review articles

Disparities in Oral Cancer Stage at Presentation in a High HIV Prevalence Setting In Sub-Saharan Africa

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abstract

PURPOSE Oral cancer is the sixth most common cancer worldwide and is the seventh most common in Botswana. Lack of improvement in oral cancer survival despite the availability of multiple treatment options may be due to the high prevalence of advanced stage at presentation. We identified risk factors for presenting with oral cancer at an advanced stage to facilitate interventions to reduce mortality from oral cancers.

METHODS A retrospective cohort analysis was conducted among individuals with biopsy-confirmed oral cancer at Princess Marina Hospital in Gaborone, Botswana, between 2010 and 2020. Data collected included age at diagnosis, sex, place of residence, HIV status, oral cancer stage, and oral subsite. Multivariable analyses were controlled for age, sex, district of residence, and oral subsite.

RESULTS Of the 218 records analyzed, 79% were male, 58% were HIV-positive, the median age was 56 years (interquartile range: 47-63), and 67% presented with advanced-stage disease. Cancers from hidden oral sites were more likely to present at an advanced stage with an adjusted odds ratio (OR) of 2.98 (95% CI, 1.29 to 6.89; $P = .01$). Residence in socioeconomically disadvantaged districts was associated with higher likelihood (OR, 2.36; 95% CI, 1.28 to 4.39; $P = .01$) of advanced stage presentation compared with other districts. HIV infection was not associated with risk of advanced lesion presentation (OR, 1; 95% CI, 0.61 to 1.61; $P = .97$).

CONCLUSION Hidden oral cancer sites and residence in districts with limited access to care were risk factors for advanced oral cancer at the time of diagnosis in Botswana. These findings support a need to increase efforts to improve access to care and increase oral cancer awareness to decrease the burden of advanced oral cancer.

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INTRODUCTION

Oral neoplasms are the sixth most common malignancy worldwide, with approximately 75% of cases and deaths attributable to oral neoplasms in developing countries.[1-4] More than 90% of oral cavity cancers in the world are squamous cell carcinomas.[3-5] On average, more than half of patients with oral cancer worldwide present with advanced-stage disease (stages III and IV).[6,7] Despite improved efficacy of surgery, radiation, and chemotherapy as treatments,[8-10] overall survival for oral cancer has not improved significantly.[11] Generally, early detection of oral cancer improves 5-year survival to more than 80%, compared with as low as approximately 20% overall 5-year survival for advanced disease across the world.[12] Major causes of diagnostic delay include the relatively painless nature of the lesion making it easy to ignore, difficulty accessing care because of distance from care sites, poverty and limited time to attend clinics, and lack of recognition by clinicians.[11] Other conditions, such as HIV, also contribute to worse outcomes.[13,14]

Botswana is a sub-Saharan African country with a high HIV prevalence and an extensive network of clinics focused on HIV care with a predominantly urban population.[15] There is strong regional correlation to poverty, and the North-West, Ghanzi, Central, and Kweneng districts are the poorest.[16] According to the Botswana Ministry of Health, 84% of the Botswana population lives within 5 km of the nearest health facility.[17] However, on average, 39% of people living in Kweneng, Central, and Ghanzi districts live 5-15 km from the nearest health facility compared with 20% in the other remaining districts.[17]

HIV treatment in Botswana has been highly successful,[18] and the burden of comorbidities from HIV resulting in morbidity and mortality is a major focus of the Ministry of Health. Cancers, including oral cancer, threaten the increased life expectancy gained with improvement in HIV outcomes.[19,20] In 2020, oral cancers were the eighth most common cancer diagnosed among women and men and the fourth most commonly diagnosed among men in Botswana.[21] However, few

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CONTEXT

Key Objective

Are there other risk factors which we could be missing that contribute to advanced-stage presentation of oral cancer in sub-Saharan African settings with high prevalence of HIV infection**?**

Knowledge Generated

Oral cancer primary site and place of residence were significantly associated with presentation of oral cancer at an advanced stage. Cancers originating from hidden oral sites, tongue, floor of the mouth, buccal mucosa, palate, maxilla, and gingiva were three fold more likely to present at an advanced stage compared with other oral sites. Individuals from poor districts were more likely to present with advanced-stage disease compared with those from districts above median income. Despite immunosuppression associated with HIV and robust HIV care infrastructure in Botswana, HIV status was neither a risk factor nor protective factor for stage at presentation.

