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Research Article

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Social Determinants of Appropriate Treatment for Muscle-Invasive Bladder Cancer

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Abstract

Background: Racial disparities in guideline-based, appropriate treatment (ApT) may be a significant driving force for differences in survival for people with nonmetastatic muscle-invasive bladder cancer (MIBC). We hypothesize that receipt of ApT is influenced by factors such as race and socioeconomic status, irrespective of neighborhood-level differences in healthcare, variations in practice patterns, and clinical characteristics of patients with nonmetastatic MIBC.

Methods: Within the National Cancer Database, we identified individuals diagnosed with MIBC between 2004 and 2013. Multivariable logistic regression and mixed effects modelling was used to examine predictors of ApT, clustered within institutions.

Results: A total of 51,350 individuals had clinically staged nonmetastatic, lymph node–negative MIBC. Black individuals comprised 6.4% of the cohort. Mean age was 72.6 years (SD 11.6) with a male predominance (71.4%). Less than half received ApT (42.6%). Fewer black individuals received ApT compared with white individuals (37% vs. 43%, $P < 0.001$). When clustered by institution, the odds of ApT were 21% lower for black individuals [odds ratio (OR), 0.79; 95% confidence interval (CI), 0.73–0.87] compared with white individuals with nonmetastatic MIBC. When restricted to higher volume centers with more diverse populations, black individuals had 25% lower odds of ApT (OR, 0.75; 95% CI, 0.61–0.91; $P < 0.01$), compared with white counterparts.

Conclusions: Racial disparities in treatment persisted after accounting for various clinical factors and social determinants of health. Future efforts should focus on addressing racial bias to improve disparities in bladder cancer treatment.

Impact: If we are not delivering evidence-based care due to these biases (after accounting for access and biology), then it is expected that patients will experience inferior outcomes.

Introduction

In 2018, there will be an estimated 81,190 new cases of malignancy of the urinary bladder with one-third of patients presenting with localized disease and one-fifth dying from bladder cancer (1). Nearly half (48%) of black patients are diagnosed with localized or regional disease with a lower 5-year survival rate of 64% compared with 77% for all races. Racial differences in stage at diagnosis, treatments utilized, and delays in treatment may be contributing to observed racial disparities in bladder cancer outcomes (2).

Guidelines from the American Urological Association (3) and the European Association of Urology (4) serve to propose what is considered best practice or appropriate treatment (ApT) for individuals with nonmetastatic muscle-invasive bladder cancer (MIBC). For muscle-invasive disease, radical cystectomy (RC) with or without neoadjuvant chemotherapy remains the gold standard while trimodal therapy remains an option for patients who wish to preserve the bladder or are unfit for cystectomy. These guidelines serve to standardize appropriate treatment to optimize outcomes such as cancer-specific survival. Nonclinical factors such as race, and socioeconomic status (SES), and access to care continue to hinder delivery of ApT, although the extent of their impact is not completely understood.

Using the bladder cancer dataset of the National Cancer Database (NCDB), a nationwide, facility-based, comprehensive clinical surveillance resource oncology dataset that currently captures 70% of all newly diagnosed malignancies in the United States annually from more than 1,500 Commission-on-Cancer accredited centers (5), we use a contextual approach to evaluate the influence of race on receipt of ApT for patients with nonmetastatic MIBC. We hypothesize that rates of ApT are influenced by factors such as race and SES, irrespective of neighborhood-level differences in healthcare, variations in practice patterns, and clinical characteristics of patients with nonmetastatic MIBC.

Materials and Methods

Within NCDB, we identified 362,091 individuals diagnosed with bladder cancer between January 1, 2004 and December 31, 2013. The NCDB, established in 1989, is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer accredited hospitals. Deidentified data on cancer staging and outcomes are included within the dataset. Those with non–muscle-invasive bladder cancer, clinical evidence of metastasis, and/or nodal

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disease on clinical staging were excluded. The final cohort was comprised of 51,350 individuals diagnosed with nonmetastatic MIBC (cT2-3Nx/oMx/o) disease. This project received exempt status from the institutional review board as this study involves the study of existing deidentified data that is publicly available.

