Race as a predictor of pathologic response to neoadjuvant chemotherapy at time of cystectomy for bladder cancer

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Introduction: *Complete pathologic response (pT0) at time of cystectomy after neoadjuvant chemotherapy (NAC) has been associated with significantly improved clinical outcomes. The goal of this study is to examine whether race is a predictor of pT0 response to NAC at time of cystectomy.*

Materials and methods: *We analyzed the records of patients diagnosed with a non-metastatic (M0) muscle-invasive (cT2+) urothelial cell bladder cancer in the National Cancer Database (NCDB) who underwent a cystectomy from 2006 to 2014. The cohort was stratified by whether the patient received NAC prior to cystectomy. Univariate and multivariate logistic regression models were used to assess for the effect of race on pathologic complete response after NAC.*

Results: *We identified 16,036 patients of which 3,195 patients (19.9 %) were treated with NAC prior to cystectomy. The total number of African American (AA) patients in this study was 848 (5.3 %). Compared to Caucasian patients receiving NAC, AA patients had a greater proportion of females and had lower income and education. The rate of pT0 in the surgery only group was 2.7% compared to 15.0% ($p < 0.001$) for patients treated with NAC. On multivariate analysis, patients of AA race that received NAC were less likely to achieve pT0 (OR = 0.55, 95% CI: 0.31-0.98, $p = 0.04$) when controlling for age, sex, co-morbidities income, education and timing of cystectomy after starting NAC.*

Conclusions: *Our results suggest that African American patients are less likely to achieve pathologic complete response to NAC prior to cystectomy.*

Key Words: urothelial cancer, pathologic complete response, racial predictors, muscle-invasive, National Cancer Database

Introduction

Bladder cancer has the fifth highest incidence for malignancies diagnosed in the United States with an estimated 80,470 new cases in 2019. Bladder cancer is three times more likely in males and with regards to urologic malignancies, represents the second leading cause of death following prostate cancer with a predicted 17,760 deaths in 2019.[1] At the time of diagnosis, approximately 25% of patients present with tumors that are muscle invasive, which negatively affects clinical outcomes and overall survival.[2] The current guidelines that were published in 2017 for the treatment of muscle invasive bladder cancer recommends the use of cisplatin-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy.[3]

The benefit of neoadjuvant chemotherapy in improving the overall survival for patients with bladder cancer was demonstrated by the Southwest Oncology Group (SWOG)-8710 trial.[4,5] It has been established that achieving pathological complete response (pT0) prior to cystectomy is associated with improved overall and disease specific survival.[6,7] Likewise, achieving pT0 following the use of neoadjuvant chemotherapy is strongly associated with improved survival outcomes.[8]

Several studies have found that outcomes are poorer in African American patients with bladder cancer.[9-12]

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A Surveillance, Epidemiology, and End Results Program (SEER) study that examined outcomes for patients with bladder cancer found that all-cause mortality was higher for African American patients following radical cystectomy.[13] A National Cancer Database (NCDB) study found that African American race was an independent predictor of inferior overall survival when compared to Caucasian patients with bladder cancer.[14] Because of the disparities in outcomes of patients with bladder cancer, identifying patients that would respond better to neoadjuvant chemotherapy can further improve bladder cancer outcomes while avoiding overtreatment and decreasing the toxicities associated with chemotherapeutics.[15,16]

We hypothesize that race is associated with pT0 response to neoadjuvant chemotherapy. The primary objective of this study is to examine whether race is a predictor of complete pathologic response to neoadjuvant chemotherapy in the final specimen from cystectomy for patients that were treated for a non-metastatic muscle-invasive urothelial cell bladder cancer.

Materials and methods

Data source

The National Cancer Database (NCDB) is a hospital sourced cancer registry sponsored by the American College of Surgeons and the American Cancer Society that collects and shares data on patient demographics, disease, and outcomes of patients diagnosed and/or treated for cancer. Only treatment centers that are accredited by the Commission on Cancer can report to this database, representing about 30% of hospitals in the United States. In 2005, 64.3% of bladder cancer diagnoses in the United States were reported to the NCDB.[17] Data in this study contained de-identified information and was exempt by the University of Maryland School of Medicine institutional review board.

