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Racial disparity and survival outcomes between African-American and Caucasian American men with penile cancer

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Portions of this study were previously presented at the Society of Urologic Oncology meeting, 2015 and the American Society of Clinical Oncology Genitourinary Cancers Symposium, 2016.

Objective

To determine whether there is a survival difference for African-American men (AAM) versus Caucasian American men (CM) with penile squamous cell carcinoma (pSCC), particularly in locally advanced and metastatic cases where disease mortality is highest.

Patients and Methods

Using the Florida Cancer Data System, we identified men with pSCC from 2005 to 2013. We compared age, follow-up, stage, race, and treatment type between AAM and CM. We performed Kaplan–Meier analysis for overall survival (OS) between AAM and CM for all stages, and for those with locally advanced and metastatic disease. A multivariable model was developed to determine significant predictors of OS.

Results

In all, 653 men (94 AAM and 559 CM) had pSCC and 198 (30%) had locally advanced and/or metastatic disease. A higher proportion of AAM had locally advanced and/or

metastatic disease compared to CM (38 [40%] vs 160 [29%], $P = 0.03$). The median (interquartile range) follow-up for the entire cohort was 12.6 (5.4–32.0) months. For all stages, AAM had a significantly lower median OS compared to CM (26 vs 36 months, $P = 0.03$). For locally advanced and metastatic disease, there was a consistent trend toward disparity in median OS between AAM and CM (17 vs 22 months, $P = 0.06$). After adjusting for age, stage, grade, and treatment type, AAM with pSCC had a greater likelihood of death compared to CM (hazard ratio 1.64, $P = 0.014$).

Conclusions

AAM have worse OS compared to CM with pSCC and this may partly be due to advanced stage at presentation. Treatment disparity may also contribute to lessened survival in AAM, but we were unable to demonstrate a significant difference in treatment utilisation between the groups.

Keywords

race, survival, African-American, squamous cell carcinoma, #PenileCancer

Introduction

Penile squamous cell carcinoma (pSCC) is uncommon in developed countries, but it is an aggressive disease with a relatively high mortality rate. In 2015, there were 1820 estimated new cases and 310 deaths expected due to pSCC in the USA [1]. Factors associated with increased risk of pSCC include: circumcision status, smoking, chronic inflammation, and human papillomavirus (HPV) infection [2,3]. Advanced clinical stage and high tumour grade are associated with decreased survival [4]. However, due to the rarity of the disease, there is limited contemporary data regarding clinical outcomes and predictors of survival.

In contrast to the USA, pSCC is more common in developing countries such as those in the African continent and Latin America [5,6]. The aetiology for the observed geographic variation in pSCC incidence is not well understood, but is thought to be related to circumcision practices and possibly rates of HPV infection [5–7]. Despite low rates of pSCC in the USA, studies suggest disparity in clinical outcomes, with African-American men (AAM) having worse survival compared to Caucasian American men (CM) [8,9]. The difference in outcomes may be due to advanced stage at presentation, as well as socioeconomic factors that may lead to decreased access to care and treatment disparity [9]. Whilst treatment of localised disease can be managed

primarily with surgery in the form of partial or radical penectomy, advanced disease requires a multi-modal approach requiring lymphadenectomy along with possibly chemotherapy and/or radiotherapy [10].

In the present study, we sought to determine whether survival outcomes for men with penile cancer differed between AAM and CM in a racially diverse, contemporary cohort of men in Florida. Given that mortality rates are highest in those with advanced and metastatic pSCC, we focused on this subgroup of men and hypothesised that AAM would have worse survival compared to CM, possibly due to disparity in the receipt of multi-modal treatment.

Patients and Methods

Data source

Study data were obtained from the Florida Cancer Data System (FCDS), a State-wide population-based cancer registry administered by the Florida Department of Health and operated by the Sylvester Comprehensive Cancer Center at the University of Miami, Miller School of Medicine, with support from the Centers for Disease Control and Prevention (CDC) and National Program for Cancer Registries (NPCR). The FCDS is the third largest registry in the country and represents ~6% of all USA cancer cases [11]. The study was approved by the University of Miami Institutional Review Board (IRB # 20150496).