Definitions

The reported histologic type was attributed to the most invasive surgical procedure the patient underwent during the study interval. Histology was classified urothelial carcinoma or variant. Race was defined as white, black, or other based upon self-report during initial recruitment for NCDB. Charlson comorbidity index (CCI) was used as a measure of overall health based on scores of zero, one, or two or greater. Education was defined as the percentage of people within the specific zip code that were without a high school diploma using the following categories: greater than 21%, 13%–20.9%, 7%–12.9%, and less than 7%. Household income was reported as a categorical variable corresponding to the percentage of people within the specific zip code in each pre-specific income range: less than $38,000, $38,000–47,999, $48,000–62,999, or greater than $63,000. Data for neighborhood-level factors such as education and household income were obtained at time of diagnosis. City type (metropolitan, urban, rural) was defined by county population sizes according to the patient's residence. Institution type such as Community Cancer Program, Academic/Research Program, Comprehensive Community Cancer Program was defined by the Cancer Accreditation program. Treatment was considered appropriate (ApT) if the patient underwent one of the following modalities: RC, neoadjuvant chemotherapy with RC, RC with adjuvant chemotherapy, and/or chemoradiation.

Summary statistics and univariate analyses

Descriptive statistics of the study cohort were generated to report demographic, clinical, and pathologic characteristics of the cohort. Means and SDs were used for parametric continuous variables. Median and interquartile ranges were used for nonparametric continuous variables. Frequency tables were used for categorical variables. Violin plots were created to visualize the distributions of reported case volume and reported proportion of black patients within patient population, stratified by institution type.

Univariate analyses by race were used to identify differences in clinical and pathologic data. ANOVA analysis was used to compare means of continuous variables with a normal distribution. Kruskal–Wallis test was used to compare continuous variables that are not normally distributed. χ^2 test was used compare categorical variables. Statistical significance level was set at 0.05.

Regression models

Multivariable logistic regression modelling was used to identify factors associated with increased odds of ApT. Clinically relevant and demographic individual-level variables such as age, clinical T stage, histology, gender, interval from diagnosis to treatment, and insurance status were included. Variables characterizing the social environment, reported within NCDB as covariates clustered by zip code, included the "great circle" distance to nearest hospital, education level, average household income, and institution type (community, academic, etc.). Variables significant on univariable analyses were included in the models. The regression models adjusted for individual-level and zip code–level covariates. The potential interaction between race and type of hospital was explored with inclusion of the interaction term in the initial logistic regression model. Given the concern bladder cancer risk is not uniform across races and genders, sensitivity analyses including factorial interaction terms were generated for potential race-gender, and race-comorbidity interactions. These were then tested in the regression models and found not to be statistically significant. These terms were thus excluded from the final regression models.

Additional sensitivity analyses were performed to examine the impact of the interaction between insurance and race on ApT by stratifying individuals into three insurance subgroups: uninsured/unknown, private, or government-funded. Multivariable logistic regression analyses adjusting for the same clinically relevant and demographic variables used in the main regression models were then performed within each subgroup.

A mixed effects logistic regression model was used to assess within-institution variance in rates of ApT. Within NCDB, each institution is identified by a unique identification number. This institution identification number was used to cluster patients by where they received treatment. The institution was used as the random effect to adjust for variation in practice patterns, resource availability, and other differences between facilities that were not discretely measured. This approach allowed us to account for unmeasured health-related factors within neighborhoods, which may influence regional/geographic differences in care. Subset analyses were conducted by restricting the analysis to facilities that reported more than 10 bladder cancer cases and whose patient cohorts contained more than 10 black patients to examine how the observed associations may differ in higher volume centers with reporting more diverse patient populations.

Results were interpreted for both clinical and statistical significance. Odds ratios (OR) were presented with 95% confidence intervals (CI) and *P* values. Statistical significance level was set at 0.05. Statistical analyses were performed using STATA 14.2 (StataCorp).

