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Trends and appropriateness of perioperative chemotherapy for muscle-invasive bladder cancer

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Abstract

Introduction: Contemporary guidelines recommend cystectomy with neoadjuvant or adjuvant cisplatin-based chemotherapy given with curative intent for patients with resectable muscle-invasive bladder cancer (MIBC). However, rates and appropriateness of perioperative chemotherapy utilization remain unclear. We therefore sought to characterize use of perioperative chemotherapy in older radical cystectomy MIBC patients and examine factors associated with use.

Methods: Using Surveillance, Epidemiology, and End Results (SEER)-Medicare data, we identified patients with MIBC diagnosed between 2004 and 2013 and treated with radical cystectomy. We classified patients into 3 treatment groups: cystectomy alone, neoadjuvant, or adjuvant chemotherapy. Chemotherapy was classified by regimen. We then fit a multinomial multivariable logistic regression model to assess association between patient factors with the receipt of each treatment.

Results: We identified 3,826 eligible patients. The majority (484; 65%) received cystectomy alone. Neoadjuvant (676; 18% overall, 69% cisplatin-based), and adjuvant chemotherapy (666, 17% overall, 55% cisplatin-based) were used in similar proportions of cystectomy patients. Over the study period, the odds of receiving adjuvant chemotherapy decreased by 7.5%, whereas neoadjuvant therapy increased by 27.5% (both $P < 0.001$). There was an increase in use of cisplatin-based regimens in the neoadjuvant setting (35 to 72%, $P < 0.001$), but not the adjuvant setting. Female gender, lower comorbidity, married status, and lower stage disease were associated with greater odds of receiving neoadjuvant chemotherapy (all $P < 0.05$).

Conclusion: From 2004 to 2013 use of neoadjuvant chemotherapy for MIBC increased while use of adjuvant chemotherapy decreased. Future studies examining barriers to appropriate chemotherapy use, and the comparative effectiveness of neoadjuvant versus adjuvant chemotherapy are warranted.

Keywords: SEER Program; Medicare; Urinary bladder neoplasms; Drug therapy; Health Services Research

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1. Introduction

For patients with locally invasive bladder cancer, radical cystectomy is the gold standard treatment. The use of chemotherapy before surgery (neoadjuvant) or after surgery (adjuvant) significantly improves survival, particularly in those patients who are most likely to develop recurrent disease [1–4]. As the multidisciplinary approach to bladder cancer evolves, chemotherapy is an increasingly integral part of treatment.

However, the extent to which guideline-driven regimens of neoadjuvant and adjuvant chemotherapy (henceforth perioperative chemotherapy) are used remains unclear. Traditionally, neoadjuvant chemotherapy has been used sparingly [5,6] although rates have gradually increased with level 1 evidence [7,8]. The use of adjuvant therapy, on the other hand, remains stagnant [9]. Nonetheless, trends in use of perioperative chemotherapy and factors associated with use are not well described in population-based data with granular billing claims regarding specific chemotherapeutic agents used.

For these reasons, we sought to characterize the use of neoadjuvant and adjuvant chemotherapy in radical cystectomy patients at the population level using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. We also sought to examine factors associated with neoadjuvant and adjuvant chemotherapy. Understanding trends in chemotherapy utilization as well as patient, demographic, socioeconomic, and clinical factors associated with its use will help formulate strategies to increase chemotherapy delivery for patients with locally invasive bladder cancer.

