

**Trends and disparities in the use of neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma**

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**Abstract**

**Introduction:** Neoadjuvant chemotherapy (NAC) prior to radical or partial cystectomy is considered the standard of care for eligible patients with muscle-invasive urothelial carcinoma. Despite guideline recommendations, adoption of NAC has historically been low, although prior studies have suggested that use is increasing. In this contemporary study, we examine trends in the use of NAC and explore factors associated with its receipt.

**Methods:** We identified patients in the National Cancer Database who underwent radical or partial cystectomy for cT2-cT4N0M0 urothelial carcinoma from 2006–2014. The proportion of patients receiving NAC during each year was examined. Logistic regression models were used to evaluate clinical and socioeconomic factors associated with the receipt of NAC.

**Results:** A total of 18 188 patients were identified who underwent radical or partial cystectomy for muscle-invasive bladder cancer. Overall, 3940 (21.7%) received NAC. We noted a significant increase in the use of NAC over time, from 9.7% in 2006 to 32.2% in 2014. Factors associated with lower use of NAC include older age, higher comorbidity score, lower cT stage, lower hospital radical cystectomy volume, treatment at a non-academic facility, lower patient income, and receipt of partial cystectomy (all  $p < 0.001$ ). Interestingly, neither sex nor race were associated with receipt of NAC.

**Conclusions:** Use of NAC has increased significantly over time to a modest rate of 32%. However, disparities still exist in the receipt of NAC and future efforts aimed at mitigating these disparities are warranted.

## Introduction

Each year in the U.S., 70,500 patients are diagnosed with bladder cancer, of whom ~25% have muscle invasive disease (MIBC) at presentation<sup>1</sup>. Traditionally, the definitive treatment for MIBC has been radical cystectomy (RC). However, in recent years, neoadjuvant chemotherapy prior to RC has been recognized to provide a significant improvement in overall survival in patients with MIBC. In 2003, the SWOG-8710 trial showed a 5% survival benefit in those receiving cisplatin based chemotherapy prior to RC<sup>2</sup>. A subsequent meta-analysis examining patients from ten randomized trials confirmed this benefit<sup>3</sup>. Nonetheless, despite this evidence and current guideline recommendations advocating the use of NAC, wide spread adoption has not occurred<sup>4-7</sup>. Factors such as patient refusal, need for immediate surgery, medical co-morbidities and lack of local access to medical oncology support serve as potential barriers for low utilization rates<sup>8</sup>.

Although several observational studies identified a significant increase in the utilization of NAC up until 2010, contemporary national cancer registry data beyond this is lacking<sup>4,9,10</sup>. As such, in this study, we examine trend of the utilization of NAC and explore factors associated with its delivery.

## Methods

### *Data source*

The National Cancer Database, a joint effort between the American Cancer Society and the American College of Surgeons Commission on Cancer, includes information from patients who received an initial diagnosis or first course of treatment for cancer at one of the nearly 1500 Commission on Cancer accredited cancer centers. The dataset includes more than 70% of incident malignancies within the United States<sup>11</sup>. Trained personnel using standardized methodology abstract clinical, pathologic, treatment and demographic data.

### *Study population*

We identified all patients in the NCDB who underwent radical or partial cystectomy between 2006-2014 for cT2-cT4N0M0 urothelial carcinoma. Patients with non-urothelial histology were excluded.

### *Outcomes of interest*

The primary aim of the study was to determine the proportion of patients receiving NAC prior to PC or RC during each year included in the study. The secondary aim was to evaluate clinical, pathologic, treatment facility, and demographic factors associated with the receipt of NAC. NAC was defined as the administration of systemic chemotherapy prior to undergoing RC or PC.

*Statistical analysis*

Baseline characteristics between patients who did versus did not receive NAC were compared using chi-square test for categorical variables and t-test for continuous variables, as appropriate in univariate analysis. The proportion of patients during each year who received NAC was calculated and trends were plotted by calendar year. Multivariable logistic regression models were utilized to examine factors associated with the receipt of NAC. The following variables were included in the model: age, hospital volume, sex, race, income, co-morbidities, treatment facility type, clinical stage and partial cystectomy. Pre-defined subgroup analyses were performed to determine the rates and trends in the utilization of NAC among patients undergoing RC and PC separately.