Patient selection

The NCDB was examined to identify patients with a non-metastatic (M0) muscle-invasive (cT2+) urothelial (ICD-O-3 8120 and 8130) cancer of the bladder (ICD-O-3 67.0-67.9) that were treated with a radical cystectomy. The patients were stratified by whether they received neoadjuvant chemotherapy prior to cystectomy. The Participant Use File 2014 for bladder cancer was utilized in this study, which examined patients diagnosed from 2006 to 2014. Patients for which the primary tumor could not be assessed pathologically (pTX) in the specimen obtained from cystectomy were excluded. Patients that were administered systemic therapy intraoperatively or radiation, hormonal or immunotherapy prior to cystectomy were excluded. Patients that only received a single agent of neoadjuvant chemotherapy were excluded. Patients that received systemic therapy after the cystectomy were not excluded.

Variables

Data regarding patient demographics, tumor characteristics, treatments and outcomes were obtained from the NCDB. Variables being studied include race (Caucasian non-Hispanic, African American, Hispanic, and Asian), age at diagnosis, sex, income, insurance, education, patient co-morbidities, clinical T/N stage and duration between when neoadjuvant chemotherapy was initiated and when the radical cystectomy was performed. The patient's level of income was estimated as the median household income for the patient's area of residence by zip code as reported in the 2012 American Community Survey results. The patient's level of education is measured as the percentage of adults within the patient's area of residence by zip code that did not complete high school as reported in the 2012 American Community Survey results. Patient comorbidities were reported as the Charlson/Deyo score. Cases for which certain variables were not recorded by the reporting facility were classified as unknown and not excluded from the study.

Outcome measures

The primary outcome of interest was pathologic response to neoadjuvant chemotherapy, defined as no evidence of primary tumor (pT0) in the final pathologic specimen obtained from cystectomy.

Statistical analyses

Pearson's chi squared test was used to examine for any associations between the variables of interest defined above and use of neoadjuvant chemotherapy. Logistic regression was used to determine odds ratios with 95% confidence intervals. Univariate and multivariate logistic regression analysis was performed to identify racial predictors of pathologic T0 response following neoadjuvant chemotherapy use. Similar analysis was performed in patients that did not receive NAC prior to cystectomy to assess for predictors specific to receipt of NAC. Variables that had a p value of less than 0.10 on univariate analysis were included in the multivariate model. Race, age, sex and co-morbidities were included in the multivariate analysis regardless of significance on univariate analysis. All p values

were reported as two-sided and p-values less than 0.05 were considered statistically significant. Analyses were performed with StataMP 15 (StataCorp, College Station, TX, USA).

Results

We initially identified 22,345 patients that met the inclusion criteria of having a non-metastatic muscle invasive urothelial bladder cancer that was treated with a radical cystectomy. From this patient group, 1,749 patients (7.83%) were excluded for unidentifiable pathologic staging (pTX), 1,574 patients (7.04%) were excluded for unknown number or single agent of chemotherapy, and 2,986 patients (13.36%) were excluded for being administered another form (radiation, hormonal, immunotherapy) of neoadjuvant therapy prior to cystectomy. Of the remaining study cohort of 16,036 patients, 3,195 patients (19.9%) were treated with neoadjuvant chemotherapy prior to cystectomy. The median age of diagnosis for the entire cohort was 69 years (IQR 25-75%, 61-76.) The median age of the group receiving neoadjuvant chemotherapy was 65 years (IQR 25-75%, 58-72) and 70 years (IQR 25-75%, 62-77) for the group that proceeded directly to cystectomy. From a longitudinal standpoint, the use of neoadjuvant chemotherapy increased from 7.5% in 2006 to 32.2% in 2014 ($p < 0.001$). The rate of pT0 in the entire study cohort improved over the study period starting with 2.0% in 2006 to 11.2% in 2014 ($p < 0.001$). For patients that received neoadjuvant chemotherapy, the rate of pT0 improved from 6.3% in 2006 to 21.2% in 2014 ($p < 0.001$).

