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Predictors of Mortality in Patients With Squamous Cell Carcinoma of the Anal Canal: Does Race Play a Role?

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Abstract: Data indicate racial disparity in patients with colorectal cancer disfavoring African Americans. The aim of our study was to determine if race affected stage at the time of presentation and survival in patients with Squamous Cell Carcinoma (SCC) of the anal canal. A retrospective review of all patients admitted to Parkland Memorial Hospital diagnosed with SCC of the anal canal from 1997 to 2005 was performed. Factors associated with mortality were assessed by Univariate Analysis (UA). Significant variables by UA were included in a Multivariate Regression Analysis (MVA) model to determine factors predicting mortality. All values are presented as Means±SE. Statistic significance was determined at a $p \leq 0.05$. Seventy-five patients with SCC of the anal canal were identified (mean age 46.1±1.1 y.o., men 75 and 9% Hispanic, 60% Caucasian, 27% African American and 4% others). The mean stage at diagnosis was 1.8±1.4 (stage I = 32, stage II =20, stage III = 11, stage IV = 1). Mortality was 29%. Univatiate analysis demonstrated factors associated with mortality were: Stage (1.6±0.3 vs. 1.0±0.2; $p = 0.047$) and history of smoking 81% in non-survivors vs. 42% in survivors (OR = 1.95; $p = 0.003$). Age or ethnicity were not associated with mortality. Women presented on the average with a more advanced grade (2.0±0.1 vs. 1.6±0.1; $p = 0.02$). However, gender was not associated with mortality. MVA of all significant factors by UA did not yield any independent predictors of mortality. In contrast to colorectal cancer, our data demonstrates no disparities among Hispanics, African Americans, or Caucasians in tumor stage, age of presentation or survival in patients with SCC of the anal canal. In agreement with previous reports, stage and history of smoking were associated with mortality across all races.

Key words: Predictors, mortality, tumor stage, SCC, MVA, smoking

INTRODUCTION

Squamous Cell Carcinoma (SCC) of the anus is rare and accounts for only 1.5% of cases of gastrointestinal tract cancer in the US. However, its incidence has increased in the United States population in the past several decades. According to Surveillance Epidemiology and End Results (SEER) data, 4,660 men and women were estimated to have been diagnosed with anal cancer in 2006 and 660 individuals were estimated to have died of the disease (Jemal *et al*., 2007).

Anal cancer appears to be more similar to genital malignancies rather than malignancies of the gastrointestinal tract. Previous studies have found associations between anal cancer incidence and infection with Human Papillomavirus (HPV) (Palefsky *et al*., 1991), lifetime number of sexual partners (Daling *et al*., 1987), cigarette smoking (Daling *et al*., 1992), genital warts, receptive anal intercourse and infection with the Human Immunodeficiency Virus (HIV) (Palefsky *et al*., 1998). In the United States, race plays in important role in the clinical presentation of patients affected with Colorectal Cancer (CRC). Patients of African American decent present with a more advanced-stage disease and had higher mortality rates compared with non-hispanic whites (Chien *et al*., 2005; Doubeini *et al*., 2002). This information is important not only epidemiologically, but assists in providing care, screening, educational programs and specific management modalities depending on specific cohort of patients affected.

In light of the fact that most of the causes of SCC of the anal canal are preventable, it is important to identify racial disparities in outcomes in order to promote specific screening and educational programs directed at a given cohort of patients affected. An analysis of the Surveillance, Epidemiology and End Results (SEER) database indicated that black men had a higher incidence rates for anal cancer and lower survival

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rates (John *et al*., 2004). Conversely, Maggard *et al*. (2003) revealed that there were no racial differences in survival in patients with localized anal cancer (Maggard *et al*., 2003).

The aim of our study, was to determine if race affected stage at the time of presentation and survival in patients with Squamous Cell Carcinoma (SCC) of the anal canal at a large county hospital.