Statistical analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, with p-values <0.05 considered statistically significant.

**Results***Baseline characteristics*

We identified 18,188 patients in the NCDB who underwent RC or PC for cT2-T4N0M0 MIBC between 2006-2014. The mean age at diagnosis was 68.5 years (+/- 10.32); 75.4% were males. The majority of patients were cT2 (80.4%). Additional patient demographic factors are listed in Table 1.

*NAC vs. No-NAC*

A total of 3940 (21.7%) received NAC prior to cystectomy. Significant baseline differences in age, Charlson co-morbidity index, insurance, income level, treatment facility, and clinical stage were identified between those receiving and not receiving NAC. The median time from diagnosis to surgery (RC or PC) in patients receiving NAC was 154 days (IQR: 125-187) vs. 52 days (IQR: 33-84) in those not receiving NAC. The median time from diagnosis to NAC initiation was 37 days (IQR: 23-56) (Table 2).

*NAC trend*

Overall, increased utilization of NAC was noted during the study period, from 9.7% in 2006 to 32.2% in 2014 (Figure 1a). In those undergoing radical cystectomy, we found an increase in utilization of 23.1% over an 8-year period. Utilization rates increased in partial cystectomy patients as well, although to a lesser degree. (Figure 1b).

*Factors associated with the receipt of NAC*

On multivariable analysis (Table 3), factors associated with lower utilization of NAC include older age, increased number of comorbidities, lower cT stage, lower hospital RC volume, treatment received at a non-academic facility, lower patient income, and receipt of partial

cystectomy (all  $p < 0.01$ ). Neither patient sex nor race was associated with the receipt of NAC (Table 3).

## Discussion

Herein, we identified that the utilization of NAC has continued to increase with time. Over an eight-year period, the rate of NAC utilization in MIBC patients tripled from 9.7% in 2006 to 32.2% in 2014. The odds of receiving NAC were significantly lower in patients with advanced age, increased co-morbidities, lower cT stage and lower income. Non-patient factors associated with decreased NAC receipt were lower hospital RC volume and treatment at non-academic centers. Uniquely, our study noted that receipt of NAC in those undergoing partial cystectomy was low despite guideline recommendations<sup>7</sup>.

It has been over a decade since Grossman et al. demonstrated a survival advantage with administration of NAC prior to RC in MIBC<sup>2</sup>. Subsequent trials and a meta-analysis of over 3000 patients have further confirmed this finding resulting in NAC being current standard of care<sup>3</sup>. Despite this robust evidence, utilization of NAC in the US has been historically low. A study in 2012 by Rehman et al. identified factors such as patient refusal, need for immediate surgery, and medical co-morbidities as reasons for patients not receiving NAC. They also found an alarming 71% of patients were not offered consultation regarding NAC prior to their RC<sup>8</sup>.

Prior NCDB analyses have shown a variety of patient, social, and medical system factors to be related with NAC use<sup>9,10</sup>. Similarly, our study noted elderly age and increased co-morbidity to be associated with decreased NAC utilization. Importantly, age and morbidity status are key factors in deciding fitness for NAC. Bladder cancer, for the most part, is a disease of the elderly with the median age of diagnosis being 73 years old. NAC itself is not definitive treatment, but rather part of a multi-modal approach ultimately ending in RC. Therefore, if potential exists for significant chemotherapy related toxicity then treating physicians often proceed directly to surgery, in part explaining the low utilization noted in our study.

Both social and societal factors influenced the use of NAC in our study. Hospitals with lower radical cystectomy volume and treatment at non-academic facilities are associated with decreased use of NAC. Studies have shown worse survival outcomes in patients treated at low volume non-academic centers<sup>12,13</sup>. In light of this, some argue radical cystectomy should be performed only in high volume centers, where access to multidisciplinary care and established perioperative care pathways improve patient outcome<sup>14</sup>. We also found patients with lower income were less likely to receive NAC in treatment of their MIBC, potentially a result of inadequate insurance coverage.

