

Perioperative complications and oncological outcomes following radical cystectomy among different racial groups: A long-term, single-center study

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Abstract

Introduction: Current literature on perioperative and oncological outcomes following radical cystectomy among different racial groups is limited, especially among Hispanics and Asians. The objective of this study was to assess the impact of racial differences on perioperative and oncological outcomes in a large cohort of bladder cancer patients who underwent radical cystectomy.

Methods: We retrospectively reviewed the records of 3293 patients who underwent radical cystectomy with curative intent at our institution between 1971 and 2017. Based on race, patients were categorized as Hispanic (n=190), Asian (n=145), African American (n=67), and Caucasian (n=2891). Baseline characteristics, pericystectomy complications, and oncological outcomes, including recurrence-free and overall survival, were compared between the racial groups.

Results: Mean patient age was 68±10.6 years. Median followup was 10.28 years. Body mass index and American Society of Anesthesiologists scores were significantly higher in Hispanic and African American population, and smoking incidence was lower in Asian patients. Hispanics presented with significantly higher clinical stage and longer time interval from diagnosis to treatment (mean 85.5 vs. 75.4 days in Caucasians, p<0.001). Overall 90-day complication and readmission rates were higher in Hispanics (41.06% and 18.95%, respectively). Oncological outcomes, however, were comparable between different race groups. In multivariate analysis, pathological nodal status and lymphovascular invasion were independent predictors of oncological outcomes, but race was not.

Conclusions: In this very large, ethnically diverse patient cohort who underwent radical cystectomy with curative intent, pericystectomy complications were more common in Hispanics; however, race was not an independent predictor of long-term oncological outcome.

Introduction

Radical cystectomy (RC) with urinary diversion is a complex urological procedure involving surgery on the genitourinary and gastrointestinal systems. This is associated with significant morbidity, as well as intra- and postoperative complications.¹ The optimal goals of RC include prevention of recurrence or metastasis, improved survival, and minimizing the decrease in quality of life. Long-term outcomes following major surgical oncological procedures has improved significantly over the last two decades; however, almost half of all patients still experience disease recurrence within five years following RC.^{2,3} Furthermore, these improvements are not consistent across all population and racial groups.² While distinctions in disease pathophysiology may explain some of these differences, variability in non-biological (i.e., social, economic, and environmental) factors may also contribute to these findings.⁴ Few data exist on the perioperative and oncological outcomes of RC in different racial groups. Among the available data, most studies include African American (AA) and Caucasian populations, and there is limited representation of Hispanic and Asian patients.⁵ The objective of this study was to assess the impact of racial differences on perioperative and oncological outcomes in a large cohort of bladder cancer patients who underwent RC in a single institution.

Methods

Patients and followup

Using our institutional review board-approved bladder cancer database, we retrospectively reviewed records of patients who underwent RC with curative intent at our institution between 1971 and 2017. Patients with missing data of interest and those who underwent salvage cystectomy after radiation therapy were excluded from enrollment. The final

cohort consisted of 3293 patients. Based on race, patients were divided into four groups: Caucasian, Hispanic, Asian American and AAs. Baseline demographic and clinical characteristics, including age, sex, body mass index (BMI), smoking status, American Society of Anesthesiologists (ASA) score, Charlson comorbidity index (CCI), time from diagnosis to treatment, neoadjuvant chemotherapy (NAC) status, clinical stage, and type of diversion, were compared between racial groups. Pathological features, including pathological stage, presence of carcinoma in situ, lymphovascular invasion (LVI), positive margins, and associated variant histology, were also compared among the racial groups. Following surgery, patients were followed every four months in the first year, every six months up to five years, and annually thereafter. Followup included physical examination, serum chemistry studies, and radiographic surveillance. The majority of patients were contacted prospectively throughout the 90-day postoperative period to inquire about recent complications or symptoms and records for followup or complications managed outside our institution were regularly obtained. To investigate the impact of racial variations on perioperative complications and oncological outcomes following RC, we compared 90-day complications and readmissions, recurrence status, overall survival (OS) and three-year recurrence-free survival (RFS) across the racial groups. OS was defined as the time from surgery to death (any cause). In the absence of an event, RFS and OS were censored at last followup.

