



Rate and Determinants of Completing Neoadjuvant Chemotherapy in Medicare Beneficiaries With Bladder Cancer: A SEER-Medicare Analysis

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OBJECTIVE	To determine the rate and determinants of neoadjuvant chemotherapy noncompletion in patients with muscle-invasive bladder cancer.
METHODS	Using Surveillance, Epidemiology, and End Results-Medicare data, we identified all patients who underwent cystectomy between 2008-2013 and received chemotherapy within 6 months. Of these, 594 patients received neoadjuvant chemotherapy, defined as the presence of a claim for chemotherapy within the 180 days preceding cystectomy. Our primary outcome was noncompletion of neoadjuvant chemotherapy. We determined regimen-specific cut points for noncompletion based on clinical trials and national guidelines.
RESULTS	Over the study period, 174 of 594 patients (29%) did not complete neoadjuvant chemotherapy. Noncompleters and completers received a median interquartile range of 4.4 (3.0-8.0) and 10.0 (7.7-11.2) weeks of chemotherapy, respectively. A total of 391 (66%) patients received a cisplatin-based regimen and 203 (34%) patients received an alternative regimen, with 27% and 33% not completing chemotherapy, respectively. After adjusting for covariates, age and geographic region were independently associated with failing to complete chemotherapy.
CONCLUSION	Nearly 30% of patients who received neoadjuvant chemotherapy did not complete their regimen. Advanced age and nonclinical factors, such as practice patterns in certain geographic regions, may influence a patient's likelihood of successfully completing chemotherapy. UROLOGY 124: 191–197, 2019. © 2018 Elsevier Inc.

Radical cystectomy is the gold standard treatment for patients with muscle-invasive bladder cancer; however the addition of neoadjuvant chemotherapy may improve survival.¹ While rates of neoadjuvant chemotherapy use are increasing, uptake remains low for several reasons.² Advanced patient age and baseline comorbidity of the bladder cancer population, chemotherapy toxicity, and delaying time to surgery are factors that discourage neoadjuvant chemotherapy administration and may impact completion of treatment.³

Among patients who receive neoadjuvant chemotherapy, the rate at which they complete their course and the risk factors associated with noncompletion are unknown.

Since the decision to pursue neoadjuvant chemotherapy is nuanced for both patients and providers, knowing completion rates and predictors of noncompletion would improve decision making in many ways. First, this knowledge may guide decision making for patients who are ambivalent about receiving systemic treatment by helping them choose neoadjuvant chemotherapy or immediate cystectomy. Second, a better understanding of disparities in chemotherapy completion may lead to innovations in cancer care for disadvantaged populations.⁴

For these reasons, we sought to determine the rate of neoadjuvant chemotherapy noncompletion and characterize determinants of noncompletion in patients with muscle-invasive bladder cancer. Understanding patterns in neoadjuvant chemotherapy completion will improve shared decision making and patient selection.

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METHODS

Data Source and Study Population

We used Surveillance, Epidemiology, and End Results (SEER)–Medicare data to identify patients aged 66 years

and older who were diagnosed with bladder cancer between 2004 and 2013. We further identified patients who underwent radical cystectomy (International Classification of Diseases, Ninth Revision [ICD-9] codes 57.7, 57.71, 57.79, and 68.8) and received chemotherapy within 6 months of the operative date. We included patients who were continuously enrolled in Medicare Parts A and B for 12 months prior to the initiation of chemotherapy and for 6 months following cystectomy. We excluded patients younger than 66 years old to ensure a 1-year window for accurate calculation of patient comorbidity.⁵ We excluded patients with prior malignancies, metastatic bladder cancer, and those patients diagnosed at autopsy or death. Patients diagnosed with prostate or urothelial cancer at the time of cystectomy were included.

Using the SEER Patient Entitlement and Diagnosis Summary File, we obtained patient demographic and pathologic information (ie, tumor grade and stage).⁶ We based cancer stage on criteria from the American Joint Committee on Cancer.⁷ Patients with missing grade (114 of 1818), missing stage (11 of 1704), and tumor stage less than T2 (351 of 1693) were excluded.