Results

The study cohort was comprised of 51,350 individuals with clinically staged nonmetastatic, lymph node negative MIBC, representing patients treated at 1,268 unique facilities. The mean age was 72.6 years (SD 11.6) with a male predominance (71.4%). The majority of patients were healthy (CCI of zero, 68.6%) with fairly even distributions in terms of neighborhood-level household income and education levels. Table 1 shows demographic and clinical characteristics for the overall cohort and cohort stratified by race. The majority used Medicare as their primary insurance provider (67.6%) and lived in metropolitan counties (79.3%). Most were seen at either comprehensive community centers (46.1%) or academic facilities (34.9%; Supplementary Fig. S1A). ApT was more frequently reported at academic facilities (45.3%) followed by comprehensive community centers (39.7%). ApT was reported in less than 10% of cases in community cancer centers (8.64%), integrated network centers (6.1%), and other facilities (0.25%, $P < 0.001$). Overall, less than half of patients received ApT (42.6%). Supplementary Table S1 shows the treatments received by patients for the entire cohort and stratified by race.

Overall, black individuals comprised 6.4% of the cohort. Females comprised a higher percentage of black patients (43.7%) than white patients (27.5%, $P < 0.001$). Black individuals

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Table 1. Demographic, neighborhood, and clinical characteristics of the cohort and stratified by race continued

Characteristic, *n* (%)	Entire cohort *n* = 51,350	White *n* = 46,573	Black *n* = 3,261	Other *n* = 1,516	*P*
Age, years (mean, SD)	72.6 (11.6)	72.9 (11.5)	70.1 (12.5)	71.3 (12.1)	<0.001
Gender					
Male	36,679 (71.4)	33,754 (72.5)	1,836 (56.3)	1,089 (71.8)	<0.001
Female	14,671 (28.6)	12,819 (27.5)	1,425 (43.7)	427 (28.2)	
Charlson comorbidity index					
0	35,225 (68.6)	31,941 (68.6)	2,165 (66.4)	1,119 (73.8)	<0.001
1	11,739 (22.9)	10,677 (22.9)	759 (23.3)	303 (20)	
2+	4,386 (8.5)	3,955 (8.5)	337 (10.3)	94 (6.2)	
Annual household income[a]					
<$38,000	9,379 (18.3)	7,702 (16.5)	1,486 (45.6)	191 (12.6)	<0.001
$38,000–47,999	12,683 (24.7)	11,636 (25)	746 (22.9)	301 (19.9)	
$48,000–62,999	13,816 (26.9)	12,819 (27.5)	575 (17.6)	422 (27.8)	
≥$63,000	15,472 (30.1)	14,416 (31)	454 (13.9)	602 (39.7)	
% Without HS education[a]					
>21%	8,634 (16.8)	7,127 (15.3)	1,216 (37.3)	291 (19.2)	<0.001
13%–20.9%	13,169 (25.7)	11,652 (25)	1,174 (36)	343 (22.6)	
7%–12.9%	17,570 (34.2)	16,492 (35.4)	588 (18)	490 (32.3)	
<7%	11,977 (23.3)	11,302 (24.3)	283 (8.7)	392 (25.9)	
Insurance status					
Not insured	1,139 (2.2)	943 (2)	145 (4.5)	51 (3.4)	<0.001
Private insurance	12,568 (24.5)	11,424 (24.5)	750 (23)	394 (26)	
Medicaid	1,681 (3.3)	1,285 (2.8)	262 (8)	134 (8.8)	
Medicare	34,733 (67.6)	31,863 (68.4)	1,996 (61.2)	874 (57.7)	
Other government	465 (0.9)	408 (0.9)	37 (1.1)	20 (1.3)	
Unknown/not reported	764 (1.5)	650 (1.4)	71 (2.2)	43 (2.8)	
Miles to hospital, median (IQR)	9.5 (4.1–25.2)	10 (4.2–26.1)	5.7 (2.8–13.2)	8.7 (3.8–24.2)	<0.001
<10 miles	25,752 (50.2)	22,753 (48.9)	2,194 (67.28)	805 (53.1)	<0.001
10–50 miles	18,085 (35.2)	16,814 (36.1)	781 (24)	490 (32.2)	
>50 miles	7,513 (14.6)	7,006 (15)	286 (8.8)	221 (14.6)	
Year of diagnosis, median (IQR)	2009 (2006–2011)	2009 (2006–2011)	2009 (2006–2011)	2009 (2007–2011)	0.6
City type					
Metropolitan	40,729 (79.3)	36,559 (78.5)	2,875 (88.2)	1,295 (85.4)	<0.001
Urban	7,587 (14.8)	7,713 (15.4)	262 (8)	152 (10)	
Rural	3,034 (5.9)	2,841 (6.1)	124 (3.8)	69 (4.6)	
Hospital type					
Community	6,308 (12.3)	5,772 (12.4)	376 (11.6)	160 (10.7)	<0.001
Comprehensive community	23,573 (46.1)	21,913 (47.2)	1,185 (36.7)	475 (31.8)	
Academic	17,834 (34.9)	15,675 (33.8)	1,424 (44.1)	735 (49.1)	
Integrated cancer network	3,319 (6.5)	2,948 (6.4)	245 (7.6)	126 (8.4)	
Other	83 (0.2)	81 (0.2)	2 (0.1)	0 (0)	
Histology present					
Urothelial CA	46,003 (89.6)	41,884 (89.9)	2,809 (86.1)	1,350 (89.1)	<0.001
Variant	5,347 (10.4)	4,729 (10.2)	452 (13.9)	166 (11)	
Mean days from diagnosis to ApT	11.3 (25.5)	10.2 (30.4)	11.2 (28.2)	11.3 (25.5)	0.03
Appropriate treatment received					
Yes	21,867 (42.6)	20,010 (43)	1,205 (37)	652 (43)	<0.001