Data analysis

Independent characteristics were compared between the study groups using frequency tables and Pearson's Chi-squared or Fisher's exact test for categorical variables and analyses of variance for continuous variables. When variables were not normally distributed, Wilcoxon rank sum test was used to assess differences. Kaplan-Meier plots were used to estimate the probabilities of OS and RFS. Cox proportional hazard models, through stepwise selection, were used to identify independent prognostic factors for oncological outcomes in multivariable setting. SAS, Version 9.3 (SAS Institute Inc., Cary, NC, U.S.) was used for all the analyses. All *p* values reported are two-sided and *p*<0.05 was considered statistically significant.

Results

A total of 3293 patients with a mean age of 68±10.6 years and median followup period of 10.28 (range 0.1–40.43) years were included in the analysis. Patient characteristics and clinical/pathological features are shown in Table 1. BMI and ASA score were significantly higher in Hispanic and AA patients (*p*<0.001, *p*=0.003, respectively). Smoking incidence was lower in Asian patients (*p*<0.001). Hispanics

presented with significantly higher clinical stage and longer time interval from diagnosis to treatment (85.5 vs. 75.4 days in Caucasians, *p*<0.001).

Perioperative complications and oncological outcomes of the patients are shown in Table 2. Ninety-day complication and readmission rates were significantly higher in Hispanics (41.06%, *p*<0.001; 18.95%, *p*=0.001, respectively). However, oncological outcomes, including recurrence rate, three- and five-year OS, and three-year RFS, were comparable between different racial groups.

In multivariate analysis, age >65, CCI ≥1, positive lymph nodes, LVI, heterotopic urinary diversion, neo-adjuvant and adjuvant chemotherapy were independent predictors of survival. Furthermore, positive lymph nodes, LVI, heterotopic urinary diversion, and neo-adjuvant chemotherapy were independent predictors of recurrence, but race was not (Table 3).

Discussion

Among available data on outcomes of bladder cancer among racial groups, most studies include AAs and Caucasians, yet little data is available for Hispanic and Asian patients. Prior publications have suggested that minorities undergoing both oncological and non-oncological surgeries may have higher postoperative complication rates compared to their Caucasian counterparts.⁶⁻⁸ Access to healthcare and the quality of care delivered to minority populations may potentially contribute to this difference. However, few conflicting data exist on urological surgeries, including RC. Using the Healthcare Cost and Utilization Project State Inpatient Databases, Barocas et al demonstrated that regardless of payer type, AAs had worse perioperative outcomes, even for those who received care at high-volume centers.⁹ On the other hand, a study of patients from Nationwide Inpatient Sample Database showed that AAs undergoing major surgical oncological procedures were more likely to experience postoperative complications (specifically vascular, wound, gastrointestinal, and infectious), in-hospital mortality, homologous blood transfusions, and prolonged hospital stay. However, AA and Hispanic patients undergoing RC experienced no disparities relative to Caucasian patients in terms of in-hospital mortality or overall postoperative complications.¹⁰

There are two other studies based on the American College of Surgeons National Surgical Quality Improvement Program Database that were specifically designed to characterize postoperative complications. The first study demonstrated that AAs had greater odds of experiencing prolonged length of stay after 10 of the 16 urological procedures studied, including RC. Although AAs had greater odds of postoperative renal complications and Hispanics had greater odds of blood transfusion compared to Caucasians, both groups showed no difference in overall complications after RC.

Table 1. Baseline characteristics and clinical features of the patients at the time of surgery