Patient demographic and tumor characteristics were stratified by whether the patient received neoadjuvant chemotherapy or proceeded directly to cystectomy, Table 1. There was no difference in distribution of patient race ($p = 0.79$) between the two treatment groups. Of the co-variates being analyzed, there was no statistical difference in patient sex ($p = 0.17$) between the two groups. The group of patients that received neoadjuvant chemotherapy were more likely to be younger ($p < 0.001$), had greater income ($p < 0.001$), private insurance ($p < 0.001$), more education ($p < 0.001$), less co-morbidities ($p < 0.001$), higher clinical T ($p < 0.001$) and higher N stage ($p < 0.001$).

At the time of cystectomy, 823 (5.1% of all cystectomies) patients had a pathologic stage of T0, of which 478 (58.0%) of these patients had been treated with neoadjuvant chemotherapy. Patients that were not administered chemotherapy achieved a pathologic complete response rate of 2.7% compared to 15.0% ($p < 0.001$) for patients treated with chemotherapy. Univariate and multivariate analysis was performed on the cohort that received neoadjuvant chemotherapy to study the effect of race on predicting pathologic response, Table 2. On univariate analysis, African American race was associated with decreased odds of pT0 (OR = 0.48, 95% CI: 0.27-0.84, $p = 0.01$). Co-variates associated with decreased odds of pT0 on univariate analysis include cT3 (OR = 0.59, 95% CI: 0.44-0.80, $p = 0.001$), cT4 (OR = 0.46, 95% CI: 0.31-0.66, $p < 0.001$) and cN2 (OR = 0.46, 95% CI: 0.25-0.83, $p = 0.01$) staging. On univariate analysis, patients with more education were more likely to achieve pT0 (OR = 1.50, 95% CI: 1.06-2.13, $p = 0.02$). On multivariate analysis, African American race (OR = 0.55, 95% CI: 0.31-0.98, $p = 0.04$), cT3 (OR = 0.60, 95% CI: 0.44-0.81, $p = 0.001$) and cT4 (OR = 0.49, 95% CI: 0.33-0.71, $p < 0.001$) were associated with decreased odds of achieving pathologic complete response when controlling for age, sex, co-morbidities, income, education and timing of cystectomy after starting neoadjuvant chemotherapy. Likewise, univariate and multivariate analysis was performed on the group of patients that did not receive neoadjuvant chemotherapy to determine which predictors were specific to receipt of neoadjuvant chemotherapy, Table 3. On multivariate analysis, African American patients that proceeded directly to cystectomy were not associated with decreased odds of achieving pT0 (OR = 1.27, 95% CI: 0.79-2.01, $p = 0.32$). However, patients with a clinical stage T3 (OR = 0.41, 95% CI: 0.26-0.64, $p < 0.001$) or T4 (OR = 0.37, 95% CI: 0.21-0.65, $p = 0.001$) were associated with decreased odds of achieving pT0 when proceeding directly to cystectomy. There were no Asian patients that achieved pT0 when proceeding directly to cystectomy and hence could not be modeled using logistic regression.

The distribution of patient demographics and tumor characteristics among Caucasian and African American patients that received neoadjuvant chemotherapy was further examined for associations, Table 4. No statistically significant difference was found with respect to the two groups with regards to patient age ($p = 0.06$), insurance ($p = 0.48$), co-morbidities ($p = 0.96$), and timing of cystectomy after start of neoadjuvant therapy ($p = 0.06$). Furthermore, there was no difference between clinical T ($p = 0.07$) and N ($p = 0.26$) stage distribution between Caucasian non-Hispanic and African American patients. Compared to Caucasian patients, African American patients that received neoadjuvant chemotherapy had a greater share of females ($p < 0.001$), had lower income ($p < 0.001$) and lower education ($p < 0.001$).