Study population, definition of outcome and variables

We identified 653 men diagnosed with pSCC, with known race and ethnicity, between 2005 and 2013. Men who were diagnosed upon death or autopsy analysis and with <6 months of follow-up were excluded. The primary outcome measure was median overall survival (OS) by race for men with 'advanced' and 'distant' pSCC, as defined by coding from the Surveillance, Epidemiology and End Results (SEER) 2000 Summary Stage Guidelines. The SEER Summary Stage Guidelines (2000) classify cases as 'localised' if the malignancy is limited to site of origin, as 'advanced' (regional) if there is local invasion, and as 'distant' if there is metastasis to distant organs or lymph nodes [12]. Secondary outcome measures were median OS for all men with pSCC by race and treatment type by race (AAM vs CM), which was determined using relevant International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes and the Healthcare Common Procedure Coding System (HCPCS) codes. Treatment was defined as primary surgery alone (partial penectomy, radical penectomy, with/without lymphadenectomy) or surgery plus additional therapy (radiotherapy and/or chemotherapy). Race was defined as either Black/African-American or White/Caucasian. Patients

who self-identified with other races were excluded from the analysis. In the multivariate analysis for OS, age was introduced as a continuous variable and grade, race, treatment type were introduced as categorical variables. In the subgroup analysis age, stage, grade, race, and treatment type were introduced as independent variables of OS.

Statistical analysis

All data were examined using numeric and graphical exploratory data analysis methods. Categorical variables are reported as counts with percentages and group differences were tested using Fisher's exact tests or Freeman and Halton's extension to the Fisher's exact test. Distributions of continuous variables are described using means with standard deviations (SDs) or medians with interquartile ranges (IQRs) and differences were tested using *t*-tests or Wilcoxon rank-sum tests when appropriate. Kaplan–Meier curves with log-rank tests were built to describe survival for the overall cohort and to compare race groups. Multivariate Cox regression models were built to predict survival in race groups, whilst controlling for demographic, disease, and treatment factors. Statistical analyses were performed using Statistical Analysis System (SAS) software, version 9.4 (SAS Institute Inc., Cary, NC, USA). For all analyses, two-sided *P* values <0.05 were considered to be statistically significant.

Results

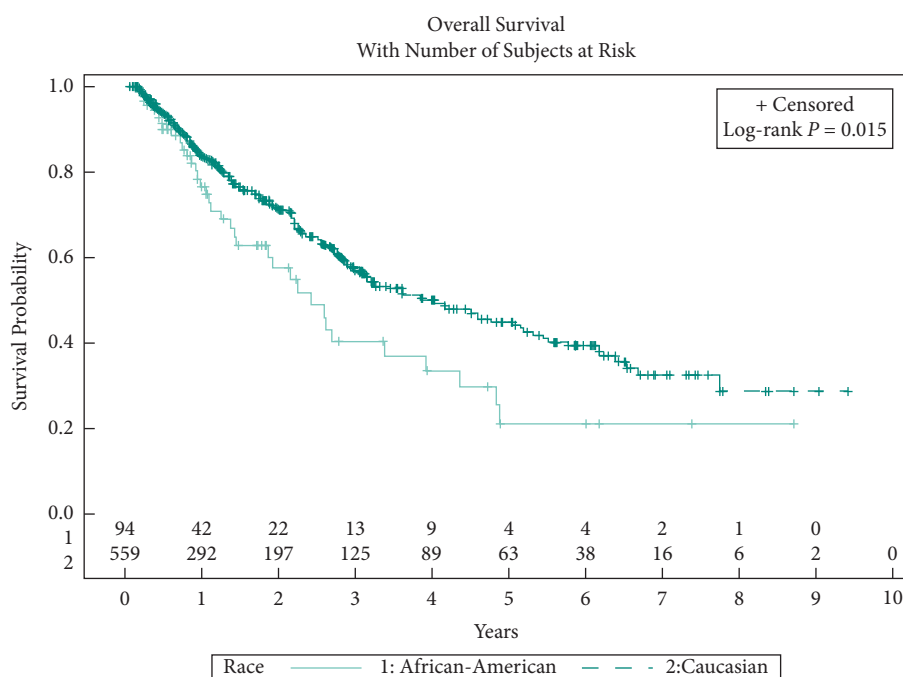
Our cohort consisted of 653 men with pSCC (Table 1). The majority of the cohort were CM ($N = 559$, 86%). AAM ($N = 94$, 14%) were significantly younger than CM (60 vs 66 years, $P < 0.001$). There was no significant difference between race groups for the median follow-up. There was a significantly higher proportion of AAM vs CM with advanced and distant pSCC (40% vs 29%, $P = 0.03$). Tumour grade (low = 1–2 vs high = 3–4) did not significantly differ between AAM and CM. A smaller percentage of AAM received surgery plus additional therapy for both localised and advanced/distant disease, but these differences were not statistically significant.