Patient characteristics	Caucasian (2891, 88%)	Hispanic (190, 6%)	Asian (145, 4%)	African American (67, 2%)	p
Age (mean ± SD), year	68±10.6	68±11.2	68.7±11.4	64.9±11.6	0.09
Sex, n (%)					
Male	2336 (80.80)	150 (78.95)	110 (75.86)	44 (65.67)	0.009
Female	555 (19.20)	40 (21.05)	35 (24.14)	23 (34.33)	
BMI (mean ± SD), kg/m ²	27.4±5.3	28.4±5.5	24.4±4.4	28.5±6.4	<0.001
Smoking	2165 (74.89)	135 (71.05)	72 (49.66)	49 (73.17)	<0.001
ASA score, n (%)					
1–2	581 (28.22)	34 (21.12)	50 (38.46)	10 (17.54)	0.003
3–4	1478 (71.78)	127 (78.88)	80 (61.54)	47 (82.46)	
CCI, n (%)					
0	1337 (49.63)	98 (52.97)	66 (58.53)	35 (53.03)	0.57
1	571 (21.20)	34 (18.38)	37 (27.21)	13 (19.70)	
≥2	786 (29.18)	53 (18.65)	33 (24.26)	18 (27.27)	
Time from diagnosis to treatment (mean ± SD), days	75.4±15.9	85.5±92.8	76.8±83.1	81.8±64.7	<0.001
Neoadjuvant chemotherapy, n (%)	407 (14.08)	36 (18.95)	25 (17.24)	10 (14.93)	0.23
Clinical stage, n (%)					
≤T2, N0	2495 (86.30)	147 (77.37)	116 (80.00)	58 (86.57)	0.001
≥T3, N0	265 (9.17)	24 (12.63)	23 (15.86)	5 (7.46)	
N+	131 (4.53)	19 (10.00)	6 (4.14)	4 (5.97)	
Pathological stage, n (%)					
≤T2, N0	1685 (58.25)	100 (52.63)	91 (62.76)	35 (52.54)	0.40
≥T3, N0	578 (19.99)	40 (21.05)	30 (20.69)	15 (22.39)	
N+	628 (21.72)	50 (26.32)	24 (16.55)	17 (25.37)	
Carcinoma in situ, n (%)	1609 (55.66)	98 (51.58)	72 (49.66)	32 (47.76)	0.21
Lymphovascular invasion, n (%)	797 (27.57)	59 (31.05)	39 (26.90)	20 (29.85)	0.73
Positive margins, n (%)	162 (5.60)	12 (6.32)	5 (3.45)	3 (4.48)	0.66
Diversion, n (%)					
Orthotopic	1659 (57.38)	116 (61.05)	93 (64.14)	36 (53.73)	0.28
Heterotopic	1232 (42.62)	74 (38.95)	52 (35.86)	31 (46.27)	
Associated variant histology, n (%)	585 (20.24)	40 (21.05)	24 (16.55)	18 (26.87)	0.37
Transfusion	1323 (45.76)	100 (52.63)	82 (56.55)	37 (55.22)	0.01

ASA American Society of Anesthesiologists; BMI: body mass index; CCI: Charlson comorbidity index; SD: standard deviation.

Interestingly, there was no disparity across Caucasian, AA, and Hispanic patients in odds of 30-day mortality after any surgery.¹¹ The second study found no significant differences in complication rates between AA and Caucasian patients for any Clavien grade after RC. Furthermore, after controlling for a higher comorbidity burden among AA patients, AA race was again not independently associated with 30-day postoperative complications for RC.¹² The results of these studies showed that although AA patients were more likely to experience postoperative complications after different urological and non-urological surgeries, there is no difference between AAs and Hispanics compared to Caucasians in terms of early complications and mortality after RC. However, there is no available data on Asian patients. Our study showed that 90-day perioperative complications and readmission rates were higher in minorities compared to Caucasians. Hispanics had the highest 90-day postoperative complication rate, followed by Asians. The transfusion rate was also higher in minorities compared to Caucasians. Among complication subgroups, only bleeding was signifi-

cantly higher in Hispanic patients. It is noteworthy that the reported postoperative complications are mostly belonging to the pre-enhanced recovery after surgery (ERAS) era in our institution and are captured retrospectively. Finally, 90-day mortality rate was the same between the four racial groups.

Studies describing racial differences in oncological outcomes following RC show conflicting results. Many of these studies are conducted based on the Surveillance, Epidemiology, and End Results Program database that mainly relies on insurance claims data.^{13–19} Older studies based on this database showed that AA race was an independent predictor of poor survival, adjusting for different variables (i.e., age, marital status, region of the country, stage, grade, treatment received, and interaction between race and region).¹⁹ Furthermore, five-year disease-specific survival was consistently worse for AAs than for other racial groups, even when stratified by stage and grade; it was reported as 82.8% in Caucasians compared with 70.2% in AAs, 80.7% in Hispanics, and 81.9% in Asian/Pacific Islanders.¹⁵ Interestingly, a recent study on the same database showed