NOTE: Year of diagnosis not shown.
Abbreviations: CA, carcinoma; HS, high school.
[a]Variables based on neighborhood-level measures.

were generally poorer than white individuals, lived in areas with a household income less than $38,000 per year (45.6% vs. 16.5%, $P < 0.001$) and lower proportions of individuals with a high school education (37.3% for black vs. 15.3%, $P < 0.001$). Medicare was the most common insurance provider across all race groups. Black individuals lived closer to their healthcare institution (5.7 miles vs. 10 miles, $P < 0.001$) and were more often treated at academic facilities (44% vs. 33.8%, $P < 0.001$) compared with white individuals (Supplementary Fig. S1B). A smaller proportion of black individuals received ApT compared with their counterparts (37% vs. 43%, $P < 0.001$).

Using a multivariable logistic regression model, socioeconomic factors such as increasing neighborhood-level household income, education level, and good health (CCI 1 or less) were associated with increased odds of ApT (Table 2). Medicare was associated with greatest odds of ApT (OR 1.54; 95% CI, 1.34–1.76; $P < 0.001$) followed by private insurance (OR 1.27; 95% CI, 1.11–1.45; $P = <0.001$) compared with being uninsured. Academic institutions were associated with the highest odds of ApT (OR 2.56; 95% CI, 2.39–2.73; $P < 0.001$), followed by Integrated Cancer Networks (OR 1.55; 95% CI, 1.41–1.70; $P = <0.001$) compared with community hospitals. Women had 12% lower odds of ApT compared with men (OR 0.88; 95% CI, 0.84–0.96; $P < 0.001$). Higher CCI was associated with lower odds of ApT (CCI 2+, OR 0.90; 95% CI, 0.84–0.96; $P = 0.03$) compared with a CCI score of zero. Black individuals had 28% lower odds of ApT (OR 0.72; 95% CI, 0.67–0.79; $P < 0.001$) compared with white individuals. In a subset analysis of higher volume centers with more diverse patient populations, black race was associated with further reduced odds of ApT (OR 0.63; 95% CI, 0.52–0.76; $P < 0.001$)

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Table 2. Predictors of ApT using multivariable logistic regression and predictors of ApT within each facility using mixed effects logistic regression model