MATERIALS AND METHODS

Clinical and laboratory data on patients who were diagnosed with squamous cell carcinoma of the anus was retrospectively analyzed. Present analysis included 75 patients admitted to the Parkland Memorial Hospital between 1997 to 2005 for squamous cell anal cancer. Histological proof of squamous cell cancer of the anus was obtained from pathology reports obtained by anoscopy or at the time of surgical resection. If histological confirmation was not present, then the diagnosis was made on the basis of a medical history, physical examination and other available data. Demographic data including: Age, race, gender, laboratory variables, tumor staging and details of therapy and follow-up were retrospectively collected for analyses. The variables selected in this study were based on previous investigations and/or our own clinical experience.

Data was analyzed by SPSS statistical program (SPSS Inc., Chicago, IL). Univariate analysis was performed for each variable by Students t test for continuous variables and by Fischers exact test for dichotomous variables. Significant variables by univariate analysis were included in a multivariate regression analysis model to determine factors predicting early mortality. All values are presented as means±SE, statistic significance was determined at a $p \leq 0.05$.

RESULTS

Patient characteristics: The characteristics of the patients in present study are shown in Table 1. A total of 75 patients with SCC of the anal canal were identified patients in the 8 ½-year period. The majority of the patients were male (75%). The mean age was 46.1±1.1 years. There was no difference between the age of presentation and race (Fig. 1). Eighty-two percent of all patients were smokers. In present cohort, 29 (38.6%) patients had stage 0 tumor, 11 (14.7 %) had stage I tumor, 20 (26.7%) had stage II tumor, 11 (14.7%) had stage III tumor, while 4 (5.3%) patients had stage IV cancer. The mean stage at diagnosis was 1.8±1.4. The majority of the patients were whites (60% Caucasian, 9% Hispanic, 27% African American and 4% others).

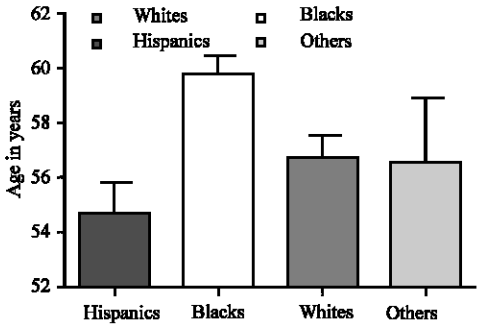

Fig. 1: Age of patients with SCC of the anal canal and ethnicity. Each bar represents the average of all patients in each ethnic group±SM

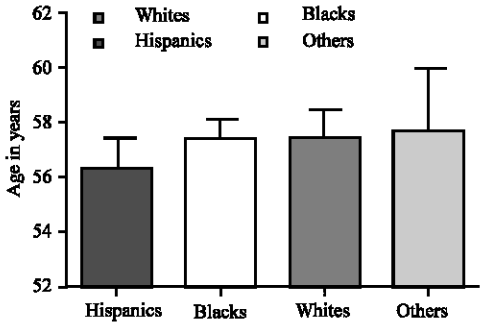

Fig. 2: Stage of patients with SCC of the anal canal and ethnicity. Each bar represents the average of all patients in each ethnic group±SE.

Table 1: Patient demographics

n = 75	
Male	75%
Squamous cell carcinoma	100%
Age	46.1±1.1 y.o
Race (%)	
Caucasians	60
African American	27
Hispanics	9
Others	4
Overall 5 year survival	71%
Mean stage at presentation	1.8±1.4
Smokers	82%

The average stage of presentation for Caucasians was 1.85±0.75 as compared to 1±1.4 for Hispanics and 1.53±0.95 for African Americans. There was no statistically significant difference in the stage of presentation between the different ethnic groups (Fig. 2). The average age of presentation for Caucasians was 45±1.3 years as compared to 50±2.2 years for Hispanics and 45±1.2 years for African Americans; there was no statistically significant difference in the age of presentation between the different ethnic groups. Women