NAC utilization in patients undergoing PC in our study cohort was low, with only 16.5% of patients receiving treatment in 2014. In highly select cases, partial cystectomy can be offered as a treatment option for MIBC<sup>7</sup>. However, it is of utmost importance that those offering PC recognize they are treating the same pathology as those undergoing RC. Therefore, adjunctive treatment and procedures such as NAC and pelvic lymph node dissection apply in the same way

they do for RC patients. In fact, when used prior to PC, NAC has been shown to have acceptable oncologic outcomes in highly selected patients<sup>15</sup>.

Underutilization of NAC for bladder cancer is not unique to the United States. Similar trends have been identified elsewhere in the world. In South Korea, Kim et al. noted very low NAC utilization rates of 8.4% in 2013. Although very low, the author's state utilization had increased significantly from prior years<sup>16</sup>. They believe the low utilization rates observed in their study relates to health care policy in their country and the lack of national support for NAC use. Contrary to our data and that of the Koreans is the NAC utilization rate in Japan. A recent publication from Anan et al. found 83% utilization rate over the past decade<sup>17</sup>. It should be noted however that 83% of their patient's cohort received carboplatin based NAC, a regimen not recommended in the United States<sup>7</sup>.

Although current guidelines recommend considering NAC in all patients with MIBC, significant efforts are underway to optimize patient selection for NAC. As an example, MD Anderson Cancer Center has developed and validated a clinical risk stratification model to identify those believed to gain the most benefit from NAC<sup>18</sup>. In this model, patients are considered high-risk based on a combination of clinical and pathologic variables (hydronephrosis, cT3b-T4a, LVI, micropapillary or neuroendocrine histology on TUR). Patients not possessing these features are considered "low risk" and not offered NAC as they were found to have similar 5-year disease specific survival to those with organ confined disease ( $\leq$ pT2)<sup>18</sup>.

Recently, we have come to understand not all MIBC's are the same, standard treatment algorithms and guidelines may not be applicable in all cases. Genomic 'subtypes' and genetic alterations with distinct molecular profiles and varied response to NAC have been described<sup>19-23</sup>. As our understanding of MIBC biology continues to evolve, more 'personalized' treatment decisions will allow us to better select chemo sensitive tumors.

We recognize several limitations to this study. First, NCDB does not include information on the type of NAC utilized or the number of cycles received. Second, we are unable to assess the proportion of patients denied NAC following appropriate medical oncology assessment versus those without consultation. Furthermore, we are unable to assess reasons for denial (i.e. co-morbidities, renal function) and/or patient refusal secondary to NCDB limitations. We know from our previous work that these factors are substantial reasons why patients do not receive NAC<sup>18</sup>. Nonetheless, we believe this contemporary study highlights an encouraging trend of increased NAC use, but also recognizes much work still needs to be done.