	Logistic regression		Mixed effects logistic regression	
Characteristic, *n* (%)	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age, years (per 10-year increase)	0.67 (0.65–0.68)	<0.001	0.69 (0.68–0.71)	<0.001
Gender				
Male (ref)	—	—	—	—
Female	0.88 (0.84–0.96)	<0.001	0.87 (0.84–0.91)	<0.001
Charlson comorbidity index				
0 (ref)	—	—	—	—
1	1.10 (1.06–1.16)	<0.001	1.11 (1.06–1.16)	<0.001
2+	0.90 (0.84–0.96)	0.03	0.90 (0.84–0.97)	0.004
Annual household income[a]				
<$38,000 (ref)	—	—	—	—
$38,000–47,999	1.10 (1.03–1.17)	0.004	1.09 (1.01–1.16)	0.02
$48,000–62,999	1.09 (1.02–1.16)	0.02	1.11 (1.03–1.20)	0.005
≥$63,000	0.97 (0.90–1.05)	0.41	1.05 (0.96–1.15)	0.3
% Without HS education[a]				
>21% (ref)	—	—	—	—
13%–20.9%	1.05 (0.99–1.12)	0.12	1.01 (0.94–1.09)	0.7
7%–12.9%	1.09 (1.02–1.17)	0.01	1.02 (0.94–1.10)	0.7
<7%	1.17 (1.08–1.27)	<0.001	1.04 (0.95–1.14)	0.4
Race				
White (ref)	—	—	—	—
Black	0.72 (0.67–0.79)	<0.001	0.79 (0.73–0.87)	<0.001
Other	0.91 (0.81–1.02)	0.11	0.92 (0.81–1.04)	0.2
Insurance status				
Not insured (ref)	—	—	—	—
Private insurance	1.27 (1.11–1.45)	<0.001	1.15 (1.00–1.32)	0.04
Medicaid	1.05 (0.89–1.24)	0.54	1.04 (0.88–1.24)	0.6
Medicare	1.54 (1.34–1.76)	<0.001	1.37 (1.19–1.58)	<0.001
Other government	1.26 (1.00–1.59)	0.05	1.14 (0.89–1.46)	0.3
Unknown/not reported	1.02 (0.83–1.26)	0.83	0.96 (0.77–1.20)	0.7
Distance to hospital (per mile increase)	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	0.05
Days from diagnosis to ApT	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	0.02
City type				
Metropolitan (ref)	—	—	—	—
Urban	1.13 (1.07–1.20)	<0.001	1.08 (1.01–1.15)	0.03
Rural	1.13 (1.03–1.25)	0.01	1.08 (0.97–1.21)	0.2
Hospital type				
Community (ref)	—	—	—	—
Comprehensive community	1.36 (1.27–1.45)	<0.001	—	—
Academic	2.56 (2.39–2.73)	<0.001	—	—
Integrated cancer network	1.55 (1.41–1.70)	<0.001	—	—
Other	3.64 (2.28–5.81)	<0.001	—	—
Histology				
Urothelial CA (ref)	—	—	—	—
Variant	0.93 (0.88–0.99)	0.04	0.93 (0.88–0.99)	0.04

NOTE: Adjusted for year of diagnosis.
Abbreviations: CA, carcinoma; HS, high school.
[a]Variables based on neighborhood-level measures.

compared with white individuals after adjusting for clinical, demographic, pathologic, and social environment factors. Of individuals uninsured or with unknown insurance status, race was not significantly associated with receipt of ApT ($P = 0.5$). Black individuals with private insurance had 27% lower odds of ApT compared with white individuals (OR 0.73; 95% CI, 0.62–0.87; $P < 0.001$). Black individuals with government-funded insurance such as Medicaid or Medicare had 32% lower odds of ApT compared with white counterparts (OR 0.68; 95% CI, 0.62–0.76; $P < 0.001$).