Relevance

Media campaigns and incorporation of intraoral examination into routine care need to be assessed to increase early-stage presentation of oral cancers.

studies describe oral cancer stage distribution and the risk factors for advanced-stage oral cancers in Botswana. To fill this gap, we conducted a retrospective analysis of oral cancer stage at presentation in Botswana to identify risk factors that might lead to improvement in intervention and ultimately morbidity and mortality.

METHODS

Study Design and Participants

This retrospective cohort analysis was carried out at Princess Marina Hospital in Gaborone, Botswana, between 2010 and 2020. Princess Marina is one of two hospitals in Botswana that provide maxillofacial surgery and oncology care. Data were abstracted from the Princess Marina Oncology Registry, National Oncology Database, Botswana Cancer Cohort Study, and the national Integrated Patient Management System electronic database. A total of 596 records of patients with oral cancer confirmed by histopathology were assessed. Only patients with complete data were included. Final analysis included 218 patients (37% of all cases reviewed). Consent waiver was granted, and the study was approved by the Ministry of Health and Wellness, Botswana, Princess Marina Hospital and the University of Pennsylvania institutional review board.

Measurement of Variables

Patients with oral cancer were categorized as early (I and II) or advanced (III and IV) stage on the basis of differences in prognosis and treatment plan.[6] Staging was assessed using the American Joint Committee on Cancer TNM staging system.[22,23] During this period, manuals in stage classification for cases included in our analysis were the seventh edition up to 2017 and eighth edition to 2020.

Age was analyzed as a continuous variable. District of residence was a priori dichotomized as lower or greater access to care on the basis of the poverty rate and distance from the nearest health facility. In 2009/2010, the average poverty rate in Botswana was 20%.[16] Districts with poverty rate above average were considered to be of high poverty rate and those with below average as having low poverty rate. The Central, Kweneng, and Ghanzi districts, which share boundaries and have high poverty rates and longer distances to health facilities,[17] were grouped as socioeconomically disadvantaged districts and compared with all other districts as a group. Oral anatomical sites included in our analyses were classified according to the tenth revision of the International Classification of Diseases (ICD-10) with codes C00-C08 and C41.[24] Anatomical cancer sites were a priori categorized on the basis of visibility of the lesion—lesions physically hidden from sight were compared with overtly visible lesions. Cancers of the salivary glands, mandible, and lip were considered overtly visible because they manifest predominantly extraorally while cancers originating from the tongue, floor of the mouth, buccal mucosa, palate, maxilla, and gingiva manifest predominantly intraorally and were, therefore, hidden from view. HIV status was extracted from Integrated Patient Management System and the National Oncology Database. HIV testing was assessed using the enzyme-linked immunosorbent assay and antibody-antigen rapid test and was categorized as known positive, negative, or unknown.

Statistical Analyses

Data were abstracted into a REDcap database, and analyses were performed using STATA 14 software (STATA Corp, College Station, TX). The primary outcome was oral cancer stage at presentation. Data distribution was tested using the skewness/kurtosis test. In unadjusted analyses, chi square tests were used to evaluate differences in categorical variables, and *t* tests were used to assess differences in continuous variables between individuals who presented with early-stage compared with advanced-stage cancers. Multivariable logistic regression was used to control for confounding variables. Statistical tests were two-sided, and $P \leq .05$ was considered statistically significant.