Outcomes

Our primary outcome was noncompletion of neoadjuvant chemotherapy. To identify neoadjuvant chemotherapy as defined in prior studies, we first identified receipt of chemotherapy within 6 months of cystectomy using chemotherapy J-codes from the Healthcare Common Procedure Coding System codes in carrier and outpatient file claims (Supplementary Table 1).⁸ We identified 1342 patients who received chemotherapy within 6 months of the operative date. A patient was defined as having received neoadjuvant chemotherapy if they possessed a claim for a chemotherapy J-code within the 6 months (180 days) preceding cystectomy (676 of 1342).

Second, we determined each unique combination of J-codes received by patients in our cohort. Based on the J-code combination, we identified the specific chemotherapeutic regimen each patient received. Next, we performed a literature search to determine the typical number of times drug is administered per cycle in each chemotherapy regimen (Supplementary Table 2). Finally, we determined the number of times drug was administered to each patient by summing the claims for chemotherapy J-code claims. We assigned each regimen a noncompletion cut point of less than 2 or 3 cycles of chemotherapy, based on clinical experience that patients who complete 2 cycles of chemotherapy tend to complete their course. Patients with a number of claims less than the regimen-specific cut point were identified as having not completed the course of chemotherapy and are subsequently referred to as “non-completers.” Patients with claims that numbered greater than or equal to the cut point are subsequently referred to as “completers.” Since our primary outcome was noncompletion of neoadjuvant chemotherapy, rather than receipt of any chemotherapy, we decided to exclude patients with a combination of J-codes that did not correspond to specific chemotherapeutic regimen and therefore could not assign a valid noncompletion cut point (68 of 676). We also excluded those patients with missing median income (14 of 608). In total, 594 patients received neoadjuvant chemotherapy with a well-described regimen of medications and underwent radical cystectomy.

Statistical analysis

We compared demographic, socioeconomic, and pathologic characteristics of completers and noncompleters using frequencies and

percentages. We categorized certain continuous variables, such as age, median household income, and population of county of residence in order to identify certain groups of patients hypothesized to be at risk of noncompletion (eg, older patients, patients not living in poverty but below the median household, and patients living in less populated and potentially lower resource counties). Univariate associations with chemotherapy noncompletion were tested using chi-square test or Fisher exact test for categorical variables. For skewed continuous variables, Wilcoxon rank sum test was used to present median and interquartile range (IQR). A univariable logistic regression model was fit to determine unadjusted odds ratios (OR) and 95% confidence intervals (CI) for noncompletion. Then, we fit a multivariable logistic regression model to calculate adjusted OR and determine factors independently associated with noncompletion. Covariates from the univariate analysis with $P < .05$ were included in the model, which included age and geographic region. We also included sex, race, comorbidity, marital status, median household income in ZIP code of residence, and T stage as potentially important variables that could confound chemotherapy completion. A sensitivity analysis was performed on regimen-specific cut point for neoadjuvant chemotherapy noncompletion. To show that the definition of our primary outcome was truly able to discriminate between noncompleters and completers, we compared the total number of chemotherapy J-codes and the duration of chemotherapy in months across our primary outcome.

Statistical analysis was performed SAS v9.4 (Cary, NC) and R (version 3.5) using the packages dplyr for data management, compareGroups for descriptive tables, ggplot2 for graphics, and rms for logistic regression analysis. Statistical significance was defined as $P < .05$. The University of Pittsburgh institutional review board deemed this study exempt from review.

RESULTS

Of the 594 patients who received neoadjuvant chemotherapy and underwent a cystectomy, 174 (29%) did not complete neoadjuvant chemotherapy. On univariable analysis, age and geographic region significantly differed between noncompleters and completers. No differences existed between sex, race, marital status, baseline comorbidity, year of diagnosis, or tumor characteristics (all $P > .05$; Table 1).

The median duration of chemotherapy for the entire cohort was 9.0 weeks (IQR 6.0-10.6). Noncompleters and completers received a median IQR of 4.4 (3.0-8.0) and 10.0 (7.7-11.2) weeks of chemotherapy, respectively. A total of 391 (66%) patients received a cisplatin-based regimen and 203 (34%) patients received an alternative regimen, with 27% and 33% not completing chemotherapy, respectively (>0.05 ; Table 2).