Table 2: Univariate analysis of factors associated with mortality

	Stage	Smoking (%)	Caucasian	African American	Alcohol use
Alive (n = 53)	1.0±0.2	42.00	68.9%	65.0%	60.0%
Dead (n = 22)	1.6±0.3	81.00	72.4%	72.0%	68.0%
p-value	0.04*	0.003*	00.79	00.57	00.14

Table 3: Multivariate logistic regression analysis of relationship of survival to clinical characteristics and outcomes in anal cancer

	95% Confidence interval		
Dependent variables	Lo	Hi	p-value
Stage	-0.05	0.29	0.45
History of smoking	-0.09	0.37	0.22

presented on the average with a more advanced grade (2.0±0.1 vs. 1.6±0.1; p = 0.02). However, gender was not associated with mortality.

Survival: At the time of analysis 22 (29%) of the patients had died over a five-year follow up. The mean overall length of survival in patients that died was 27.7 months. In all cases, death occurred as a result of disease progression. There was no significant difference in survival time among the different ethnic groups.

Univariate analysis: Patients were grouped into alive (n = 53) and dead (n = 22). Univariate analysis demonstrated factors associated with mortality were: stage (1.6±0.3 vs. 1.0±0.2; p = 0.047) and history of smoking 81% in non-survivors vs. 42% in survivors (OR = 1.95; p = 0.003). African-American ethnicity was not associated with a higher mortality rate (p = 0.57). Therefore, our study indicates that ethnicities were not associated with mortality. These findings are tabulated in Table 2.

Multivariate analysis: All variables found to be statistically significant by univariate analysis (i.e., stage of cancer presentation and history of smoking) were subsequently included in the multivariate regression analysis model. The multivariate analysis of the factors did not yield any independent predictors of mortality. These findings are summarized in Table 3.

DISCUSSION

SCC of the anal canal represents approximately 1.5% of the newly diagnosed cancers of the gastrointestinal tract. In general, it is more common in women than men and most commonly occurs in the sixth or seventh decade of life. Over the past few decades, the incidence of this disease has increased in the United States and Europe, especially in the male population. The annual incidence for SCC of the anal canal in the United States is 0.7 per 100,000 for men, with a slightly higher incidence for women. The incidence of this disease in the male homosexual population is significantly higher, with incidence rates reported as high as 37 per 100,000. Although the rates of anal cancer incidence does not vary greatly between black women and white women, black men have a substantially higher incidence rates compared with white men; this may be attributed to the higher incidence of HIV infection in black men.

Risk factors for anal cancer include a history of persistent high-risk genotype Human Papillomavirus (HPV) infection, infection with multiple HPV genotypes, cervical dysplasia or cancer, HIV seropositivity, low CD4 count, cigarette smoking, anoreceptive intercourse and immunosuppression following solid organ transplant. Most of these risk factors are preventable. In order to target, educational and screening programs as well as to determine forms of management at the time of presentation, it is important to determine if there are ethnic disparities such that programs may be implemented accordiningly.

The current study evaluated patients with SCC of the anus who presented to a large county hospital. The majority of the patients were white males. Eighty-two percent of the patients were smokers, which confirm previous studies that associate cigarette smoking with an increased risk of anal cancer (Daling *et al*., 1992; Frisch *et al*., 1999). Additionally, the majority of patients presented with stage II cancer. The overall 5 year survival in our cohort was 71%, which is in accordance with previous studies (Johnson *et al*., 2004).

Univariate analysis revealed that relative survival for our patients with anal cancer was inversely associated with disease stage. This observation is in agrement with the current literature that suggests that the most important prognostic factors in anal cancer are the stage of presentation. The local relapse rates in Stage 3 and 4 lesions approaches 50%, more than double the figure in patients with stage 1 and 2 tumors (Salman *et al*., 1986). The five-year, cancer-specific survival in the present study was 71%, which is higher than the range reported by previous RCTs (Shepherd *et al*., 1990; Salman *et al*., 1986). It is important to note that some of the increased survival may be a function of lead-time bias in which survival seems longer because the disease was diagnosed sooner, but the natural history was unchanged. However, it does seem that a significant portion of the improved survival may be attributed to better treatment, because the receipt of radiation improved with time.