Table 2. Perioperative complications and oncological outcomes stratified by race

Patient characteristics	Caucasian	Hispanic	Asian	African American	p
90-day complications, n (%)					
Low-grade	534 (18.47)	50 (26.32)	49 (33.79)	14 (20.90)	<0.001
High-grade	214 (7.40)	28 (14.74)	13 (8.97)	6 (8.96)	
90-day complication subgroups, n (%)					
Cardiac	173 (5.98)	9 (4.74)	19 (13.10)	3 (4.48)	0.004
Pulmonary	67 (2.32)	4 (2.11)	3 (2.07)	1 (1.49)	0.97
GI	558 (19.30)	45 (23.68)	39 (26.90)	17 (25.37)	0.46
GU	354 (12.24)	35 (18.42)	13 (8.97)	9 (13.43)	0.46
DVT	143 (4.95)	10 (5.26)	8 (5.52)	6 (8.96)	0.52
Infection	508 (17.57)	43 (22.63)	31 (21.38)	19 (28.36)	0.31
Neurologic	96 (3.32)	3 (1.58)	4 (2.76)	1 (1.49)	0.48
Bleeding	143 (4.95)	21 (11.05)	13 (8.97)	5 (7.46)	<0.001
Surgical	176 (6.09)	13 (6.84)	9 (6.21)	6 (8.96)	0.78
Wound	95 (3.29)	9 (4.74)	4 (2.76)	5 (7.46)	0.2
Other	182 (6.30)	14 (7.37)	17 (11.72)	4 (5.97)	0.08
90-day readmission, n (%)	312 (10.97)	36 (18.95)	21 (14.85)	12 (17.91)	0.001
Operative mortality	45 (1.56)	4 (2.11)	2 (1.38)	0 (0)	0.55
Recurrence, n (%)					
Local	189 (6.54)	11 (5.79)	11 (7.59)	2 (2.98)	–
Distant	649 (22.45)	39 (20.53)	30 (20.69)	18 (26.87)	
Overall survival (mean± SD)					
3-year	68±1%	70±3%	71±3%	64±6%	0.90
5-year	60±1%	56±4%	55±5%	57±6%	
3-year RFS (mean ± SD)	70±1%	71±3%	69±5%	68±5%	0.97

DVT: deep vein thrombosis; GI gastrointestinal; GU: genitourinary; RFS: recurrence-free survival; SD: standard deviation.

that bladder cancer-specific mortality is not higher in AAs compared to Caucasians. Kaye et al, based on the analysis of patients between 1973 and 2011, stated that although AAs had worse all-cause and cancer-specific mortality by univariable analysis, after accounting for sex, age, year of diagnosis, marital status, region of treatment, and stage at cystectomy, all-cause mortality was significant (hazard ratio [HR] 1.2) but bladder cancer-specific mortality was not.¹⁴

Studies done based on other databases also showed this controversy. Studies on the Florida Cancer Data System, the Agency for Health Care Administration Data Sets, and the U.S. National Cancer Database demonstrated that AA race was statistically significantly and independently associated with poor outcome and OS compared to Caucasians.²⁰⁻²² On the other hand, Schinkel et al showed that although AA patients were more likely to present with muscle-invasive bladder cancer than Caucasians, no significant racial differences in OS (HR 0.96) or RFS (HR 0.94) were observed after adjustment for demographic variables, tumor characteristics and treatment.²³ Manoharan et al showed that Hispanic patients present with higher disease stage; however, disease-free and cancer-specific survivals, as well as OS are not significantly different compared to non-Hispanic white patients.²⁴ Similarly, Hispanics in our study presented with significantly higher clinical stage and longer time interval from diagnosis to treatment. However, the pathological features were comparable between different racial groups. Interestingly, oncological outcomes were also comparable between four different racial groups.

One may hypothesize that tumor biology and genetic factors can partly account for the observed racial differences in bladder cancer oncological outcomes. However, non-genetic factors, such as health systems, healthcare providers, and unequal access to care, may likely also contribute to health disparities.⁴ Nearly 50% of AAs are either uninsured or use other public insurance, which is about two-fold more than Caucasians.²⁵ AAs receive a greater proportion of their care at low-volume hospitals, which can affect their survival rates.²⁶ Furthermore, they are less likely to receive cystectomy by high-volume surgeons and undergo evidence-based care (i.e., standard pelvic lymph node dissection and continent diversion) and more likely to have partial rather than RC.⁹ There is some evidence that patients suffering from both urological and non-genitourinary malignancies with equivalent access to care and treatment have similar outcomes, regardless of race or ethnicity.²⁷⁻²⁹ For instance, race/ethnicity was not a preoperative risk factor for mortality or prolonged hospital length of stay after cystectomy among patients treated at Veterans Affairs Medical Centers nationwide.²⁹ Based on the available data, the effect of race on oncological outcome following RC is yet to be proven, and multi-institutional studies on large cohorts are needed to show the specified relationship.