After adjusting for covariates, both age and geographic region remained independently associated with failing to complete chemotherapy (Fig. 1). Compared with patients aged 66-69, those aged 80 and older were more likely to be noncompleters (adjusted OR 2.6, 95% CI 1.4-4.8). However, patients from the central region were less likely to be noncompleters compared to patients from the northeast region (adjusted OR 0.3, 95% CI 0.2-0.6). Patients with greater comorbidity did not have a significantly increased risk of noncompletion ($P > .05$).

Sensitivity analysis of the primary outcome, regimen-specific cut point for neoadjuvant chemotherapy noncompletion, showed significant discrimination between noncompleters and completers. The median number of chemotherapy J-codes for

Table 1. Patient characteristics of the study population

Characteristic	Chemotherapy Completers (n = 420)	Chemotherapy Noncompleters (n = 174)	P Value*
Age at diagnosis, n (%)			.02
66-69	126 (30)	37 (21)	
70-74	141 (34)	65 (37)	
75-79	109 (26)	41 (24)	
80 and older	44 (11)	31 (18)	
Sex, n (%)			.5
Male	300 (71)	130 (75)	
Female	120 (29)	44 (25)	
Race/ethnicity, n (%) [†]			.2
White	382 (91)	>141 (>81)	
Black	12 (3)	<11 (<6)	
Hispanic	15 (4)	<11 (<6)	
Other	11 (3)	<11 (<6)	
Marital status, n (%)			.2
Married	289 (69)	111 (64)	
Not married	131 (31)	63 (36)	
Comorbidity, n (%)			.3
0	214 (51)	81 (47)	
1	127 (30)	51 (29)	
2 or more	79 (19)	42 (24)	
Education in ZIP code of residence (%)			.7
Low: 75% or fewer with high school education	46 (11%)	22 (12)	
High: >75% with high school education	374 (89%)	152 (87)	
Population of county of residence (%)			.9
1,000,000 or more	232 (55)	98 (56)	
250,000-999,999	81 (19)	35 (20)	
249,999 or less	107 (26)	41 (24)	
Median household income in ZIP code of residence, n (%)			.6
\$40,000 or less	55 (13)	27 (16)	
\$40,001-\$60,000	168 (40)	63 (36)	
\$60,001 or more	197 (47)	84 (48)	
Geographic region, n (%)			.003
Northeast	84 (20)	49 (28)	
South	92 (22)	45 (26)	
Central	87 (21)	16 (9)	
West	157 (37)	64 (37)	
T Stage, n (%)			.5
T2	244 (58)	106 (61)	
T3	102 (24)	44 (25)	
T4	74 (18)	24 (14)	
N Stage, n (%)			.7
NO/NX	353 (84)	149 (86)	
N+	67 (16)	25 (15)	
Year of diagnosis, n (%) [†]			.4
2004	33 (8)	11 (6)	
2005	20 (5)	<11 (<6)	
2006	27 (6)	13 (7)	
2007	31 (7)	13 (7)	
2008	35 (8)	20 (12)	
2009	44 (11)	14 (8)	
2010	57 (14)	>28 (>16)	
2011	64 (15)	15 (9)	
2012	54 (13)	21 (12)	
2013	56 (13)	>28 (>16)	

Bolded p-values have met the significance threshold of <0.05.

Abbreviations: IQR, interquartile range.

Percentages may not add to 100 due to rounding or missing data.

Cell sizes <11 were suppressed in accordance with SEER-Medicare guidelines.

* P values determined using Chi-square or t tests.

[†] Exact numbers are not shown in all cells to comply with SEER-Medicare guidelines.