Using a mixed effects logistic regression model (Table 2), we examined predictors of ApT when clustered by institution. Age (per decade increase, OR 0.69; 95% CI, 0.68–0.71; $P < 0.001$) and CCI score maintained their associations with ApT (CCI 2+ OR 0.90, 95% CI, 0.84–0.97, $P = 0.004$; CCI 1, OR 1.11 95% CI, 1.06–1.16, $P < 0.001$). Neighborhood-level, education level ($P > 0.5$ for all strata), and rural city type ($P = 0.2$) were no longer associated with ApT. Female gender (OR 0.87; 95% CI, 0.84–0.91; $P < 0.001$) remained associated with decreased odds of ApT compared with male gender (Table 2). When clustered by institution, the odds of ApT were 21% lower for black individuals (OR 0.79; 95% CI, 0.73–0.87; $P < 0.001$) compared with white counterparts. In a subset analysis of higher volume centers with more diverse patient populations, odds of ApT were 25% lower for black individuals (OR 0.75; 95% CI, 0.61–0.91; $P < 0.01$) compared with white counterparts after adjusting for clinical, demographic, pathologic, and social environment factors.

Discussion

Our study shows less than half (42.6%) of individuals received ApT, with the lowest percentage (37%) in black individuals. Black

race was associated with decreased odds of ApT at the national and when clustered by institution, after adjusting clinical characteristics, and neighborhood-level variables, and within-institution variations in practice. Black patients had 21% lower odds of ApT compared with their white counterparts with the same disease characteristics treated in the same institution. And this disparity is widened further to 25% when the analysis is restricted to higher volume institutions and 32% when restricted to individuals with government-funding insurance such as Medicaid or MediCare. Our findings suggest the presence of implicit bias may influence who receives standard, established treatment despite adequate access to care.

Previous studies have demonstrated how racial bias impacts medical treatment, irrespective of clinical indications (6–8). Additional factors within a patient's social environment, such as the type of hospital providing care (9), provider density (10) and the travel burden to the nearest hospital have also been shown to dictate care more than race or biological factors (11). Our study showed that factors such as private or government-funded insurance were associated with increased odds of ApT. Yet even among those with private insurance or government-funded insurance, black patients remained at decreased odds of ApT compared with white counterparts. Interestingly, it was only among the uninsured that race was not significantly associated with ApT. Perhaps, the interaction of race with these social determinants of health drives outcomes more than race alone. Specifically, in patients with MIBC, studies of regional cohorts have reported that black individuals underwent RC less frequently, and received lower quality of care when RC was performed (low-yield lymph node dissection, low-volume hospital, no continent diversion, etc.) implicating race as a significant driver of disparity (12–15). Numerous studies have acknowledged the relationship between socioeconomic factors and outcomes (16, 17), although these commonly limit the quantification of SES to individual-level characteristics such as education and insurance. Corcoran and colleagues looked at institution-level characteristics and reported the impact of hospital type on quality measures (such as receipt of neoadjuvant chemotherapy, time to treatment, and lymph node yield) for 23,279 patients with muscle-invasive urothelial carcinoma (9). They noted that receiving treatment at an academic hospital was associated with the greatest odds of meeting these quality measures. Relying solely on patient-level factors such as education and insurance or only institution-specific factors may underestimate and obscure the true effect of an individual's combined social environment (18, 19). When accounting for as many social determinants of health as possible, our findings support race as a significant driver of treatment disparities in a nationwide, contemporary cohort, inclusive of all guideline-based treatments for patients with MIBC.