TABLE 1. **Patient demographics and tumor characteristics of the study cohort, with further stratification by whether the patient received neoadjuvant chemotherapy to examine for association with its use**

Variable		All patients n (% of total) n = 3,195	NAC n (% within NAC) n = 12,841	No NAC n (%)	p value
Race	Caucasian non-Hispanic	14,357 (89.53%)	2,860 (89.51%)	11,497 (89.53%)	0.79
	African American	848 (5.29%A)	174 (5.45%)	674 (5.25%)	
	Hispanic	339 (2.11%)	67 (2.10%)	272 (2.12%)	
	Asian	262 (1.63%)	45 (1.41%)	217 (1.69%)	
	Other	230 (1.43%)	49 (1.53%)	181 (1.41%)	
Age (years)	< 60	3,316 (20.68%)	952 (29.80%)	2,364 (18.41%)	< 0.001
	60-64	2,215 (13.81%)	548 (17.15%)	1,667 (12.98%)	
	65-69	2,689 (16.77%)	616 (19.28%)	2,073 (16.14%)	
	70-74	2,974 (18.55%)	564 (17.65%)	2,410 (18.77%)	
	75+	4,842 (30.19%)	515 (16.12%)	4,327 (33.70%)	
Sex	Male	11,783 (73.48%)	2,418 (75.68%)	9,365 (75.03%)	0.17
	Female	3,983 (24.84%)	777 (24.32%)	3,206 (24.97%)	
Median income quartile (2012)	< $38,000	2,482 (15.48%)	436 (13.65%)	2,046 (15.93%)	< 0.001
	$38,000-$47,999	4,009 (25%)	719 (22.50%)	3,290 (24.62%)	
	$48,000-$62,999	4,462 (27.82%)	888 (27.79%)	3,574 (27.83%)	
	$63,000 +	4,850 (30.24%)	1,108 (34.68%)	3,742 (29.14%)	
	Unknown	233 (1.45%)	44 (1.38%)	189 (1.47%)	
Insurance	Private insurance	5,008 (31.23%)	1,274 (39.87%)	3,734 (29.08%)	< 0.001
	Medicaid	692 (4.32%)	172 (5.38%)	520 (4.13%)	
	Medicare	9,580 (59.74%)	1,571 (49.17%)	8,009 (62.37%)	
	Other government	156 (0.97%)	40 (1.25%)	116 (0.90%)	
	Not insured	415 (2.59%)	92 (2.88%)	323 (2.55%)	
	Unknown	175 (1.09%)	46 (1.44%)	129 (1.00%)	
Education (% did not graduate high school)	> 29%	2,263 (14.11%)	382 (11.96%)	1,881 (14.65%)	< 0.001
	20%-28.9%	4,109 (25.62%)	796 (24.91%)	3,313 (25.80%)	
	14%-19.9%	5,507 (34.34%)	1,107 (34.65%)	4,400 (34.27%)	
	< 14%	3,935 (24.54%)	868 (27.17%)	3,067 (23.88%)	
	Unknown	222 (1.38%)	42 (1.31%)	180 (1.40%)	
CDCC score	0	11,108 (69.27%)	2,385 (74.65%)	8,723 (67.93%)	< 0.001
	1	3,746 (23.36%)	648 (20.28%)	3,098 (24.13%)	
	2+	1,182 (7.37%)	162 (5.07%)	1,020 (7.94%)	
Clinical T stage	T2 (T2a, T2b)	12,396 (77.3%)	2,290 (71.67%)	10,106 (78.70%)	< 0.001
	T3 (T3a, T3b)	2,154 (13.43%)	519 (16.24%)	1,635 (12.73%)	
	T4 (T4a, T4b)	1,486 (9.27%)	386 (12.08%)	1,100 (8.57%)	
Clinical N stage	0	13,631 (85%)	2,661 (83.29%)	10,970 (85.43%)	< 0.001
	1	600 (3.74%)	191 (5.98%)	409 (3.19%)	
	2	525 (3.27%)	150 (4.69%)	375 (2.92%)	
	3	61 (0.38%)	21 (0.66%)	40 (0.31%)	
	Unknown	1,219 (7.60%)	172 (5.38%)	1,047 (8.15%)	
RC after NAC started (days)	< 60 days		247 (7.73%)	N/A	
	60-120 days		1,590 (49.77%)	N/A	
	120-240 days		1,300 (40.69%)	N/A	
	> 240 days		58 (1.82%)	N/A	