2. Methods

2.1. Study population

We used SEER-Medicare data to identify patients diagnosed with bladder cancer between 2004 and 2013 who underwent radical cystectomy using International Classification of Diseases, Ninth Revision (ICD-9) codes 57.7, 57.71, 57.79, 68.8 and Healthcare Common Procedure Coding System (HCPCS) codes 51590, 51595, 51596, 51580, 51585, 51570, 51575, 51597 [10]. SEER-Medicare data represent a population-based cancer registry linked to Medicare claims for patients over 65 years, capturing approximately 30% of incident cancer in the United States. Since the median age of bladder cancer diagnosis is 72, this dataset generalizable to most bladder cancer patients. We included patients 66 years or older who were continuously enrolled in Medicare Parts A and B during the 12 months prior to cystectomy and 6 months after cystectomy. We also included those who died within 6 months of cystectomy to identify patients who died within our study timeframe, but still received perioperative chemotherapy. We excluded patients with nonmuscle invasive disease, as systemic chemotherapy is not indicated in this population. We also excluded patients with coexisting nonurothelial malignancy, including prostate cancer, diagnosed prior to cystectomy as this could confound treatment decisions around chemotherapy use. We included those with prostate cancer if diagnosed at the time of cystectomy since this was unlikely to impact decisions regarding chemotherapy use.

2.2. Outcomes

The primary outcome was receipt of perioperative chemotherapy. Outcomes were categorized as radical cystectomy alone, chemotherapy prior to radical cystectomy (neoadjuvant) and receipt of chemotherapy after radical cystectomy (adjuvant). Chemotherapy use was identified in the Medicare outpatient and carrier files by using HCPCS codes including specific regimens when possible (see Appendix). As defined in prior studies [7,8], neoadjuvant chemotherapy was defined as chemotherapy administration within the 6 months prior to cystectomy, while adjuvant chemotherapy was defined as chemotherapy administration within the 6 months following cystectomy. These time windows were selected based on the consensus of the research team to balance possible misclassification of chemotherapy for metastatic recurrence and despite to capture as much chemotherapy administered with adjuvant intent as possible. Patients ($N = 109$) who received both neoadjuvant and adjuvant chemotherapy were included in the neoadjuvant group only, as this was the initial therapy intended.

Patient demographic and pathological information was obtained using the SEER Patient Entitlement and Diagnosis Summary File (PEDSF). This information was classified as shown in Table 1 [1]. As part of the demographic information, local census tract information (ZIP code-level educational attainment, population of the county of residence, and ZIP code-level median household income) were obtained. Geographic region (northeast, south, central, west) was categorized based on SEER region at the time of the bladder cancer diagnosis. Pathologic information included tumor grade and stage. Tumor stage was based on the American Joint Committee on Cancer, 6th edition, T-stage data derived through the SEER Collaborative Stage algorithm [11,12]. Patient comorbidity was determined using the Charlson-Klabunde method in the 12 months prior to first therapy (cystectomy or chemotherapy) [13].

2.3. Statistical analysis

For the main study outcome, we classified patients into 3 treatment groups: cystectomy alone, neoadjuvant chemotherapy, and adjuvant chemotherapy. We compared demographic, socioeconomic, and pathologic characteristics of the study population using chi-square tests to assess categorized variables. We then performed a univariable analysis to examine factors associated with each treatment. Next, we fit a multinomial multivariable logistic regression model to examine the association of patient factors with the receipt of each treatment. We included variables from the

Table 1
Demographic, socioeconomic, clinical, and pathological characteristics of SEER-Medicare beneficiaries with muscle invasive bladder cancer 2004-2013