TABLE 1. Baseline Characteristics of Patients Diagnosed With Oral Cancer at Princess Marina Hospital Between 2010 and 2020

Variable	Early-Stage Oral Cancer (n = 73; 33%)	Advanced-Stage Oral Cancer (n = 145; 67%)	Total (N = 218)	*P*
Sex, No. (%)				.02
Male	51 (70)	121 (83)	172	
Female	22 (30)	24 (17)	46	
Mean age, years (SD)	52 (13.9)	56 (13.4)	55	.04
HIV status, No. (%)				
Positive	33 (45)	53 (37)	86	.21
Negative	39 (53)	84 (58)	123	
Unknown	1 (1)	8 (6)	9	
District, No. (%)				
Central, Kweneng, or Ghanzi	23 (32)	73 (51)	96	.007
Others	50 (68)	71 (49)	121	
Tumor site, No. (%)				.002
Overt sites (salivary gland, mandible, and lip)	18 (25)	13 (9)	31 (14)	
Hidden sites (tongue, floor of mouth, buccal mucosa, palate, maxilla, and gingiva)	55 (75)	132 (91)	187 (86)	

Covariates significantly associated with advanced-stage oral cancer at presentation in univariate analysis were fit into the model, and age was considered clinically relevant and, therefore, forced into the model irrespective of *P* value. Included variables were sex, HIV status at time of diagnosis, hidden vs overt oral cancer primary site, district of residence, age at date of diagnosis, and oral cancer stage. Other risk factors such as human papilloma virus and Epstein-Barr virus status were excluded as they are not routinely tested during histopathology analysis.

Power and Sample Size

A sample size of 218 was determined to provide 80% power to detect a 20% difference in the prevalence of any risk factor between those presenting early compared with late stage, assuming a prevalence of the risk factor as low as 10% in early-stage individuals and a ratio of 2:1 late-stage: early-stage individuals.

RESULTS

Patient baseline characteristics are summarized in Table 1 according to early- and advanced-stage cancer at presentation. The study cohort was predominantly male, and more than two-thirds presented with advanced oral cancer. Patients with advanced cancers were significantly older than those with early-stage cancer. HIV status did not significantly differ between the groups. Among patients with HIV, median CD4 count did not differ between patients with early-stage (452 cells/μL, interquartile range: 209-596) and late-stage disease (350 cells/μL, interquartile range: 216-515). Additionally, there was a significant difference in cancer stage at presentation among individuals residing in the Central,

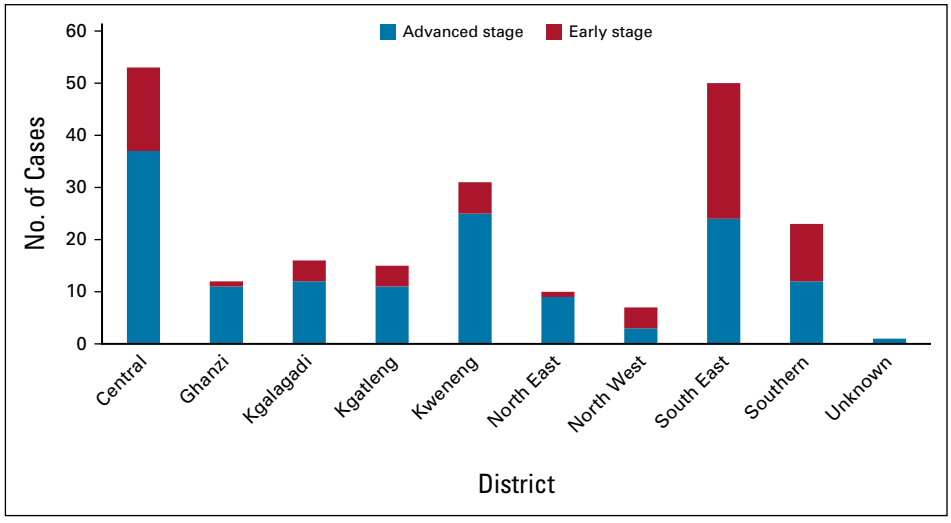

FIG 1. Distribution of oral cancer stages at presentation by district of residence.