NAC = neoadjuvant chemotherapy; RC = radical cystectomy; CDCC = Charlson/Deyo Comorbidity Classification

TABLE 2. **Univariate and multivariate logistic regression analysis describing predictors of pathologic T0 to neoadjuvant chemotherapy**

Variable		Univariate		Multivariate	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Race	Caucasian non-Hispanic	1.00		1.00	
	African American	0.48 (0.27-0.84)	0.01	0.55 (0.31-0.98)	0.04
	Hispanic	0.64 (0.29-1.41)	0.27	0.78 (0.35-1.74)	0.55
	Asian	1.37 (0.66-2.87)	0.40	1.50 (0.70-3.18)	0.29
	Other	1.07 (0.50-2.30)	0.86	1.17 (0.53-2.55)	0.68
Age (years)	< 60	1.00		1.00	
	60-64	0.82 (0.61-1.10)	0.19	0.79 (0.59-1.07)	0.13
	65-69	0.87 (0.66-1.15)	0.33	0.84 (0.63-1.12)	0.25
	70-74	0.81 (0.60-1.08)	0.15	0.78 (0.58-1.05)	0.11
	75+	0.77 (0.56-1.04)	0.09	0.73 (0.53-1.00)	0.06
Sex	Male	1.00		1.00	
	Female	0.88 (0.70-1.11)	0.29	0.96 (0.76-1.22)	0.75
Median income quartile (2012)	< $38,000	1.00		1.00	
	$38,000-$47,999	1.39 (0.98-1.97)	0.07	1.19 (0.82-1.73)	0.35
	$48,000-$62,999	1.26 (0.90-1.78)	0.18	1.04 (0.71-1.54)	0.83
	$63,000 +	1.36 (0.98-1.90)	0.06	1.12 (0.74-1.69)	0.61
Insurance	Not insured	1.00		1.00	
	Private insurance	1.66 (0.85-3.26)	0.14		
	Medicaid	1.27 (0.57-2.79)	0.56		
	Medicar	1.34 (0.69-2.63)	0.39		
	Other government	0.91 (0.27-3.10)	0.88		
Education (% did not graduate high school)	> 29%	1.00		1.00	
	20%-28.9%	1.28 (0.88-1.85)	0.19	1.13 (0.77-1.68)	0.52
	14%-19.9%	1.50 (1.06-2.13)	0.02	1.31 (0.88-1.95)	0.19
	< 14%	1.33 (0.93-1.91)	0.12	1.14 (0.72-1.79)	0.58
CDCC score	0	1.00		1.00	
	1	0.95 (0.75-1.22)	0.71	0.98 (0.76-1.26)	0.88
	2+	0.74 (0.45-1.21)	0.22	0.74 (0.45-1.21)	0.23
Clinical T stage	T2 (T2a, T2b)	1.00		1.00	
	T3 (T3a, T3b)	0.59 (0.44-0.80)	0.001	0.60 (0.44-0.81)	0.001
	T4 (T4a, T4b)	0.46 (0.31-0.66)	< 0.001	0.49 (0.33-0.71)	< 0.001
Clinical N stage	0	1.00		1.00	
	1	0.86 (0.57-1.31)	0.49	0.99 (0.65-1.53)	0.98
	2	0.46 (0.25-0.83)	0.01	0.56 (0.30-1.03)	0.06
	3	0.87 (0.26-2.98)	0.83	0.97 (0.28-3.35)	0.96
RC after NAC started (days)	< 60 days	1.00		1.00	
	60-120 days	1.42 (0.95-2.14)	0.09	1.39 (0.92-2.11)	0.12
	120-240 days	1.30 (0.86-1.98)	0.21	1.28 (0.84-1.95)	0.26
	> 240 days	0.56 (0.19-1.65)	0.29	0.54 (0.18-1.63)	0.28