Weiner and colleagues also looked at racial disparities in outcomes for patients with stage III–IV bladder cancer, noting that black patients were more likely to present with later stage disease (OR 1.51; 95% CI, 1.44–1.59; $P < 0.001$) and experience delays in treatment (18.4% vs. 12.7%, $P < 0.001$) compared with white patients. Black patients were less likely to undergo cystectomy compared with white patients (18.3% vs. 26.9%, $P < 0.001$) and worse 3-year survival rates (16.2% vs. 21.5%, $P < 0.001$). The authors postulate that while lower SES portends more advanced stage disease as well as poorer outcomes, this may not completely explain the observed racial disparities (2), reaching a conclusion concordant with ours. Similar observations have been described across almost every discipline in medicine. Recently, Friedlander and colleagues used NCDB to demonstrate significant racial differences in institution-level rates of definitive treatment for prostate cancer, suggesting that these differences contribute to mortality differences observed between white and black men (20). In 1999, Shulman and colleagues conducted a survey-based study of physicians using simulated patients with chest pain to evaluate predictors of receiving treatment (7). Black race was associated with 40% lower odds of a physicians' recommendation for cardiac catheterization ($P = 0.02$), irrespective of clinical characteristics. Two studies, nearly twenty years later, continued to examine the impact of physician bias in treatment disparities (6, 21). Hoffman and colleagues showed that half (50%) of medical students and residents harbored false beliefs of race-based biological differences between white and black patients in a survey-based study of pain perception and management. The authors noted that those who harbored these false beliefs both rated black patients as feeling less pain and exhibited lower accuracy in recommendations for pain management. A separate retrospective study of patients with acute myelogenous leukemia in the California Cancer Registry demonstrated that black patients had 26% lower odds of receiving treatment ($P = 0.004$) and 38% lower odds receiving stem cell transplantation ($P = 0.005$) compared with white patients in adjusted logistic regression models. The authors further report an increased risk of overall mortality (HR 1.14; 95% CI, 1.04–1.25; $P = 0.004$), which is reduced to baseline when adjusted for receipt of treatment (HR 1.09; 95% CI, 0.85–0.98; $P = 0.05$).

In our cohort, we identify significant racial disparity in receipt of guidelines-based treatment for patients with MIBC after adjusting for demographic, clinical, pathologic, and social environment–related factors. As observed in various diseases, this disparity may confer a disproportionate increase in mortality risk. In this era of improving cancer outcomes and providing value-based care, addressing implicit bias may provide an opportunity to improve outcomes for patients with bladder cancer. Yet we must acknowledge that racial bias is one of various factors that influence if and when care is delivered. A significant history of disenfranchisement leading to social and economic inequality, deep-rooted distrust in the medical system, patient understanding and preferences, lack of social support, a poor provider–patient relationship, and various cultural beliefs may further exacerbate these disparities by dissuading black individuals from seeking and accepting appropriate therapies. Without confronting these issues, the medical community loses the opportunity to better educate both patients and providers while fostering more trusting relationships between communities and health care systems to deliver high-quality, guidelines-based care to patients with bladder cancer. Merely improving access by mechanisms such as the Affordable Care Act does not address underlying, and likely more important, disparities in care. If we are not delivering evidence-based care due to biases (after accounting for access and biology), then it is expected that patients will experience inferior outcomes. Acknowledgement of this bias is critical and future efforts must face this reality head on, starting with physicians. Efforts to address implicit and explicit bias within medical practitioners should be expanded, along with efforts to increase culture competence, education, and diversity within our discipline.

Our study does have limitations, which should be considered. The lower rates of ApT could be affected by several factors, which were unmeasured in our study such as provider knowledge of the

most current guidelines, barriers to care, marital status, lack of social support, poor patient understanding or patient–provider relationships, or patient preferences. Some variation in the rates of specific treatment modalities can be attributed to the individualized risk assessment for complications, which may lead some providers to recommend treatments incongruent with guidelines, although each of these are taken into account in our composite outcome measure. As a population-level study, we have limited granularity in our observations. Yet the strengths of this study are important. This provides a population-level assessment of adherence to guidelines-based treatment for our cohort. Our analysis takes into account differences in physician preferences in treatment modalities by using a broad definition of ApT and adjusting for histologic type. Using a hierarchical approach, we are able to take into account provider-level differences within each hospital and adjust for community-level SES factors. We restricted our study to patients seen and diagnosed with MIBC, thereby limiting the impact of potential bias due to patient mistrust with doctors and treatment variation due to cancer stage. With further investigation, we can adjust this paradigm and reduce health disparities in outcomes for patients with bladder cancer.

