Race- and Sex-Based Disparities in the Therapy and Outcomes of Squamous Cell Carcinoma of the Anus

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Abstract

Background: Squamous cell carcinoma of the anus (SCCA) is one of the few cancers with an increasing incidence in the United States. We aimed to characterize race- and sex-based disparities in receipt of therapy and overall survival (OS) of SCCA using the SEER database. **Methods:** Cases of locoregional SCCA (T2–T4 any N M0) diagnosed between 2000 and 2012 in the SEER database were included. Demographics, tumor characteristics, type of therapy, and outcomes were extracted. Univariable and multivariable Cox proportional hazard models were constructed to test factors associated with OS. Data were reported as hazard ratios (HRs) and 95% CIs. **Results:** A total of 7,882 cases of locoregional SCCA were identified, with a median age of 58 years, 61.2% of whom were women, and 86.3% were white. Most patients (82.3%) received radiation therapy (RT), with the lowest rate in black men (76.7%) and the highest in white women (86.1%). The median OS was 135 months; OS was lower in elderly patients (age ≥65 years; 68 months), men (108 months), blacks (109 months), and those who did not receive RT (121 months). In multivariable analysis, age (HR, 1.19; 95% CI, 1.17–1.21 per 5 years increase), sex (HR, 1.59; 95% CI, 1.47–1.73, men vs women), race (HR, 1.51; 95% CI, 1.34–1.71, black vs white), and RT (HR, 0.90; 95% CI, 0.82–0.99) were independently associated with OS ($P < .05$). **Conclusions:** Significant race- and sex-based disparities exist in survival of patients with locoregional SCCA. Further investigation into the causes of these disparities and methods for elimination are warranted.

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Background

The NCI estimated that 8,080 new diagnoses of anal cancer and 1,080 deaths from the disease occurred in the United States in 2016.¹ It remains one of few cancers in the United States with an increasing incidence over the past 3 decades^{2–4}: from 0.8 per 100,000 persons in 1975 to 1.9 per 100,000 persons in 2013, with the most rapid increase seen in black men.⁵

Squamous cell carcinoma of the anus (SCCA) is the most common histologic subtype of anal cancer, accounting for approximately 74% to 85% of cases.^{4,6} SCCA is strongly associated with human papilloma virus (HPV) and HIV infection.⁷ Therapy for locoregional

SCCA has largely remained unchanged over the past 2 decades, with combination chemotherapy and radiation therapy (RT) considered first-line therapy, and salvage surgery used for resistant or recurrent disease.⁸ Race and sex disparities related to access to care and outcomes have been studied for several malignancies, including pancreatic, breast, and lung cancers.^{9–11} Characterizing disparities can trigger investigations into the role of environmental risk factors, socioeconomic variables, and genetic predisposition across race and sex groups.^{12–15} However, studies on disparities of SCCA are limited.

Because SCCA has an increasing incidence with a historic predisposition to underserved and at-risk

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populations, we aimed to study trends in race- and sex-based disparities in therapy for and outcomes of SCCA using the SEER database.

Methods

The NCI's SEER program contracts with population-based cancer registries to provide data on all cancer cases and their tumor and epidemiologic characteristics. SEER*Stat was used for all data extraction, incidence, and survival rates. Individuals diagnosed with anal carcinoma (primary site C21.0–C21.2) from 2000 through 2012 were included, and only those with locoregional disease, defined as T2–T4 any N M0 and confirmed squamous histology (ICD-O histology codes 8010 and 8051–8081). Cases with nonsquamous cell histology, carcinoma in situ, and diagnosis by autopsy data/death certificate only were excluded. Age-standardized incidence rates per 100,000 for 2000 through 2012 were generated via SEER's Rate Session for white men, white women, black men, and black women. The trend of change in incidence rate between groups was compared by testing the interaction between time and group in the linear regression model. This study was considered exempt by the Institutional Review Board in accordance with the NIH Office for Human Research Protections (45 CFR 46.101(b)(4)).

Patient characteristics were described by age, sex, race, year of diagnosis, and receipt of radiation and surgery. Summary statistics for patient characteristics were reported using median and interquartile range for continuous variables, and using counts and percentages for discrete variables. The primary end point was overall survival (OS), which was defined as time (in months) from date of SCCA diagnosis until death from all causes as identified in SEER files. OS was estimated using the Kaplan-Meier survival method. Univariable and multivariable Cox regression analyses were used to assess the association between OS and patient characteristics. Hazard ratios (HRs) and 95% CIs were reported. A secondary analysis to study predictors of receipt of RT was performed. Univariable and multivariable logistic regression analysis were used to identify the predictors for RT receipt. Odds ratios and 95% CIs were reported, and the interaction effect between age and sex on the likelihood of receiving RT was explored. Two-sided *P* values were reported, and *P* < .05 was considered statistically sig-

nificant. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

There were 19,511 cases of anal cancer identified in SEER, of which 7,882 cases met inclusion criteria (Figure 1). Median age at diagnosis was 58 years, 61.2% were women, and 86.3% were white. Baseline patient characteristics are summarized in Table 1.