Univariate analysis of the study results also revealed that compared with non-smokers, active smokers have significantly worse cause-specific survival for SCC of the anus. A previous trial reported that smoking was an important and independent predictor of cancer-related death after surgery for cancer of the large bowel (Munro *et al*., 2006). Present findings suggest active smoking can exert an adverse effect by increasing the number of deaths due to anal cancer is interesting. This finding insinuates that smoking may a biological effect on anal cancer. Smoking can increase expression of genes induced by hypoxia and subsequently promote growth to residual cancer cells (either by promoting angiogenesis and invasion, or by inducing resistance to chemotherapy) (Cairns and Hill, 2004; Maxwell *et al*., 1997). Smoking can increase mortality by having an effect on the metabolism of drugs used in adjuvant chemotherapy (Faber *et al*., 2005), decreasing immune competence (OByrne *et al*., 2000); and inducing susceptibility to genetic damage (Hoffmann *et al*., 2005). Alternatively, it is possible that smokers may engage in higher risk life style that predisposes them to the development of SCC of the anal canal.

Both univariate and multivariate regression analysis did not show that race independently predicted mortality. While there is strong data showing that blacks have lower survival rates for colorectal cancer than whites (Chien *et al*., 2005), this relationship is more ambiguous for anal cancer. A large retrospective study analyzing patients with anal canal cancer in the SEERS cancer registry showed that black patients presented with less localized disease than white patients. Accordingly, black patients had higher percentages of both regional and distant stage disease. Interesting, when adjusted for stage and receipt of radiation there was no statistically significant difference in cancer specific survival between black vs. white patients (Maggard *et al*., 2003). This tends to correlate with the findings of the present study. Conversely (Johnson *et al*., 2004). found that the stage-specific relative survival was poorer at 5 years for black patients compared with white patients (local disease, 65 vs. 80%; regional or distant disease, 38 vs. 49%). They proposed that black patients with anal cancer may not be receiving adequate treatment because of factors such as higher poverty. In patients with cervical cancer, African-American women receiving the same level of care as did their white counterparts had similar 5 year survival rates (Farley *et al*., 2001). This suggests that inequality in care can play a major role in the observed inequality in survival rates for patients with anal cancer. It has also been report that patients with HIV positive patients with anal cancer were more likely to have treatment-related toxicity and therefore were likely to die of anal cancer after treatment. Because the black population has a higher rate of HIV, differences in treatment response may also play a role in racial differences in survival (Kim *et al*., 2001). The present study had the particular advantage that our patient population was homogeneously treated at a county hospital such that the same financial restrains on patients and same form of treatment are likely to be uniform.

The limitations of the study include the following. This is a retrospective study with a limited sample size. Thus, the lack of statistical significance may not exclude the presence of an actual association. Additionally, we did not have data on the HIV status of patients evaluated. The presence of HIV may have had an adverse prognostic effect, especially in the African-American population. However, the aim of our study was to determine if there was an association between ethnicity and mortality in all comers. Present analysis failed to demonstrate such as association.

CONCLUSION

In conclusion, in contract to colon cancer, our data demonstrates no disparities among Hispanics, African Americans, or Caucasians in tumor stage, age of presentation or survival in patients with SCC of the anal canal. In agreement with previous reports, stage and history of smoking were associated with mortality across all races. This data suggests that it is imperative that we detect anal cancer at an earlier stage so as to improve overall survival. Educational and screening programs should target patient populations at risk (i.e., HPV positive, HIV positive) regardless of ethnic background. Anti-smoking programs should also be instituted in high risk patients with a history of smoking.

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