Conclusion

Our findings show that black patients with nonmetastatic MIBC are less likely to receive appropriate, guideline-based treatment than white patients despite adjustment for various clinical factors and social determinants of health. Future efforts should focus on addressing bias to reduce disparities in bladder cancer outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
2. Weiner AB, Keeter MK, Manjunath A, Meeks JJ. Discrepancies in staging, treatment, and delays to treatment may explain disparities in bladder cancer outcomes: an update from the National Cancer Data Base (2004–2013). Urol Oncol 2018;36:237.
3. Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, et al. Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO Guideline. J Urol 2017;198:552–9.
4. Witjes JA, Lebret T, Compérat EM, Cowan NC, De Santis M, Bruins HM, et al. Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. Eur Urol 2017;71:462–75.
5. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol 2008;15:683–90.
6. Hoffman KM, Trawalter S, Axt JR, Oliver MN. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. Proc Natl Acad Sci U S A 2016;113:4296–301.
7. Schulman KA, Berlin JA, Harless W, Kerner JF, Sistrunk S, Gersh BJ, et al. The effect of race and sex on physicians' recommendations for cardiac catheterization. N Engl J Med 1999;340:618–26.
8. Kinlock BL, Thorpe RJ Jr, Howard DL, Bowie JV, Ross LE, Fakunle DO, et al. Racial disparity in time between first diagnosis and initial treatment of prostate cancer. Cancer Control 2016;23:47–51.
9. Corcoran AT, Handorf E, Canter D, Tomaszewski JJ, Bekelman JE, Kim SP, et al. Variation in performance of candidate surgical quality measures for muscleinvasive bladder cancer by hospital type. BJU Int 2015;115:230–7.
10. Yao N, Foltz SM, Odisho AY, Wheeler DC. Geographic analysis of urologist density and prostate cancer mortality in the United States. PLoS One 2015;10:e0131578–11.
11. Lin CC, Bruinooge SS, Kirkwood MK, Olsen C, Jemal A, Bajorin D, et al. Association between geographic access to cancer care, insurance, and receipt of chemotherapy: geographic distribution of oncologists and travel distance. J Clin Oncol 2015;33:3177–85.
12. Konety BR, Allareddy V, Carroll PR. Factors affecting outcomes after radical cystectomy in African Americans. Cancer 2007;109:542–8.
13. Fedeli U, Fedewa SA, Ward EM. Treatment of muscle invasive bladder cancer: evidence from the National Cancer Database, 2003 to 2007. J Urol 2011;185:72–8.
14. Prout GR, Wesley MN, McCarron PG, Chen VW, Greenberg RS, Mayberry RM, et al. Survival experience of black patients and white patients with bladder carcinoma. Cancer 2004;100:621–30.
15. Barocas DA, Alvarez J, Koyama T, Anderson CB, Gray DT, Fowke JH, et al. Racial variation in the quality of surgical care for bladder cancer. Cancer 2013;120:1018–25.
16. Kelly SP, Van Den Eeden SK, Hoffman RM, Aaronson DS, Lobo T, Luta G, et al. Sociodemographic and clinical predictors of switching to active treatment among a large, ethnically diverse cohort of men with low risk prostate cancer on observational management. J Urol 2016;196:734–40.
17. Mahal BA, Chen YW, Muralidhar V, Mahal AR, Choueiri TK, Hoffman KE, et al. Racial disparities in prostate cancer outcome among prostate-specific antigen screening eligible populations in the United States. Ann Oncol 2017;28:1098–104.
18. Braveman PA, Cubbin C, Egerter S, Chideya S, Marchi KS, Metzler M, et al. Socioeconomic status in health research: one size does not fit all. JAMA 2005;294:2879–88.
19. Alio AP, Richman AR, Clayton HB, Jeffers DF, Wathington DJ, Salihu HM. An ecological approach to understanding black–white disparities in perinatal mortality. Matern Child Health J 2009;14:557–66.
20. Friedlander DF, Trinh QD, Krasnova A, Lipsitz SR, Sun M, Nguyen PL, et al. Racial disparity in delivering definitive therapy for intermediate/high-risk localized prostate cancer: the impact of facility features and socioeconomic characteristics. Eur Urol 2017 Aug 1 [Epub ahead of print].
21. Patel MI, Ma Y, Mitchell B, Rhoads KF. How do differences in treatment impact racial and ethnic disparities in acute myeloid leukemia? Cancer Epidemiol Biomarkers Prev 2015;24:344–9.

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