The incidence rate had the highest rate of increase for white women and black men (0.06/100,000 cases annually), whereas rates for black women and white men increased by 0.04 and 0.02/100,000 cases annually, respectively. The overall test for difference in trend among the 4 groups had a *P* value of 0.0099.

Black and male patients were younger and had lower proportion of grade 3/4 disease, compared with white and female patients, respectively. On stratification of patients by race and sex, black patients (78.5%) and male patients (77.5%) had a lower rate

Figure 1. Flow diagram of the study.

Table 1. Demographics and Baseline Characteristics	
	n (%)
Sex	
Male	3,057 (38.8)
Female	4,825 (61.2)
Age at diagnosis, y	
18–49	1,943 (24.7)
50–64	3,281 (41.6)
≥65	2,658 (33.7)
Age at diagnosis, y (median, IQR)	58 (50–69)
Race	
White	6,805 (86.3)
Black	859 (10.9)
Other	180 (2.3)
Unknown	38 (0.5)
Period of diagnosis	
2000–2003	2,157 (27.4)
2004–2006	1,464 (18.6)
2007–2009	1,896 (24.1)
2010–2012	2,365 (30.0)
Tumor grade at diagnosis	
Grade 1/2	3,938 (66.2)
Grade 3/4	2,011 (33.8)
Surgery	
Received	347 (4.4)
Did not receive	7,464 (95.6)
Radiation	
Received	6,408 (82.3)
Did not receive	1,377 (17.7)

Abbreviation: IQR, interquartile range.

of RT use than white patients (82.9%) and female patients (85.4%), respectively. Supplemental eTable 1 summarizes the characteristics of patients stratified by race and sex ([available with this article at JNCCN.org](#)).

Median OS of the cohort was 135 months. Kaplan-Meier curves for survival of patients with SCCA comparing white women (ref), white men (HR, 1.35; 95% CI, 1.24–1.47), black women (HR, 1.29; 95% CI, 1.09–1.53), and black men (HR, 1.62; 95% CI, 1.38–1.91) are presented in Figure 2 (log rank test $P<.0001$). Median OS for white women was 148 months, followed by black women (146 months), white men (111 months), and black men (82 months).

Figure 2. Kaplan-Meier curve demonstrating overall survival of squamous cell carcinoma of the anus in SEER from 2000–2012 among the 4 racial/sex groups. Abbreviation: HR, hazard ratio.

On univariable analysis, younger age, female sex, white race, receipt of RT, and nonreceipt of surgery were associated with improved survival, whereas period of diagnosis and grade of tumor were not (Table 2). On multivariable analysis, increasing age (HR, 1.19; 95% CI, 1.17–1.21 per 5-year increase), sex (HR, 1.59; 95% CI, 1.47–1.73, men vs women), race (HR, 1.51; 95% CI, 1.34–1.71, black vs white), and receipt of RT (HR, 0.90; 95% CI, 0.82–0.99), were all independently associated with OS (all $P<.05$; Table 3). The multivariable logistic regression analysis suggested that there was no interaction between age and sex in the likelihood of receiving RT ($P=.358$). Table 4 includes the results of univariable logistic regression analysis and multivariable logistic regression analyses with and without the interaction term.

Additional analysis was performed to understand factors predicting receipt of RT (Table 4). After multivariable adjustment, advanced age (age ≥ 65 years vs 18–49 years), male sex (vs female), and grade 1/2 disease (vs grade 3/4) were independently associated with lower rates of RT receipt. Black race was associated with a lower rate of RT receipt on univariable analysis, which did not persist after multivariable adjustment.

Discussion

Using a nationally representative cohort, we demonstrate significant race- and sex-based disparities in the treatment and outcomes of patients with locoregional SCCA. Black men had the lowest median

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Table 2. Summary Data for Univariable Cox Regression Analysis for Survival