NAC = neoadjuvant chemotherapy
RC = radical cystectomy; CDCC = Charlson/Deyo Comorbidity Classification

TABLE 3. **Univariate and multivariate logistic regression analysis describing predictors of pathologic T0 for patients that proceeded to radical cystectomy without neoadjuvant treatment**

Variable	Univariate		Multivariate	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Race				
Caucasian non-Hispanic	1.00		1.00	
African American	1.15 (0.74-1.81)	0.53	1.27 (0.79-2.01)	0.32
Hispanic	0.67 (0.28-1.64)	0.39	0.70 (0.28-1.71)	0.43
Asian	0.00		0.00	
Other	1.66 (0.81-3.41)	0.17	1.61 (0.78-3.32)	0.19
Age (years)				
< 60	1.00		1.00	
60-64	1.05 (0.74-1.49)	0.78	1.08 (0.76-1.53)	0.67
65-69	0.89 (0.63-1.25)	0.49	0.92 (0.65-1.30)	0.64
70-74	0.81 (0.58-1.13)	0.22	0.85 (0.60-1.19)	0.34
75+	0.61 (0.45-0.83)	0.002	0.64 (0.47-0.87)	0.005
Sex				
Male	1.00		1.00	
Female	0.89 (0.69-1.15)	0.37	0.92 (0.71-1.19)	0.51
Median income quartile (2012)				
< $38,000	1.00		1.00	
$38,000-$47,999	0.95 (0.66-1.38)	0.79	0.99 (0.66-1.47)	0.95
$48,000-$62,999	1.32 (0.94-1.87)	0.11	1.29 (0.87-1.93)	0.21
$63,000 +	1.38 (0.98-1.95)	0.06	1.35 (0.87-2.10)	0.18
Insurance				
Not insured	1.00			
Private insurance	1.19 (0.60-2.36)	0.62		
Medicaid	0.74 (0.30-1.80)	0.51		
Medicare	0.88 (0.45-1.73)	0.71		
Other government	0.61 (0.13-2.88)	0.53		
Education (% did not graduate high school)				
> 29%	1.00		1.00	
20%-28.9%	0.80 (0.55-1.16)	0.24	0.75 (0.51-1.12)	0.16
14%-19.9%	1.31 (0.87-1.70)	0.25	1.05 (0.71-1.55)	0.83
< 14%	1.19 (0.84-1.70)	0.33	0.94 (0.60-1.48)	0.79
CDCC score				
0	1.00		1.00	
1	0.83 (0.64-1.08)	0.16	0.87 (0.66-1.13)	0.29
2+	0.71 (0.45-1.12)	0.14	0.74 (0.47-1.17)	0.20
Clinical T stage				
T2 (T2a, T2b)	1.00		1.00	
T3 (T3a, T3b)	0.41 (0.26-0.64)	< 0.001	0.41 (0.26-0.64)	< 0.001
T4 (T4a, T4b)	0.38 (0.22-0.66)	0.001	0.37 (0.21-0.65)	0.001
Clinical N stage				
0	1.00		1.00	
1	0.61 (0.29-1.29)	0.20	0.81 (0.28-1.75)	0.60
2	0.95 (0.50-1.81)	0.88	1.38 (0.71-2.67)	0.34
3	0.89 (0.12-6.52)	0.91	1.38 (0.19-10.25)	0.75

CDCC = Charlson/Deyo Comorbidity Classification

TABLE 4. **Distribution of patient and tumor characteristics for patients that received neoadjuvant chemotherapy, stratified by race (Caucasian non-Hispanic and African American)**