	Cystectomy alone (*N* = 2,484)	Neoadjuvant (*N* = 676)	Adjuvant (*N* = 666)	*P* value
Age at diagnosis (%)				<0.001
66–69	406 (16)	178 (26)	163 (25)	
70–74	620 (25)	230 (34)	218 (33)	
75–79	695 (28)	173 (26)	170 (26)	
80 and older	763 (31)	95 (14)	115 (17)	
Sex (%)				0.002
Male	1724 (69)	498 (74)	503 (76)	
Female	760 (31)	178 (26)	163 (25)	
Race (%)				0.85
White	2170 (87)	602 (89)	587 (88)	
Black	104 (4)	28 (4)	29 (4)	
Hispanic	113 (5)	26 (4)	25 (4)	
Other	97 (4)	20 (3)	25 (4)	
Marital status (%)				<0.001
Married	1512 (61)	456 (68)	478 (72)	
Not married	891 (36)	206 (31)	170 (26)	
Unknown	81 (3)	14 (2)	18 (3)	
Education level in the ZIP code of residence (%)				0.449
Low (<75% with high school education)	286 (12)	79 (12)	73 (11)	
High (>75% with high school education)	2148 (87)	581 (86)	583 (88)	
Missing	50 (2)	16 (2)	10 (2)	
County of residence population (%)				0.4
1,000,000 or more	1359 (55)	368 (54)	358 (54)	
250,000–999,999	425 (17)	134 (20)	127 (19)	
Less than 250,000	700 (28)	174 (26)	181 (27)	
Median household income in ZIP code of residence, $ (%)				0.389
40,000 or less	403 (16)	96 (14)	104 (16)	
40,001–59,999	935 (38)	255 (38)	228 (34)	
60,000 or more	1095 (44)	309 (46)	323 (49)	
Missing	51 (2)	16 (2)	11 (2)	
U.S. geographic region (%)				0.293
Northeast	516 (21)	146 (22)	138 (21)	
South	612 (25)	163 (24)	153 (23)	
Central	347 (14)	114 (17)	88 (13)	
West	1009 (40)	253 (37)	287 (43)	
Year of cystectomy (%)				<0.001
2004	255 (10)	20 (3)	65 (10)	
2005	300 (12)	47 (7)	91 (14)	
2006	310 (13)	38 (6)	66 (10)	
2007	273 (11)	51 (8)	89 (13)	
2008	273 (11)	68 (10)	91 (14)	
2009	234 (9)	58 (9)	61 (9)	
2010	215 (9)	82 (12)	62 (9)	
2011	212 (9)	88 (13)	49 (7)	
2012	195 (8)	92 (14)	46 (7)	
2013*	217 (9)	132 (20)	46 (7)	
Months from diagnosis to cystectomy (%)				<0.001
2 or less	1372 (55)	21 (3)	407 (61)	
2.1 to 4	731 (29)	108 (16)	175 (26)	
4.1 or more	381 (15)	547 (81)	84 (13)	
Grade (%)				0.027
Well/moderately differentiated	157 (6)	27 (4)	30 (5)	
Poorly/undifferentiated	2327 (94)	649 (96)	636 (96)	
T stage (%)				<0.001
T2	1345 (54)	398 (59)	177 (27)	
T3	802 (32)	165 (24)	318 (48)	
T4	337 (14)	113 (17)	171 (26)	
N stage (%)				<0.001
N0/NX	2148 (87)	561 (83)	332 (40)	
N+	336 (14)	115 (17)	334 (50)	
M stage (%)				0.902
M Stage: M0/MX	2484 (100)	676 (100)	666 (100)	

Percentages might not sum to 100 due to rounding.