Table 2. Chemotherapy regimen received by the study population

Characteristic	Chemotherapy Completers <i>n</i> = 429	Chemotherapy Noncompleters <i>n</i> = 179	<i>P</i> Value *
Chemotherapy duration, median (IQR) in weeks	10.0 (7.7-11.2)	4.4 (3.00-8.00)	<.001
Regimen classification, <i>n</i> (%)			.2
Cisplatin-based	284 (68)	107 (62)	
Not cisplatin-based	136 (32)	67 (39)	
Specific regimen, <i>n</i> (%)			<.001
Gem/Cis	230 (55)	82 (47)	
Gem/Carbo	98 (23)	28 (16)	
High dose MVAC	38 (9)	12 (7)	
Cis monotherapy	13 (3)	13 (7)	
Other chemotherapy regimen †	41 (10)	39 (22)	

Abbreviations: IQR, interquartile range; Gem, Gemcitabine; Cis, Cisplatin; Carbo, Carboplatin; Pac, Paclitaxel; Doxo, Doxorubicin.

* *P* values determined using Wilcoxon rank sum test for chemotherapy duration and Chi-square tests for chemotherapy regimens.

† Other chemotherapy regimens are grouped together due to low numbers and include Gem monotherapy, Gem/Carbo/Pac, Carbo monotherapy, Carbo/Pac, Gem/Pac, Pac monotherapy, and Cis/Doxo.

noncompleters (median 5.0, IQR 3.0-6.0) significantly differed from that of completers (median 11.0, IQR 9.0-13.0) (Fig. 2A, *P* < .001). Also, the median duration of chemotherapy in

months for noncompleters (median 1.0, IQR 0.7-1.9) and completers (median 2.3, IQR 1.8-2.6) significantly differed (Fig. 2B, *P* < .001).