Variable		All patients n (% of total) n = 3,195	Caucasian n (%) n = 2,860	African American n (%) n = 174	p value
pT0	Yes	478 (14.96%)	345 (12.06%)	12 (6.90%)	0.04
	No	2,717 (85.04%)	2,515 (87.94%)	162 (93.10%)	
Age (years)	< 60	952 (29.80%)	833 (29.13%)	63 (36.21%)	0.06
	60-64	548 (17.15%)	496 (17.34%)	23 (13.22%)	
	65-69	616 (19.28%)	554 (19.37%)	36 (20.69%)	
	70-74	564 (17.65%)	495 (17.31%)	34 (19.54%)	
	75+	515 (16.12%)	482 (16.85%)	18 (10.34%)	
Sex	Male	2,418 (75.68%)	2,201 (76.96%)	92 (52.87%)	< 0.001
	Female	777 (24.32%)	659 (23.04%)	82 (47.13%)	
Median income quartile (2012)	< $38,000	436 (13.65%)	336 (11.75%)	78 (44.83%)	< 0.001
	$38,000-$47,999	719 (22.50%)	648 (22.66%)	43 (24.71%)	
	$48,000-$62,999	888 (27.79%)	815 (28.5%)	28 (16.09%)	
	$63,000 +	1,108 (34.68%)	1,020 (35.66%)	25 (14.37%)	
Insurance	Private insurance	1,274 (39.87%)	1,147 (40.1%)	69 (39.66%)	0.48
	Medicaid	172 (5.38%)	135 (4.72%)	13 (7.47%)	
	Medicare	1,571 (49.17%)	1,425 (49.83%)	83 (47.7%)	
	Other government	40 (1.25%)	36 (1.26%)	1 (0.57%)	
	Not insured	92 (2.88%)	80 (2.8%)	4 (2.3%)	
Education (% did not graduate high school)	> 29%	382 (11.96%)	286 (10.00%)	59 (33.91%)	< 0.001
	20%-28.9%	796 (24.91%)	696 (24.34%)	61 (35.06%)	
	14%-19.9%	1,107 (34.65%)	1,026 (35.87%)	31 (17.82%)	
	< 14%	868 (27.17%)	813 (28.43%)	23 (13.22%)	
CDCC score	0	2,385 (74.65%)	2,131 (74.51%)	130 (74.71%)	0.96
	1	648 (20.28%)	583 (20.38%)	36 (20.69%)	
	2+	162 (5.07%)	146 (5.10%)	8 (4.6%)	
Clinical T stage	T2 (T2a, T2b)	2,290 (71.67%)	2,079 (72.69%)	113 (64.94%)	0.07
	T3 (T3a, T3b)	519 (16.24%)	456 (15.94%)	33 (18.97%)	
	T4 (T4a, T4b)	386 (12.08%)	325 (11.36%)	28 (16.09%)	
Clinical N stage	0	2,661 (83.29%)	2,399 (83.88%)	137 (78.74%)	0.26
	1	191 (5.98%)	168 (5.87%)	10 (5.75%)	
	2	150 (4.69%)	125 (4.37%)	13 (7.47%)	
	3	21 (0.66%)	20 (0.70%)	1 (0.57%)	
RC after NAC started (days)	< 60 days	247 (7.73%)	221 (7.73%)	16 (9.2%)	0.06
	60-120 days	1,590 (49.77%)	1,447 (50.59%)	71 (40.8%)	
	120-240 days	1,300 (40.69%)	1,147 (40.1%)	82 (47.13%)	
	> 240 days	58 (1.82%)	45 (1.57%)	5 (2.87%)	

NAC = neoadjuvant chemotherapy; RC = radical cystectomy

Discussion

The benefit of neoadjuvant chemotherapy for the treatment of muscle-invasive bladder cancer was demonstrated by the SWOG trial 8710 which showed that patients treated with a combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) neoadjuvant chemotherapy and surgery had a median survival of 77 months as compared to the surgery only treatment group with a median of

46 months.[4] Improved survival outcomes in bladder cancer has been strongly associated with achieving pathological T0 at time of cystectomy following the use of neoadjuvant chemotherapy.[18] To date, only a few studies have looked at variables that influence tumor response to neoadjuvant chemotherapy. A single institution study by Pokuri et al looked at the response at the pathologic response of different histologies of bladder cancer to neoadjuvant chemotherapy.[19] Our retrospective study, using the large cohort analysis provided by the NCDB, examined whether patient race is associated with tumor response to neoadjuvant chemotherapy.