## Conclusion

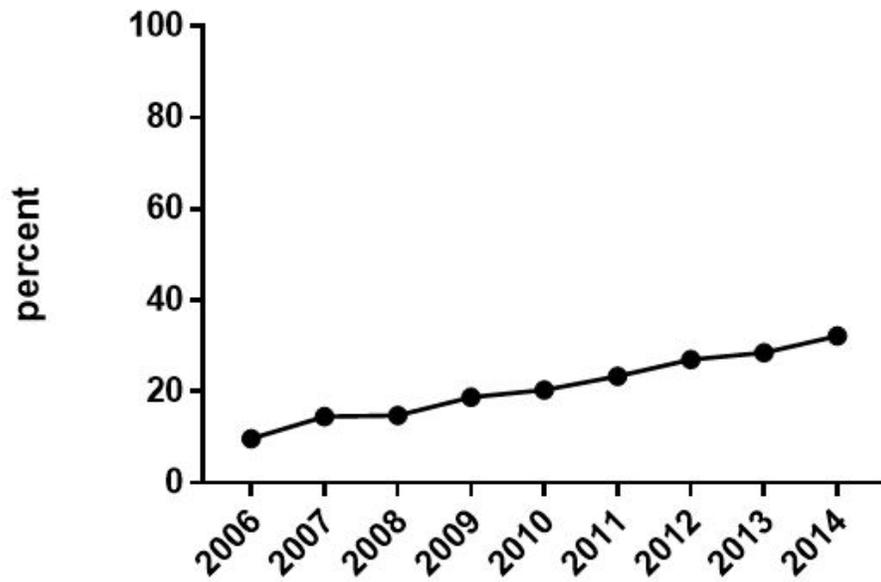
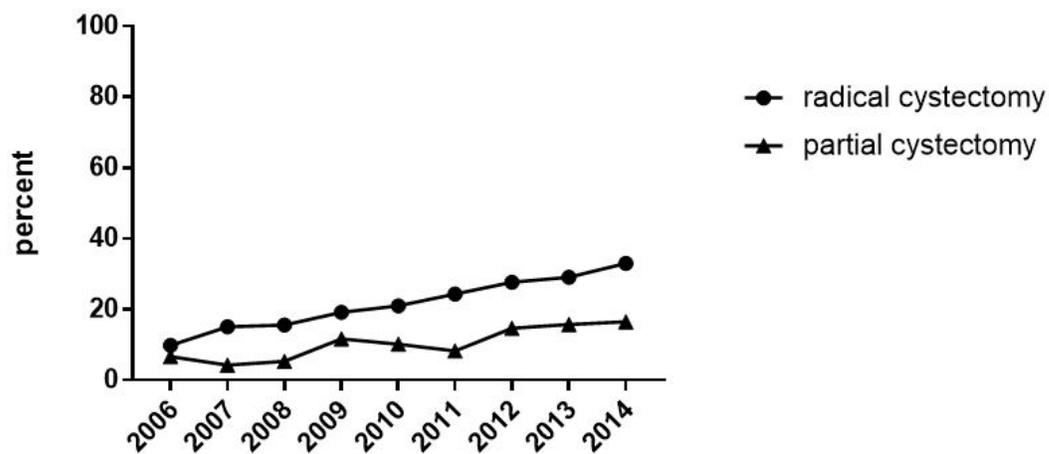
NAC utilization continues to increase over time, however significant disparities exist in who receives it. Continued efforts aimed at understanding and mitigating these disparities are required. Improved risk stratification and identification of those with chemo sensitive tumor types are potential strategies that will increase the utilization and effectiveness of NAC.

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## Figures and Tables

*Fig. 1A.* Neoadjuvant chemotherapy use from 2006–2014 in all patients.*Fig. 1B.* Neoadjuvant chemotherapy use from 2006–2014 in patients undergoing radical (n=17157) or partial cystectomy (n=1031).

<b>Table 1. Patient demographics of those undergoing partial or radical cystectomy from 2006–2014</b>	
<b>Number of patients</b>	18188
Mean age (SD)	68.49 (10.32)
<b>Surgery</b>	
Radical cystectomy	17 157 (94.3)
Partial cystectomy	1031 (5.6)
<b>Sex</b>	
Male	13 706 (75.4)
Female	4482 (24.6)
<b>Race</b>	
White	16 681 (91.7)
Black	938 (5.2)
Other	407 (2.2)
Unknown	162 (0.9)
<b>Charlson comorbidity index</b>	
$\leq 2$	16 874 (92.8)
$\geq 2$	1314 (7.2)
<b>Insurance</b>	
Government	11 890 (65.4)
No insurance	451 (2.5)
Private insurance	5620 (30.9)
Unknown	227 (1.2)
<b>Income</b>	
$\leq 46\ 000$	10 438 (57.4)
$> 46\ 000$	7079 (38.9)
Unknown	671 (3.7)
<b>Community</b>	
Metro	13 815 (76)
Urban	2656 (14.6)
Rural	1078 (5.9)
NA	639 (3.5)
<b>Treatment facility</b>	
Community cancer program/comprehensive community cancer program	9034 (49.7)
Academic/research program	9070 (49.9)
Other	84 (0.5)
<b>Clinical stage</b>	
cT2	14 631 (80.4)
cT3	2198 (12.1)
cT4	1359 (7.5)

SD: standard deviation.