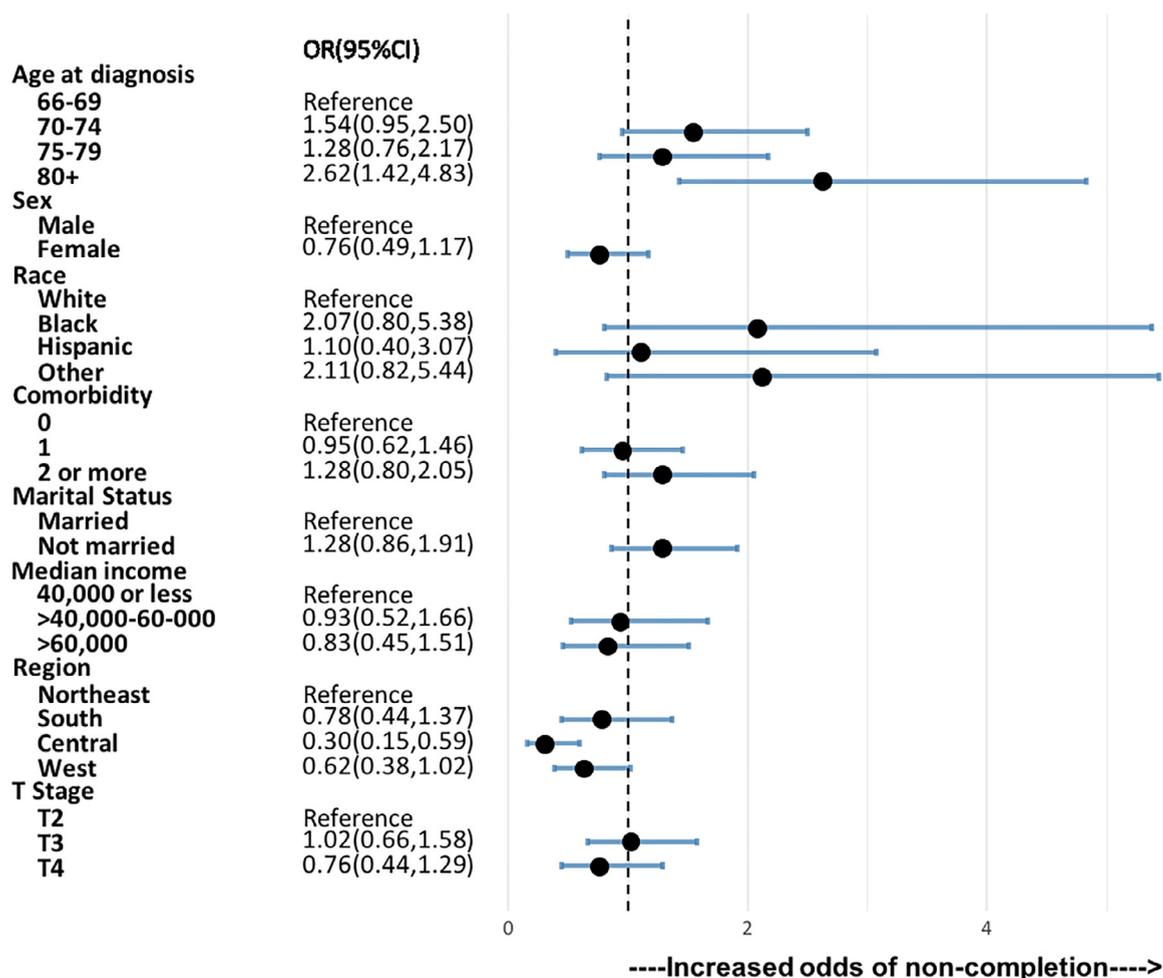


Figure 1. Forest plot of adjusted odds ratios for completing neoadjuvant chemotherapy. Abbreviations: OR, odds ratio; CI, confidence interval. Multivariable analysis used a logistic regression model. Estimates are adjusted for all covariates. (Color version available online.)

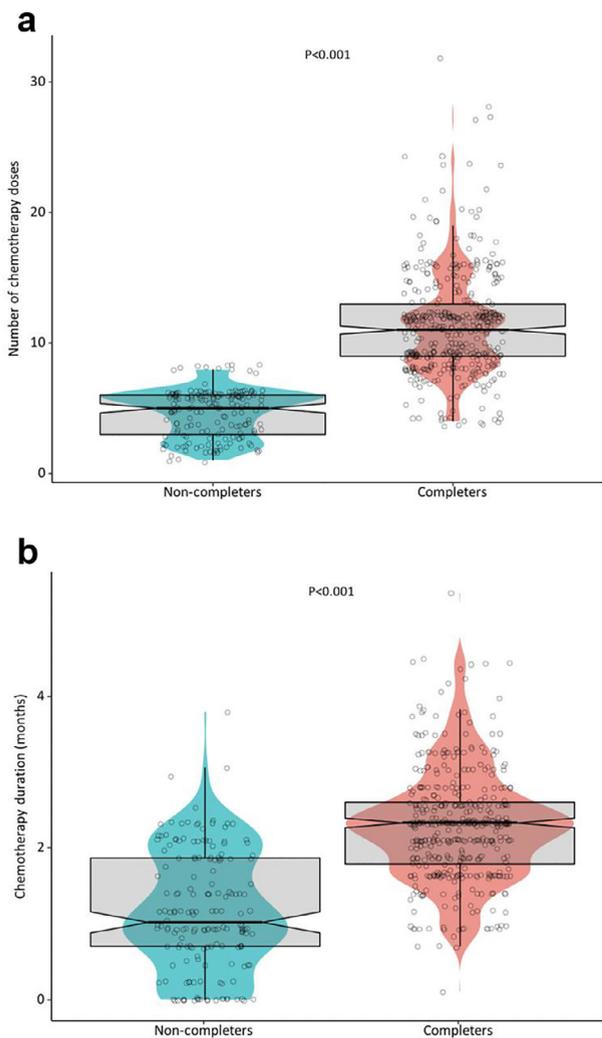


Figure 2. Violin plot of number of chemotherapy doses and duration stratified by completion status. (A) Median doses of neoadjuvant chemotherapy, measured by number of J-codes, stratified by completion status. (B) Median duration of neoadjuvant chemotherapy in months stratified by completion status. The width of the colored shape indicates the probability density of patients with each result. The grey notched box plot represents the median (thick black horizontal line), 95% confidence interval (notched portion of box), interquartile range (ie, 25th-75th percentile, upper and lower boundaries of box), and 1.5 times the interquartile range (solid vertical line). Both plots show significant discrimination between noncompleters and completers. (Color version available online.)