In our study, the variables were adjusted for different confounding factors, including time intervals by decades. Based on the multivariable analysis, the negative independent predictors of both survival and recurrence were positive

Table 3. Cox proportional hazards of factors associated with survival and recurrence

Prognostic factors	Survival		Recurrence	
	HR (95% CI)	p	HR (95% CI)	p
Race				
Caucasian	Referent		Referent	
Hispanic	0.977 (0.758–1.260)	0.86	0.845 (0.613–1.167)	0.31
Asian	0.985 (0.742–1.307)	0.91	0.967 (0.686–1.362)	0.85
African American	1.226 (0.850–1.767)	0.27	0.976 (0.601–1.586)	0.92
Decades				
1971–1979	Referent		Referent	
1980–1989	0.670 (0.354–1.265)	0.22	1.235 (0.390–3.908)	0.72
1990–1999	0.750 (0.395–1.425)	0.38	1.318 (0.416–4.177)	0.64
2000–2009	0.607 (0.319–1.155)	0.13	1.291 (0.409–4.080)	0.66
2010–2017	0.455 (0.236–0.878)	0.02	1.367 (0.429–4.357)	0.60
Age				
≤65	Referent		Referent	
>65	1.810 (1.596–2.052)	<0.001	1.108 (0.950–1.294)	0.19
Sex				
Male	Referent		Referent	
Female	0.862 (0.750–0.990)	0.03	1.038 (0.869–1.239)	0.68
Charlson comorbidity index				
0	Referent	<0.001	Referent	0.54
≥1	1.308 (1.168–1.466)		0.955 (0.822–1.108)	
Pathologic lymph node status				
Negative	Referent	<0.001	Referent	<0.001
Positive	1.559 (1.234–1.969)		1.703 (1.323–2.191)	
Lymphovascular invasion				
Negative	Referent	<0.001	Referent	<0.001
Positive	1.965 (1.742–2.217)		2.810 (2.407–3.280)	
Urinary diversion				
Orthotopic	Referent		Referent	
Heterotopic	1.451 (1.274–1.653)	<0.001	1.293 (1.095–1.526)	0.002
Neoadjuvant chemotherapy				
No	Referent		Referent	
Yes	1.307 (1.100–1.555)	0.002	1.835 (1.507–2.235)	<0.001
Adjuvant chemotherapy				
No	Referent	<0.001	Referent	0.55
Yes	0.739 (0.637–0.856)		1.055 (0.885–1.258)	

CI: confidence interval; HR: hazard ratio.

lymph nodes, LVI, heterotopic urinary diversion, and NAC. This is in contrast to the randomized trials that showed significant increase in survival with neoadjuvant therapy.³⁰ The reason for that is most of the patients who received NAC in our cohort were those with high-stage (i.e., T3/T4 and/or bulky lymph nodes) disease. This selection bias may affect the results.

Limitations

An important limitation of our study was its retrospective nature and the relatively small percentage of AA patients available for analysis. Furthermore, results of this study may be associated with referral bias, as most of our patients were insured and presumably from higher socioeconomic status. However, this potentially also highlights the fact that racial disparities seen in most other studies could be a con-

sequence of socioeconomic inequalities. In addition, this study represents one of the largest cohorts of Caucasian, Hispanic, and Asian patients who underwent standardized surgery by expert urological oncologists with curative intent. Furthermore, all the specimens were reviewed by expert genitourinary pathologists.

Conclusions

In this very large, ethnically diverse, long-term followup study of RC with curative intent, perioperative complications were more common in Hispanics. Furthermore, this racial group presented with significantly higher clinical stage and longer time interval from diagnosis to treatment. Presence of positive lymph nodes, LVI, heterotopic urinary diversion, and NAC were independent predictors of long-term oncological outcome (OS and RFS), but race was not.

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