	5-Year Survival, % (95% CI)	Median OS, mo	Univariable Analysis	
			HR (95% CI)	P Value ^a
Overall	66.0 (64.8, 67.2)	135	NA	
Sex				
Female	69.0 (67.4, 70.5)	148	ref	
Male	61.4 (59.4, 63.3)	108	1.36 (1.26, 1.47)	<.0001
Age at diagnosis				
Per 5 years increase	NA	NA	1.16 (1.15, 1.18)	<.0001
Race				
White	66.9 (65.5, 68.1)	137	ref	
Black	57.9 (53.9, 61.7)	109	1.28 (1.14, 1.44)	<.0001
Other	68.5 (59.6, 75.8)	140	0.96 (0.73, 1.25)	.75
Period of diagnosis				
2000–2003	66.4 (64.4, 68.4)	138	ref	
2004–2006	66.2 (63.7, 68.6)	NR	1.02 (0.92, 1.14)	.66
2007–2009	63.9 (61.4, 66.3)	NR	1.08 (0.97, 1.20)	.13
2010–2012	NA	NR	0.92 (0.80, 1.05)	.22
Tumor grade at diagnosis				
Grade 1/2	65.8 (64.1, 67.5)	137	ref	
Grade 3/4	62.8 (60.3, 65.2)	122	1.09 (0.99, 1.20)	.06
Surgery				
Did not receive	67.1 (65.9, 68.4)	141	ref	
Received	43.9 (37.8, 49.8)	43	1.91 (1.64, 2.22)	<.0001
Radiation				
Did not receive	63.6 (60.7, 66.4)	121	ref	
Received	66.7 (65.3, 68.0)	141	0.85 (0.77, 0.93)	.0008

Abbreviations: HR, hazard ratio; NA, not applicable; NR, not reported; OS, overall survival.

^aP value based on Cox regression analysis.

survival. After adjusting for tumor and treatment variables, race and sex were independent predictors of survival, suggesting inherent differences in tumor biology.

Standard treatment for locoregional SCCA comprises a combination of chemotherapy and RT, with salvage surgery reserved for those with residual or recurrent disease.¹⁶ Race- and sex-based disparities in outcomes have been reported in the context of several other cancers.^{17–21} Understanding health-care disparities in SCCA is crucial because it largely affects at-risk and vulnerable populations, including ethnic minorities and individuals with HIV. Data from other cancer types demonstrate that nonwhite patients experience delays in diagnosis and treatment, and are less likely to receive guideline-adherent treatment.^{22–24} These disparities are a result of a complex interplay of social, economic, biologic,

Table 3. Summary Data for Multivariable Cox Regression Analysis for Survival

	Multivariable Analysis	
	HR (95% CI)	P Value ^a
Sex		
Women	ref	
Men	1.59 (1.47, 1.73)	<.0001
Age at diagnosis		
Per 5 years increase	1.19 (1.17, 1.21)	<.0001
Race		
White	ref	
Black	1.51 (1.34, 1.71)	<.0001
Other	1.01 (0.77, 1.32)	.95
Radiation		
Did not receive	ref	
Received	0.90 (0.82, 0.99)	.04

Abbreviation: HR, hazard ratio.

^aP value based on Cox regression analysis.

Table 4. Summary of Logistic Regression Analysis for Variables Affecting Odds of Receiving Radiation as Part of Therapy

		Univariable Analysis		Multivariable Analysis With Interaction		Multivariable Analysis Without Interaction	
		Odds Ratio (95% CI)	P Value ^a	Odds Ratio (95% CI)	P Value ^a	Odds Ratio (95% CI)	P Value ^a
Sex							
Female		ref		^b		ref	
Male		0.59 (0.52, 0.66)	<.0001		<.0001	0.64 (0.55, 0.73)	<.0001
Age at diagnosis, y							
18–49		ref		^b	<.0001	ref	
50–64		1.64 (1.41, 1.90)	<.0001			1.26 (1.05, 1.52)	.0127
≥65		1.11 (0.96, 1.28)	.1649			0.69 (0.58, 0.83)	<.0001
Age at diagnosis							
Per 5 years increase		0.99 (0.96, 1.01)	.1808				
Sex and age at diagnosis interaction							
Men	18–49 y	ref	.0374	ref	.3578		
Men	50–64 y	1.55 (1.27, 1.89)		1.33 (1.04, 1.70)			
Men	≥65 y	1.19 (0.96, 1.48)		0.79 (0.61, 1.02)			
Women	18–49 y	ref		ref			
Women	50–64 y	1.43 (1.14, 1.80)		1.15 (0.87, 1.52)			
Women	≥65 y	0.82 (0.66, 1.02)		0.60 (0.46, 0.79)			
Race							
White		ref		ref		ref	
Black		0.75 (0.63, 0.90)	.0017	0.84 (0.67, 1.05)	.12	0.83 (0.67, 1.04)	.0980
Other		1.11 (0.74, 1.67)	.6528	0.89 (0.56, 1.41)	.61	0.88 (0.55, 1.40)	.5969
Period of diagnosis							
2000–2003		ref		ref		ref	
2004–2006		1.47 (1.23, 1.75)	<.0001	1.34 (1.09, 1.65)	.006	1.34 (1.09, 1.64)	.0061
2007–2009		1.27 (1.09, 1.49)	.0026	1.11 (0.92, 1.34)	.26	1.11 (0.92, 1.34)	.2611
2010–2012		1.50 (1.29, 1.75)	<.0001	1.32 (1.10, 1.58)	.003	1.32 (1.10, 1.58)	.0033
Grade							
Grade 1/2		ref		ref		ref	
Grade 3/4		2.01 (1.71, 2.36)	<.0001	1.92 (1.63, 2.26)	<.0001	1.93 (1.64, 2.27)	<.0001
Surgery							
Did not receive		ref					
Received		0.28 (0.23, 0.35)	<.0001				