DISCUSSION

Although neoadjuvant chemotherapy use is increasing, with up to 11% of muscle-invasive bladder cancer patients receiving neoadjuvant chemotherapy,² a significant proportion of bladder cancer patients do not complete a full course. In this study, 29% of patients did not complete their course of chemotherapy and were considered non-completers. In our cohort, noncompleters were

significantly more likely to be older (age >80 years). Also, significant regional variation existed, with patients from the central United States having lower odds of noncompletion. Interestingly, marital status, higher comorbidity, median household income, and tumor stage were not significantly associated with failure to complete chemotherapy. Our findings suggest that age plays an important role in the likelihood of completing an intended course of neoadjuvant chemotherapy.

There are a number of reasons why age may play a role in the ability to complete chemotherapy. First, this trend may reflect the fact that older cancer patients receive different treatments than younger patients despite their willingness to undergo invasive diagnostic and therapeutic procedures.⁹ Therefore, it is plausible that noncompletion in older patients may result from physician biases that lead to early discontinuation of chemotherapy.¹⁰ Second, there are known age-related disparities in the literature, as age is consistently associated with decreased odds of receiving neoadjuvant chemotherapy.^{2,11} In our study, older age remained a significant factor after adjusting for patient comorbidity, however, other associated factors that may impact tolerance of chemotherapy, such as frailty or renal function, also have an impact. Additionally, age may be a surrogate for poorer social determinants of health, such as decreased medical literacy or poor numeracy, which may complicate a patient's understanding of risks and subsequent decision making.^{12,13}

Socioeconomic barriers to care may especially impact elderly Medicare beneficiaries, since nearly half of the elderly poor live alone, and median per capita income decreases with age. However, financial hardship is only 1 marker of low socioeconomic status. Socioeconomic status is a composite measure of multiple attributes that interact with health care in complex ways.¹⁴ In our study, variables with increased but not significant odds of noncompletion included nonwhite and nonHispanic races, unmarried partnership status, and low household income. These characteristics may represent poor social support systems that increase the risk receiving an incomplete course of chemotherapy.¹⁵ Studies have shown that poor social support and a lack of transportation impact chemotherapy receipt, especially in patients without private insurance.¹⁶ Also, low socioeconomic status is associated with poor patient-physician communication, which some patients cite as their greatest barrier to care.¹⁷

Nonclinical factors investigated in this study were significantly associated with noncompletion of chemotherapy. We did find evidence of regional variation in the proportion of patients that complete neoadjuvant chemotherapy, with lower odds of noncompletion in patients from the central region compared to the northeast. Studies have shown significantly higher rates of chemotherapy use in the northeastern United States compared to other regions, but extrapolating trends in chemotherapy use to

noncompletion rates is not straightforward.¹⁸ Nonetheless, the lower rate of both chemotherapy use and chemotherapy noncompletion in the central United States may represent more stringent selection criteria which translates to a population enriched with patients more likely to complete chemotherapy.

While understanding determinants of chemotherapy receipt is important, estimating a patient's risk of noncompletion is also useful. Until now, we lacked population-based data on chemotherapy completion rates in patients with muscle-invasive bladder cancer. To compare our results with existing data, we extrapolated completion rates from randomized controlled trials (Supplementary Table 3). We identified 8 such trials in the literature in which chemotherapy noncompletion ranged from 10%–23% of the patients recruited. In 2 studies, approximately 20% of patients in both treatment arms received fewer than the intended number of chemotherapy sessions.^{2,19} In fact, 22% of patients in 1 study completed >1 full cycle of neoadjuvant chemotherapy.² Two studies had noncompletion rates of around 15%,^{20,21} while approximately 10% of patients from another 4 studies did not receive the intended number of sessions.^{22–25} These proportions exclude patients that required toxicity-related dose modifications but otherwise completed chemotherapy. In total, 1582 patients in these trials received at least 1 chemotherapeutic drug and 244 (15%) did not complete the intended number of sessions. In our study, the noncompletion rate of 30% is twice that of these randomized trials. This difference in noncompletion rate is expected, given the rigorous methodology of a randomized controlled trial compared to the real-world effects detected in retrospective studies, and reflects the difference between efficacy and effectiveness. Also, this shows that our estimate of the rate of noncompletion was conservative, as intended, with minimal misclassification of completers as noncompleters.