<b>Table 2. Patient demographics of those receiving vs. not receiving NAC prior to radical or partial cystectomy from 2006–2014</b>			
	<b>No NAC</b>	<b>NAC</b>	<b>p</b>
Total number of patients (%)	14248 (78.3)	3940 (21.7)	
Radical cystectomy	13323 (77.7)	3834 (22.3)	
Partial cystectomy	925 (89.7)	106 (10.3)	
Age, mean (SD)	69.41 (10.33)	65.17(9.57)	<0.001
Sex			0.219
Male	10707 (75.1)	2999 (76.1)	
Female	3541 (24.9)	941 (23.1)	
Race			0.798
White	13065 (91.7)	3616 (91.8)	
Black	740 (5.2)	198 (5)	
Other	313 (2.2)	94 (2.4)	
Unknown	130 (0.9)	32 (0.8)	
Charlson comorbidity index $\geq 2$			<0.001
$\leq 2$	13134 (92.2)	3740 (94.9)	
$\geq 2$	1114 (7.8)	200 (5.1)	
Insurance			<0.001
Government	9679 (67.9)	2211 (56.1)	
No insurance	346 (2.4)	105 (2.7)	
Private	4063 (28.5)	1557 (39.5)	
Unknown	160 (1.1)	67 (1.7)	
Income			<0.001
$\leq 46\ 000$	8353 (58.6)	2085 (52.9)	
$>46\ 000$	5373 (37.7)	1706 (43.3)	
Unknown	522 (3.7)	149 (3.8)	
Community			0.74
Metro	10804 (75.8)	3011 (76.4)	
Urban	2082 (14.6)	574 (14.6)	
Rural	858 (6)	220 (5.6)	
Unknown	504 (3.5)	135 (3.4)	
Treatment facility			<0.001
Community cancer program/comprehensive community cancer program	7388 (51.9)	1646 (41.8)	
Academic/research program	6800 (47.7)	2270 (57.6)	
Other	60 (0.4)	24 (0.6)	
Clinical stage			<0.001
cT2	11608 (81.5)	3023 (76.7)	
cT3	1673 (11.7)	525 (13.3)	
cT4	967 (6.8)	392 (9.9)	

Median time from diagnosis to surgery, days (IQR)	52 (33–84)	154 (125–187)	
Median time from diagnosis to NAC, days (IQR)	-	37 (23–56)	

IQR: interquartile range; NAC: neoadjuvant chemotherapy; SD: standard deviation.

**Table 3. Multivariable regression model of factors associated with delivery/receipt of NAC**

	Odds ratio	95% CI	p
Age (per each increased year)	0.96	0.95-0.97	<0.001
Hospital volume			
<20	0.87	0.79-0.95	<0.001
≥20	1.00	-	-
Sex			
Male	1.00	-	-
Female	1.00	0.91-1.09	0.98
Race			
White	1.00	-	-
Black	0.89	0.75-1.06	0.19
Other	0.96	0.75-1.23	0.76
Income			
≤46 000	1.00	-	-
>46 000	1.28	1.19-1.39	<0.001
Comorbidities			
≤2	1.00	-	-
≥2	0.70	0.60-0.82	<0.001
Facility			
Community cancer program/comprehensive community cancer program	0.75	0.69-0.81	<0.001
Academic/research program	1.00	-	-
Clinical stage			
cT2	1.00	-	-
cT3	1.28	1.15-1.43	<0.001
cT4	1.56	1.37-1.78	<0.001
Type of surgery			
Radical cystectomy	1.00	-	-
Partial cystectomy	0.50	0.40-0.62	<0.001

CI: confidence interval.