^aP value based on Logistic regression analysis.^bSee interaction term.

and cultural factors; these in turn influence disease prevention, time of detection, diagnosis, treatment, and posttreatment quality of life, which can manifest as an observable difference in survival and mortality rates.²⁵ Patients with low socioeconomic status are more likely to lack health insurance, have lower health literacy, have poor geographic access to healthcare, and harbor higher rates of distrust of the healthcare system.^{26–28} These findings are highly

relevant for SCCA, wherein patients presenting to a public safety net hospital with a higher rate of Hispanic and black patients had higher rates of delayed or interrupted RT and poorer OS compared with those presenting to a private hospital.²⁹

HIV and HPV status may represent indirect influences on the observed disparities of SCCA outcomes. HIV-positive individuals with SCCA are more likely to be younger, male, and black.³⁰ A

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recent study identified 1997 as the time point when the rates of SCCA shifted most dramatically.⁶ Because the risk of SCCA is highest in patients with HIV after ≥ 15 years of infection,³¹ this has been correlated with the time course of the HIV epidemic, which began in the early 1980s. The increasing rate of anal cancer incidence in the United States has been correlated to the HIV epidemic in men, but is reported to be independent of HIV infection in women.³² Compared with HIV-negative men who have sex with men, those who are HIV-positive have a higher risk of harboring high-risk HPV types 16 and 18,³³ which are known to be associated with anal dysplasia and SCCA.³⁴ Studies evaluating prognosis of HIV based on sex have observed that male patients with HIV have faster disease progression and earlier mortality than female patients.^{35,36}

Disparities in outcomes between men and women have been observed in a number of solid malignancies, including colorectal,³⁷ hepatocellular,³⁸ and lung cancers.³⁹ In metastatic colorectal cancer, premenopausal women have been observed to have a survival advantage over similarly aged men, which is lost after menopause.³⁷ Women have been reported to also have a survival advantage in oropharyngeal squamous cell cancer, which, like SCCA, is a HPV-associated malignancy.⁴⁰ In anal cancer, our findings suggest that female patients are more likely to receive radiation as part of therapy, and it has been reported that women are more likely to adhere to therapy as well.⁴¹ The exact mechanism of the observed survival advantage in women remains unknown, although it is likely a result of an interaction between biological and behavioral differences, comorbidities such as HIV status, healthcare utilization, and compliance with therapy. Further investigation into causes of this disparity could shed light on means to improve outcomes in male patients.

Our findings that black men have poor survival after adjusting for tumor and treatment characteristics suggest an impact not only of potential delays in

treatment, but also underlying tumor biology. With the advent of highly active antiretroviral therapy (HAART), HIV-positive patients with SCCA have had management strategies and survival rates comparable to those of HIV-negative patients.^{42–44} Lower rates of HAART adherence in black patients may further contribute to poorer cancer outcomes.^{45,46} We have identified treatment disparities as one of the factors likely influencing the differences in outcome among patients with SCCA.

Our study has notable limitations that are inherent to a large database analysis. Impact of treatment delays, quality of RT, administration of concurrent chemotherapy, and treatment toxicities could not be assessed. We were unable to stratify our analysis based on HIV and HPV status, and molecular characterization of cancers was not available.

Conclusions

Race- and sex-based disparities reflect the fact that SCCA diagnosis and management is complex and requires coordination among multiple specialties and healthcare teams. Recognizing multiple opportunities to optimize anal cancer care along the cancer care continuum is essential to help improve outcomes and reduce disparities.^{47,48} Successful screening strategies to identify anal cancer in at-risk populations can help close this gap.⁴⁹ The effectiveness of these strategies is affected by factors at the patient, provider, and system levels. Patient education on the importance of self-management of comorbid conditions (HIV), lifestyle modification, and identifying and following up on nonmalignant anogenital warts is necessary. Primary care physicians can identify high-risk individuals to enable targeted screening efforts. Healthcare systems can engage patient support groups and use electronic medical record data fields to offer practice alerts and for screening and counseling.

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