AAM with pSCC had a significantly worse median OS compared to CM (26 vs 36 months, $P = 0.03$) on univariate Kaplan–Meier analysis (Fig. 1). When analysed as advanced and/or distant pSCC, the median OS was still worse for AAM vs CM (17 vs 22 months) but not statistically significant ($P = 0.06$), probably due to the small number of AAM at risk ($n = 38$; Fig. 2). Multivariate Cox regression analysis showed that age was a significant predictor of OS with older men exhibiting lessened survival independent of other predictor variables (10-year hazard ratio [HR] 1.26, 95% CI 1.14–1.42; $P < 0.001$). Additional predictors of worse OS included: advanced stage (HR 1.51, 95% CI 1.08–2.10; $P = 0.01$) and distant stage (HR 10.3, 95% CI 5.72–18.7; $P < 0.001$). Patients with high-grade

Table 1 Demographic and clinical/pathological features for AAM and CM with penile cancer.

Variable	AAM N = 94	CM N = 559	P
Age, years, mean (SD)	60 (14)	66 (14)	<0.001
Months of observation, median (IQR)	11 (5–22)	13 (6–33)	0.10
N (%)			
Stage			
<i>In situ</i> + localised	56 (60)	399 (71)	0.03
Advanced + distant	38 (40)	160 (29)	
Grade			
Low (1–2)	55 (58)	283 (50)	0.35
High (3–4)	11 (12)	85 (15)	
Unknown	28 (30)	191 (34)	
Treatment type (all patients)			
Surgery alone	85 (90)	493 (88)	0.60
Surgery + AT	9 (10)	66 (12)	
Treatment type (advanced + distant)			
Surgery alone	30 (79)	118 (74)	0.67
Surgery + AT	8 (21)	42 (26)	
All patients OS, years, median (95% CI)	2.1 (1.1–2.7)	3 (2.5–3.6)	0.03
Advanced + distant OS, years, median (95% CI)	1.4 (0.73–2.1)	1.9 (1.2–3.0)	0.06

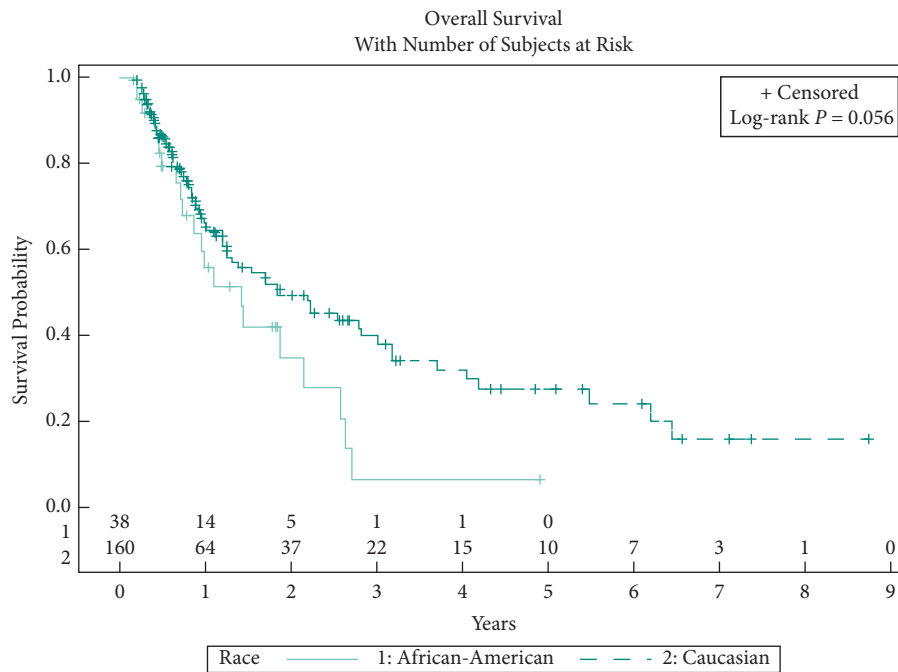
AT, additional therapy: chemotherapy and/or radiotherapy.