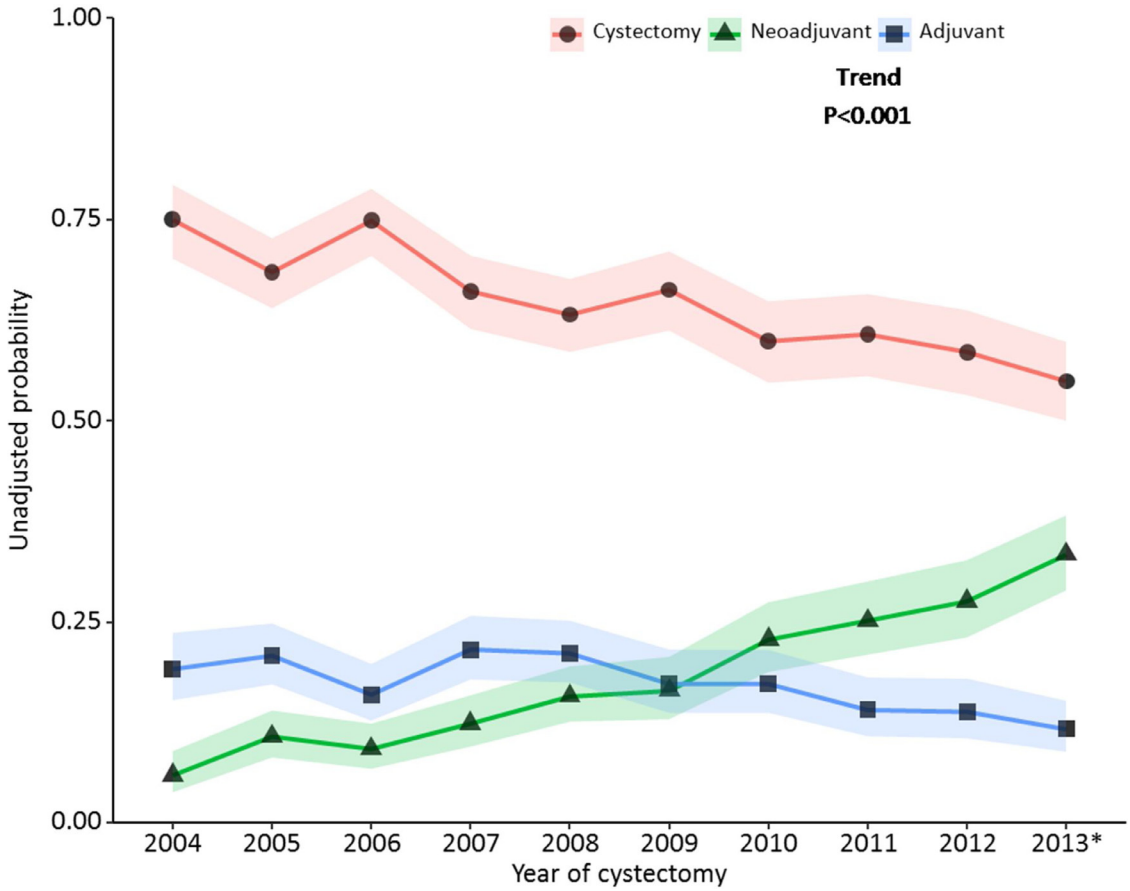

Fig. 1. Trends in use of neoadjuvant chemotherapy, adjuvant chemotherapy and cystectomy alone 2004-2013.
From 2004 to 2013 use of neoadjuvant chemotherapy increased 28%, use of adjuvant chemotherapy decreased 7.5% and there was a 22% decline in the use of cystectomy alone ($P < 0.001$; test for trend).

univariable analysis with a $P < 0.05$ and/or factors deemed clinically important (age, sex, race, comorbidity, marital status, stage, and grade). Odds ratios (OR) and 95% confidence intervals (CIs) were calculated. We also presented the odds of receiving each treatment based on the year of cystectomy (Fig. 1). A sensitivity analysis excluding T and N stage was performed given potential the potential for coding errors in the SEER registry between clinical and surgical staging. A secondary analysis assessed trends in cisplatin-based therapy in the neoadjuvant and adjuvant setting over time, using chi-squared test for trend.

All analyses were performed using SAS v9.4 (Cary, NC) and R (version 3.4.1) using the packages dpylr [14] for data management, compareGroups [15] for descriptive tables, ggplot2 [16] for graphics, and nnet [17] multinomial logistic regression. Statistical significance was set at 0.05. The study protocol was deemed exempt by the University of Pittsburgh Institutional Review Board.

3. Results

The demographic, socioeconomic, clinical, and pathological information for the study groups is summarized in Table 1. During the study period, 3,826 cystectomy patients met the inclusion criteria. Most patients ($n = 2,484$ [65%]) received cystectomy alone. A similar number of patients received neoadjuvant ($n = 676$ [18%]) and adjuvant chemotherapy ($n = 666$ [17%]). Most patients were ≥70 years old (80%), male (71%), white (88%), and married (64%). There were no differences in education level, median household income, population of county of residency, and SEER region among patients who received cystectomy alone, neoadjuvant chemotherapy, and adjuvant chemotherapy (all $P > 0.05$). Among those getting neoadjuvant chemotherapy, 468 (69%) received a cisplatin-based regimen, and 208 (31%) did not. For adjuvant, 367 (55%) received cisplatin-based chemotherapy, and 299 (45%) did not. Additional details regarding the type of chemotherapy administered to Medicare beneficiaries with muscle-invasive bladder cancer are shown in Table 2.