Based on univariate and multivariate logistic regression analysis, our study demonstrates that patients of African American race are less likely to achieve pT0 following the use of neoadjuvant chemotherapy when compared to Caucasian patients. We also found that higher clinical T stage was associated with decreased odds of achieving pT0 however this was a finding seen both in patients that were treated with neoadjuvant chemotherapy as well as patients that proceeded directly to cystectomy. The findings from this study are consistent with observations seen in other cancers which show that African American patients treated with neoadjuvant chemotherapy are less likely to reach a specified clinical endpoint when compared to Caucasian patients.[20] Given that pT0 status at time of cystectomy is a surrogate for improved survival outcomes, the findings from our study are consistent with studies that have demonstrated negative survival outcomes for African American patients with bladder cancer.[10,11,14]

The explanation as to why African American patients have negative outcomes with bladder cancer is likely multifactorial, with the proposed theories including a more aggressive disease at time of diagnosis, lower socioeconomic status and increased barriers to healthcare access, and a difference in exposures and risk factors that predispose to bladder cancer.[21] In our study, we looked specifically at the preoperative clinical T stage and N stage as a marker of disease aggressiveness at time of diagnosis. On multivariable analysis, we found that both African American race and preoperative clinical T stage were associated with decreased likelihood of achieving pT0. However when examining for differences in patient variables between African American and Caucasian patients that received neoadjuvant chemotherapy, we found no statistically significant difference in preoperative clinical T and N stage between the two cohorts. Alternatively, the presence of molecular subtypes of bladder cancer has been elucidated by a recent study which found differences in response to neoadjuvant chemotherapy and overall survival between the different molecular subtypes.[22,23] It is possible that there is a heterogeneous distribution of the molecular subtypes among patients of different races with African American patients more likely to have a molecular subtype that is less responsive to neoadjuvant chemotherapy, which may explain why African American patients had decreased odds of pT0 when treated with neoadjuvant chemotherapy but not cystectomy when compared to Caucasian patients. We also examined socioeconomic factors in the form of income quartile, insurance status and education but found that these co-variates were not associated with pathologic response after neoadjuvant chemotherapy. These findings suggest that African American race as compared to socioeconomic status is associated with lower odds of achieving pathologic complete response after neoadjuvant chemotherapy. Exposure to known risk factors to bladder cancer, such as smoking history is not information we have access through the NCDB. Lastly, it is possible for African American patients to have decreased completion of a chemotherapy regimen for a variety of reasons, but studies examining completion of treatment regimens by race in other cancer types have not had consistent results regarding this topic.[24]

Limitations

The NCDB compiles its data through submissions from centers accredited by the CoC in order to ensure strict reporting guidelines and hence, only cases that meet the standard of treatment of CoC accredited facilities were included in this study. An important set of details that are not included in the NCDB is the type and duration of the chemotherapy regimen that was administered to patients. Additionally, factors such as performance status and renal function which heavily influence whether a patient is administered neoadjuvant chemotherapy is not included in the NCDB. Further limitations of the study include the retrospective observational study design and a relatively small population of 174 African American patients treated with neoadjuvant chemotherapy when compared to the 2,860 Caucasian non-Hispanic patients treated.

Conclusions

Our data suggest that there is a significant difference in likelihood of achieving pT0 following the use of neoadjuvant chemotherapy for patients of African American race compared to patients of Caucasian

race. Despite limitations, we believe that our data provide insight into the racial differences in response to neoadjuvant chemotherapy for patients with bladder cancer. Further studies are warranted to identify why African American patients respond poorly to the current neoadjuvant chemotherapy regimen.

Disclaimer

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. □

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