Fig. 1 Median OS for all men with penile cancer by race (AAM and CM).

tumours had a non-significant risk of worse OS (HR 1.44, 95% CI 0.99–2.11; $P = 0.06$). Treatment type did not significantly affect OS. However, when controlling for age, stage, grade and treatment type, African-American race was a significant independent predictor of decreased OS in men with pSCC (Table 2). For advanced and distant disease, African-American race ($n = 38$) was not a statistically significant independent predictor of decreased OS (HR 1.60, 95% CI 0.94–2.63; $P < 0.08$) (Table 3).

Discussion

Penile cancer remains an aggressive disease with a high mortality rate in contemporary series. However, due to the low incidence of pSCC in the USA, data regarding predictors of outcome and information to identify populations at risk of mortality remain limited. We hypothesised that AAM would have worse survival for pSCC compared to CM and found that indeed, when controlling for age, stage, grade, and treatment type, AAM had significantly worse OS. For

Fig. 2 Median OS for all men with advanced and/or distant penile cancer by race (AAM and CM).**Table 2** Multivariable model demonstrating predictors of OS for men with penile cancer.

Variable	HR (95% CI)	P
Age (per year)	1.02 (1.01–1.04)	<0.001
Stage (overall)		<0.001
Localised	Ref.	–
Advanced	1.51 (1.08–2.10)	0.01
Distant	10.3 (5.72–18.7)	<0.001
Grade (overall)		0.16
Low (Grade 1 or 2)	Ref.	–
High (Grade 3 or 4)	1.44 (0.99–2.11)	0.06
Unknown	1.04 (0.69–1.58)	0.84
Race		
Caucasian	Ref.	–
African-American	1.64 (1.10–2.44)	0.01
Treatment		
Surgery alone	Ref.	–
Surgery + AT	1.18 (0.69–1.82)	0.66

AT, additional therapy: chemotherapy and/or radiotherapy.

advanced and/or distant pSCC, the survival disparity persisted, but the difference was not statistically significant, probably due to the few patients in this subgroup. We also found that a relatively smaller proportion of AAM compared to CM with advanced and/or distant disease received multi-modal therapy (21% vs 26%). This difference was not significant and we cannot conclude that poor survival in AAM is directly due to treatment disparity. Whilst treatment disparity is well documented in other urological malignancies, few studies have been able to conclusively show an association with pSCC, possibly due to small sample sizes in

Table 3 Multivariable model demonstrating predictors of OS for men with advanced and/or distant penile cancer.

Variable	HR (95% CI)	P
Age (per year)	1.01 (0.99–1.03)	0.27
Grade (overall)		0.61
Low (Grade 1 or 2)		
High (Grade 3 or 4)	0.88 (0.54–1.42)	0.60
Unknown	0.67 (0.30–1.53)	0.34
Race		
Caucasian		
African-American	1.58 (0.94–2.63)	0.08
Treatment		
Surgery alone		
Surgery + AT	1.16 (0.67–2.02)	0.59

AT, additional therapy: chemotherapy and/or radiotherapy.

a rare disease entity. Moreover, few studies have ventured to analyse independent predictors of OS in advanced penile cancer. Notable to mention is a study by Pond et al. [13], wherein visceral metastasis and/or a score ≥ 1 on the Eastern Cooperative Oncology Group Performance Scale were shown to be independent predictors of OS. Nevertheless, their prognostic modelling did not factor in the demographic component of race and its impact on outcome. However, based on our present findings, AAM with pSCC are at greater risk of mortality and these data suggest that external factors such as disease biology, access to care, or a combination of both may play a role.