Over the study period, the odds of receiving neoadjuvant chemotherapy increased by 28%; whereas, the odds of receiving adjuvant chemotherapy decreased by 7.5% (Fig. 1) (both $P < 0.001$; test for trend). Over time, proportion of patients receiving cisplatin-based regimens increased from 35% to 72% ($P < 0.001$) in the neoadjuvant setting, but there was no significant change in the adjuvant setting (P 0.167).

Table 2
Chemotherapy regiments received by Medicare beneficiaries with muscle-invasive bladder cancer between 2004 and 2013

Chemotherapy regimens	Neoadjuvant chemotherapy 676 (%)	Adjuvant chemotherapy 666 (%)
Stratified by cisplatin use		
Cisplatin-based	468 (69%)	367 (55%)
Not cisplatin-based	208 (31%)	299 (45%)
Stratified by regimen		
Gemcitabine/Cisplatin	312 (46%)	257 (39%)
Gemcitabine/Carboplatin	126 (19%)	187 (28%)
MVAC[a]	50 (7%)	28 (4%)
Cisplatin monotherapy	26 (4%)	14 (2%)
Other regimen[b]	80 (12%)	68 (10%)

[a] Methotrexate, vinblastine, adriamycin (doxorubicin), cisplatin.
[b] Included gemcitabine monotherapy, carboplatin monotherapy, single and multi-agent paclitaxel-based regimens as well as generic codes for infusion of cytotoxic chemotherapy with no specific agent identified.

The results of the multinomial multivariable analysis are shown in Table 3. Female gender, lower comorbidity, married status, and lower stage disease were associated with higher odds of receiving neoadjuvant chemotherapy compared to cystectomy alone (all $P < 0.05$). Node-positive patients were more likely to receive adjuvant chemotherapy compared to cystectomy alone (OR 5.27; 95% CI 4.27−6.50). Higher stage disease was associated with increased use of perioperative chemotherapy. Similarly, being diagnosed later in the study period was associated with a significant association with receipt of perioperative chemotherapy beginning in 2010 (Table 3 and Fig. 1). In the sensitivity analysis, where T and N stage were excluded, there was no change in the overall direction of the associations noted in the *a priori* model (Supplementary Figure 1, Supplementary Table 1).

4. Discussion

We performed a population-based analysis of Medicare beneficiaries with muscle-invasive bladder cancer investigating factors associated with receipt of perioperative chemotherapy. There are several notable findings. First, we observed that patients who were unmarried and had more comorbidities are less likely to receive perioperative chemotherapy. Second, we note that patients with the more advanced stage (higher T stage and positive lymph nodes) are more likely to receive perioperative chemotherapy. Third, during the study period, the probability of receiving neoadjuvant chemotherapy increased by 28% whereas the probability receiving adjuvant chemotherapy decreased by 7.5% over the study period. Finally, while overall use of perioperative chemotherapy has increased, a large proportion of patients receive less effective, non−cisplatin-based regimens.

This large population-based analysis demonstrates that patient factors are associated with receipt of perioperative chemotherapy. The present study adds a few elements to prior studies on this topic. First, we used the contemporary SERR-Medicare files available, which use specific methodology to capture a population-level denominator, in contrast to prior studies on this subject using hospital-based data [6]. SEER-Medicare data also has the advantage of identifying the specific chemotherapy regimens used. This allows for granular analysis of therapy as used in the real-world, representing a huge range of centers and trial-ineligible patients [18], which would have been missed by prior meta-analyses [1]. As expected, those with more advanced disease were more likely to be treated with perioperative chemotherapy. However, patients who were older, had more comorbidities, and who were unmarried were less likely to receive perioperative chemotherapy in addition to cystectomy. Analysis of the hospital-based National Cancer Database noted similar trends, as well as decreased chemotherapy utilization with increasing travel distance to the treating cancer center [9]. After 2013, the end date of this analysis, the landscape of bladder cancer management has continued to rapidly evolve and may soon include genomic sub-typing as part of management [19]. Additionally, programmed death ligand-1 receptors have moved into the forefront of treatment for platinum ineligible patients [20]. In a rapidly evolving landscape for bladder cancer treatment in which newer, more costly drugs and personalized biomarkers are key to determining the best chance for cure, older, more comorbidity patients with fewer financial and social resources may be at risk of a widening disconnect between evidence-based care and reality [21].

