
2nd quartile	673	79 (11.7)	594 (88.3)	
3rd quartile	673	85 (12.6)	588 (87.4)	
4th quartile	673	93 (13.8)	580 (86.2)	
Stage				0.008
II	1024	154 (15.0)	870 (85.0)	
III	871	91 (10.4)	780 (89.6)	
IV	843	99 (11.7)	744 (88.3)	
Hydronephrosis				0.103
No	2492	305 (12.2)	2187 (87.8)	
Yes	246	39 (15.9)	207 (84.1)	
Grade				0.629
Low	119	14 (11.8)	105 (88.2)	
High	2561	325 (12.7)	2236 (87.3)	
Charlson comorbidity index				0.020
0	1704	228 (13.4)	1476 (86.6)	
1	664	88 (13.3)	576 (86.7)	

Characteristic	Patients (*n*)	Patients, *n* (%)		*p* value
		NAC	No NAC	
2	213	17 (8.0)	196 (92.0)	
≥3	157	11 (7.0)	146 (93.0)	

NAC = neoadjuvant chemotherapy.

Table 2 –

Multivariable model for predictors of receipt of neoadjuvant chemotherapy

Covariate	OR (95% CI)	*p* value
Year of diagnosis		
2001	Reference	
2002	1.41 (0.70–2.84)	0.334
2003	1.71 (0.86–3.37)	0.125
2004	1.80 (0.92–3.52)	0.084
2005	1.39 (0.69–2.79)	0.352
2006	2.09 (1.07–4.09)	0.031
2007	2.20 (1.14–4.28)	0.020
2008	3.26 (1.71–6.21)	<0.001
2009	3.89 (2.04–7.43)	<0.001
2010	4.89 (2.60–9.18)	<0.001
2011	3.59 (1.79–7.20)	<0.001
Age group		
66–69 yr	Reference	
70–74 yr	0.92 (0.68–1.25)	0.596
75–79 yr	0.69 (0.50–0.96)	0.026
≥80 yr	0.39 (0.26–0.57)	<.001
Sex		
Male	Reference	
Female	1.14 (0.88–1.47)	0.315
Race		
White	Reference	
Black	0.98 (0.56–1.73)	0.950
Hispanic	0.60 (0.28–1.29)	0.192
Other	0.89 (0.51–1.57)	0.690
Marital status		
Single	Reference	
Married	0.93 (0.67–1.29)	0.666
Unknown	0.69 (0.46–1.03)	0.068
Census region		
West	Reference	
Northeast	1.24 (0.91–1.71)	0.179
Midwest	1.22 (0.82–1.82)	0.317
South	1.25 (0.90–1.73)	0.193
Median household income		
1st quartile	Reference	
2nd quartile	1.06 (0.74–1.50)	0.761
3rd quartile	1.12 (0.78–1.61)	0.534
4th quartile	1.24 (0.86–1.79)	0.243

Covariate	OR (95% CI)	*p* value
Grade		
Low	Reference	
High	1.03 (0.57–1.85)	0.932
Unknown	0.56 (0.19–1.69)	0.305
Stage		
II	Reference	
III	0.72 (0.54–0.95)	0.022
IV	0.83 (0.63–1.11)	0.208
Hydronephrosis		
No	Reference	
Yes	1.33 (0.90–1.95)	0.152
Chronic renal disease		
No	Reference	
Yes	1.44 (0.88–2.36)	0.146
Charlson comorbidity index		
0	Reference	
1	0.92 (0.70–1.21)	0.548
2	0.47 (0.27–0.81)	0.006
≥3	0.41 (0.20–0.82)	0.012

CI = confidence interval; OR = odds ratio.

Table 3 –

Cox regression model assessing the association between NAC receipt and overall survival[a]

	HR (95% CI)	*p* value
All stage II patients		
No NAC	Reference	
Single-agent NAC	1.51 (1.03–2.19)	0.033
Combined NAC regimen	0.74 (0.53–1.03)	0.072
Stage II patients who received NAC		
Single-agent NAC	Reference	
Combined NAC regimen	0.48 (0.24–0.95)	0.036

CI = confidence interval; HR = hazard ratio; NAC = neoadjuvant chemotherapy.

[a]All models were controlled for patient demographics and clinical variables including: year of diagnosis, age group, sex, race, marital status, region, median household income, tumor grade, hydronephrosis, chronic renal disease, comorbidity, and time from cancer diagnosis to radical cystectomy. The detailed model parameters and coefficients for variables from these four models are reported in the Supplementary material.