Our findings may impact medical decision-making from both patient and provider perspectives. First, evidence suggests that decision support tools improve patient understanding of treatment choices.²⁶ These tools help patients choose therapies that better align with their preferences and facilitate realistic expectations of potential outcomes. Patients that are ambivalent about neoadjuvant chemotherapy, for example, may be appropriately encouraged or discouraged depending on age and social determinants. Shared decision-making that also emphasizes nonclinical characteristics may improve how patients perceive a physician's response to their concerns. This would particularly impact older low-income patients, who have been shown to perceive greater barriers to receiving healthcare.¹⁷ Second, this data may impact the patients deemed good candidates for neoadjuvant chemotherapy. This especially applies to patients with risk factors for chemotherapy noncompletion and low-risk clinical features: for example absence of hydronephrosis, lymphovascular invasion, palpable mass on bimanual examination, or

variant histology.²⁷ These low-risk patients have been shown to have an 80% 5-year disease specific survival if they remain low-risk on final pathology. Even if high-risk features are present on final pathology, 5-year disease specific survival can be maintained at 80% with the addition of adjuvant chemotherapy.²⁷ Considering determinants of chemotherapy completion and clinical risk factors may allow surgeons to proceed to immediate cystectomy with greater confidence or emphasize other promising preoperative optimization strategies, like nutritional support or prehabilitation. Third, our results can form the basis for patient centered research regarding administration of neoadjuvant chemotherapy in elderly patients with socioeconomic hardships. Given the increased emphasis on quality and efficient healthcare, comparative effectiveness research of clinically high-risk patients with risk factors for chemotherapy noncompletion may be particularly impactful.

Our findings should be considered in light of some limitations. First, determining the external validity of our study was not straightforward given a lack of comparable studies. We compensated for this by determining the rate of chemotherapy noncompletion in a compilation of randomized trials (15% vs 30% in our study). Second, the use of Medicare claims data restricts our findings to Medicare beneficiaries over the age of 65 living in specific geographic regions of the United States. However, this is an appropriate population in which to study bladder cancer as the median age at diagnosis is approximately 70 years of age.²⁸ Of the 11 million cancer patients in the United States, 60% are over the age of 65 and SEER registries capture 26% of this population.²⁹ Third, determining a true denominator of all patients eligible for neoadjuvant chemotherapy was difficult. We used receipt of chemotherapy prior to cystectomy as a proxy for patient fitness and eligibility for neoadjuvant chemotherapy. The ideal cohort would consist of all patients with clinical stage T2N0 cancer, however, clinical staging in SEER is incomplete. Therefore, we rely on the collaborative staging algorithm, which includes a combination of clinical and pathologic staging. Finally, some information that would deepen our understanding of chemotherapy completion is not available in Medicare claims. SEER-Medicare lacks the granular clinical data necessary to determine eligibility for and reasons for noncompletion of neoadjuvant chemotherapy, such as functional status, renal function, and frailty. Additionally, we did not account for other important factors that may impact receipt of chemotherapy such as travel distance to a cancer center, patient preferences, or physician practice patterns. Despite the known limitations of SEER-Medicare, our findings remain important by providing the first estimate of chemotherapy noncompletion in a population-based cohort of bladder cancer patients. Future studies enriched with clinically relevant patient-level data, in

the form of a multi-institutional prospective cohort study or secondary analyses of randomized controlled trials, may address these limitations.

CONCLUSION

In our study, nearly 30% of patients who received neoadjuvant chemotherapy did not complete their regimen. Advanced age and nonclinical factors, such as practice patterns in certain geographic regions, may influence a patient's likelihood of receiving or successfully completing neoadjuvant chemotherapy. Calling attention to risk factors for chemotherapy noncompletion may assist in patient decision-making and decrease treatment regret. Analyses of patient-level clinical data may further identify factors associated with neoadjuvant chemotherapy noncompletion.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.urology.2018.11.001>.

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