The significant increase in neoadjuvant chemotherapy may be explained by several factors. First, with level 1 evidence and guideline recommendations supporting neoadjuvant chemotherapy use, increased adoption overtime is expected [2,3,7,22]. Furthermore, with improvements in chemotherapy, such as the use of gemcitabine and cisplatin combination or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin, neoadjuvant treatment is more tolerable with decreased toxicity, reduced time to cystectomy, and comparable efficacy to older regimens [23−25]. These improvements have made neoadjuvant chemotherapy a

Table 3
Estimated effect of each covariate on receiving neoadjuvant vs. cystectomy alone vs. adjuvant chemotherapy vs. cystectomy alone*

Predictor	Adjusted OR (95% CI) Cystectomy alone vs. neoadjuvant	Adjusted OR (95% CI) Cystectomy alone vs. adjuvant
Age at diagnosis		
66–69	Reference	Reference
70–74	0.87 (0.68–1.12)	0.83 (0.64–1.08)
75–79	**0.62 (0.48–0.80)**	**0.58 (0.44–0.76)**
80 or older	**0.31 (0.23–0.42)**	**0.34 (0.25–0.45)**
Sex		
Male	Reference	Reference
Female	0.89 (0.72–1.11)	**0.74 (0.59–0.92)**
Race		
White	Reference	Reference
Black	1.07 (0.67–1.69)	1.07 (0.67–1.72)
Hispanic	0.75 (0.47–1.19)	0.78 (0.48–1.26)
Other	0.75 (0.45–1.25)	0.89 (0.54–1.46)
Comorbidity		
0	Reference	Reference
1	**0.71 (0.58–0.88)**	**0.74 (0.59–0.94)**
2 or more	**0.33 (0.26–0.41)**	**0.59 (0.47–0.74)**
Marital status		
Married	Reference	Reference
Not married	0.86 (0.70–1.05)	**0.69 (0.55–0.85)**
Unknown	1.01 (0.58–1.78)	0.55 (0.30–1.00)
Year of cystectomy		
2004	Reference	Reference
2005	**2.04 (1.17–3.56)**	1.19 (0.80–1.77)
2006	1.63 (0.92–2.89)	0.78 (0.51–1.18)
2007	**2.59 (1.49–4.51)**	1.22 (0.82–1.82)
2008	**3.49 (2.04–5.98)**	1.28 (0.86–1.91)
2009	**3.53 (2.04–6.11)**	1.08 (0.70–1.66)
2010	**5.42 (3.19–9.23)**	1.16 (0.75–1.78)
2011	**6.03 (3.55–10.24)**	1.04 (0.66–1.62)
2012	**6.89 (4.06–11.71)**	0.89 (0.56–1.41)
2013	**8.72 (5.21–14.59)**	0.89 (0.56–1.40)
Grade		
Well/moderately differentiated	Reference	Reference
Poorly/undifferentiated	1.49 (0.96–2.32)	1.05 (0.68–1.61)
T stage		
T2	Reference	Reference
T3	**0.76 (0.61–0.94)**	**2.33 (1.86–2.91)**
T4	**1.34 (1.03–1.76)**	**2.64 (2.01–3.46)**
Nodal stage		
N0/Nx	Reference	Reference
N+	**1.44 (1.11–1.86)**	**5.17 (4.20–6.37)**

Abbreviations: OR = odds ratio; CI = confidence interval.
Bolded values $P < 0.05$.
* Multinomial multivariable logistic regression. Cystectomy alone is referent group. Estimates are adjusted for age, sex, race, comorbidity, marital status, year of cystectomy, tumor grade, tumor stage, and nodal status.

more attractive treatment option for eligible patients and likely impacted utilization.