A recent study of patients from the National Cancer Database demonstrated similar findings with Black race being a

significant predictor of worse OS amongst men with pSCC. Compared to White men, Black men presented at a younger age and with a higher stage [9]. Interestingly, even amongst low-stage pSCC (pT1, N0), which is relatively curable, Black men had worse OS and the authors suggested that access to care may partly explain the difference in outcome. Other studies have failed to show an association between race and survival amongst men with both low-risk and advanced pSCC [14]. This difference may likely be due to small sample size and a low event rate. However, Rippentrop *et al.* [8] analysed race and outcome amongst an older series (1973–1998) of patients in the SEER database and demonstrated, similar to the present study, that AAM presented at a younger age and had lower disease-specific survival compared with CM. In addition, they found that AAM had a 2.2-fold greater risk of death when controlling for age, stage, lymph node status, and marital status [8]. It is noteworthy that despite the difference in time periods between the present study and that of Rippentrop *et al.* [8], the trends in presentation and outcomes of AAM have not significantly changed and suggest that there may be socioeconomic factors leading to racial disparity in survival outcomes.

The findings that AAM in our present cohort present at a younger age and with more advanced disease compared to CM is concerning and emphasises the need to improve access to care in this population to help improve mortality. AAM with signs of pSCC may be less likely to seek medical attention, thereby delaying diagnosis, which can lead to detrimental outcomes. Moreover, in our present cohort the median age of presentation for AAM was 60 years (vs 66 years for CM), which is below the age of eligibility for Medicare in the USA (65 years), which may bolster the delay in seeking medical treatment in this group. There is very little data regarding public education for pSCC; however, given the significant harm related to delay in diagnosis and treatment, it is possible that educational programmes targeted towards AAM may be of benefit. Alternatively, our present findings could be explained by a difference in tumour biology between AAM and CM; however, there is very limited data to support this hypothesis. Studies suggest a role for HPV in pSCC, and its role in other malignancies, in particular, cervical cancer is well established [15]. Emerging data suggest a racial difference in HPV positivity amongst African-American females and European females, but no such data exist in men [16]. It is possible that a potential difference in HPV exposure may play a role in the differences noted for pSCC presentation and outcomes between AAM and CM, and further investigation in this field is needed. Additionally, due to the high likelihood of advanced disease in AAM, we recommend trials with promising, newer, targeted therapies directed towards programmed death-ligand 1 and epidermal growth factor receptor [17–19].

Strengths of the present study include the relatively large sample size from a contemporary cohort of pSCC, and the proportion of AAM (14%), which is slightly higher than recent national USA census estimates (12.6%). Other studies have been limited by the relatively low representation of AAM in those series [14]. However, there are limitations to the present study that are worth mentioning. First, we did not have sufficient data to incorporate socioeconomic status in our analysis and therefore cannot conclude that the poor outcomes in AAM are mainly due to access to care and treatment disparity. Second, the FCDS does not provide information on cause of death and comorbidity, therefore we cannot comment on cancer-specific survival or whether differences in OS are due to competing risks amongst men with pSCC. Third, we do not have sufficiently granular treatment data to determine the exact sequence of treatments for those receiving multimodal care, exact type of multimodal therapy or the timing of surgical therapy (penectomy and lymphadenectomy), all of which can impact treatment outcome. Fourth, we were unable to incorporate changing trends and utilisation of multimodal therapy during our study time-frame in our model. Nevertheless, our present findings underscore the need for further investigation in a rare disease entity with significant racial disparity in outcomes.

In conclusion, AAM with pSCC present at a younger age and with advanced stage relative to CM. There was significant racial disparity in survival, with AAM having a shorter median OS compared to CM. African-American race was also predictive of worse OS when controlling for known predictors of survival including: age, grade, stage, and treatment type. Further research is necessary to define the socioeconomic and possible biological factors leading to racial disparity in pSCC outcomes.

Conflict of Interest

None of the contributing authors have any conflict of interest, including specific financial interest or relationships and affiliations to the subject matter or materials discussed in the manuscript.

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Abbreviations: AAM, African-American men; CM, Caucasian American men; FCDS, Florida Cancer Data System; HPV, human papillomavirus; IQR, interquartile range; OS, overall survival; pSCC, penile squamous cell carcinoma; SEER, Surveillance, Epidemiology and End Results.