There are several potential reasons for the concomitant decrease in adjuvant chemotherapy as well. First, patients undergoing neoadjuvant chemotherapy may be down staged at the time of cystectomy and therefore are adjuvant chemotherapy may not be clinically indicated [2,3,23]. Second, patients may not tolerate chemotherapy after surgery due to postoperative complications. A study of bladder cancer patients at a high-volume tertiary cancer center found that 30% of the 1,142 patients undergoing radical cystectomy were likely unable to receive adjuvant chemotherapy due to postoperative complications [26].

The final observation of this study is the existence of a quality improvement opportunity to address the appropriateness of perioperative chemotherapy selection. For patients having neoadjuvant chemotherapy, if the patient cannot tolerate a cisplatin-based regimen and has a surgically resectable tumor, there is no data to support use of alternate regimens prior to cystectomy [27]. However, in

this cohort up to a third of patients treated with neoadjuvant therapy were given suboptimal non−cisplatin-based agents. In the postcystectomy setting, there are may be a higher proportion of patients who are not eligible for first-line treatment due to surgical complications, reduced renal function; however, nearly half of patients receiving adjuvant chemotherapy were not given first-line therapy. These observations may be explained in part by the older age and increased frailty of the Medicare population compared to the clinical trial population. As such, some of the adjuvant chemotherapy captured in this analysis may have been given with palliative, rather than curative, intent [28]. Going forward, future studies should investigate rates of adherence to guideline-based regimens, chemotherapy completion, dose reductions and their impact on outcomes in the real-world setting.

The findings of this study should be considered in the context of several limitations. First, we used Medicare claims, thus potentially limiting the generalizability of our findings. Nonetheless, the majority of patients with bladder cancer are in the seventh decade of life and have Medicare coverage [29]. Second, we did not include provider variability in our analysis, which affects practice patterns for chemotherapy administration. However, it would be difficult to identify which providers (urologist vs. medical oncologist) are influencing the decision to pursue chemotherapy for a patient from claims data. Thirdly, we lack data on renal function which is a major determinant of chemotherapy selection. Fourth, NAC given up to 6 months prior the cystectomy may be less efficacious; however, efficacy was not the intended endpoint of this analysis. Lastly, our findings are based on retrospective observational data, which is limited by unmeasured confounding that may not be corrected for in our adjusting analyses. However, we adjusted for several measurable clinical and nonclinical factors to minimize confounding, such as age, comorbidity, and tumor stage.

5. Conclusion

We have demonstrated that utilization of neoadjuvant chemotherapy has increased, while utilization of adjuvant chemotherapy has decreased over the study period. Describing the current use of perioperative chemotherapy in patients undergoing radical cystectomy in the United States illuminates the degree to which it has been adopted in locally advanced bladder cancer care and identifies factors associated with use of perioperative chemotherapy. Finally, a gap between evidence and practice is noted with up to one third of patient receiving suboptimal neoadjuvant therapy and up to half of patients receiving suboptimal adjuvant therapy. Since perioperative chemotherapy is an important component of multidisciplinary bladder cancer care, this information can help guide quality improvement to increase access for patient groups with low rates of chemotherapy use and improve standardization of practice. Furthermore, this study highlights the need for future studies comparing the effectiveness of neoadjuvant and adjuvant chemotherapy.

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Author contributions

Conceptualization: Fam, Hale, Jacobs; Data curation: Yabes; Formal analysis: Fam, Yabes, Lopa, Jacobs; Funding acquisition: Jacobs; Investigation: Fam, Yabes, Lopa, Jacobs; Methodology: Fam, Yabes, Jacobs; Project administration: Jacobs; Supervision: Turner, Davies, Jacobs; Visualization: Fam, Yabes; Writing − original draft: Fam, Yabes, Jacobs; Writing − review & editing: Macleod, Turner, Yu, Gingrich, Borza, Skolarus, Davies, Jacobs.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.04.006.

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