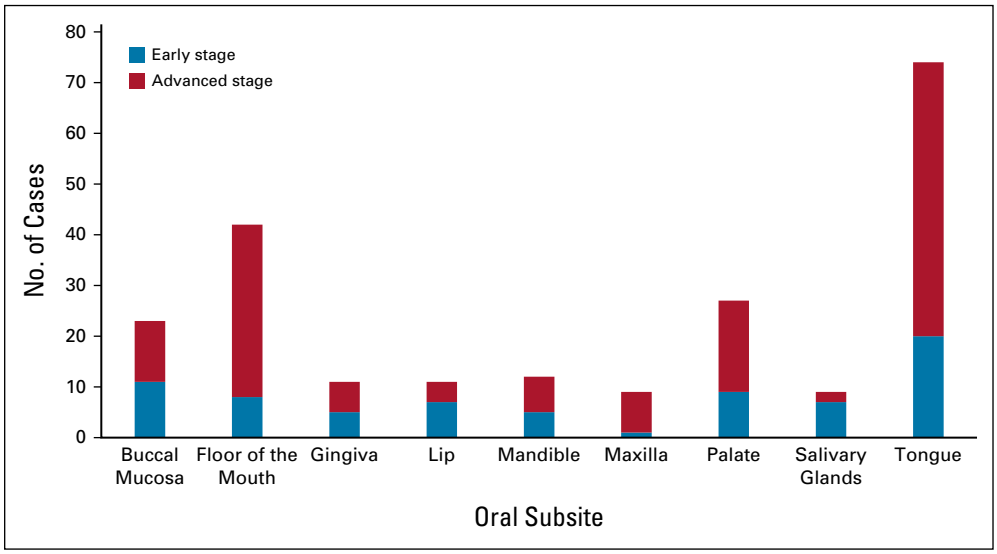

FIG 2. Stage distribution of oral cancer subsite at presentation.

Kweneng, and Ghanzi districts, with most patients from these districts presenting with advanced-stage oral cancer compared with other districts. When comparing tumors from the salivary gland, mandible, and lip versus cancers originating from other sites in the mouth, stage at presentation was significantly associated with location of the primary tumor (Table 1). More than half (58%) of the population with cancers originating from overt anatomical sites presented with early-stage oral cancer compared with 29% of cancers originating from hidden sites

Figure 1 shows the number of patients diagnosed with early- and advanced-stage oral cancers and their respective districts of residence. Oral cancer stage at presentation differed significantly across districts ($P = .009$). All districts except South East had more patients with advanced-stage compared with early-stage cancer.

Figure 2 displays differences in oral cancer stage at presentation across oral sites ($P = .003$). Most patients presented with advanced-stage oral cancer for most oral subsites except cancers originating from the lip and salivary gland. The tongue was the most frequently involved oral cavity site, followed by floor of the mouth and palate. Maxilla, lip, and gingiva were the least common cancer sites.

Table 2 displays unadjusted and adjusted odds ratios of the association of various characteristics with advanced-stage oral cancer at presentation. The adjusted model included all listed variables in univariate analysis except HIV status. Males were much more likely than females to present with advanced-stage oral cancer. Living in poor districts with less access to care and having cancer in hidden sites significantly increased the risk of presenting with advanced tumors. These findings remained significant in adjusted models except for male sex. There was no effect of HIV status on stage at presentation in the univariate analysis.

DISCUSSION

Oral cancer is a pressing global public health problem. Lack of improvement in survival of advanced-stage disease despite advances in therapeutic options presents a continuing challenge, especially in regions where most patients present with advanced-stage disease. In this retrospective cohort analysis in a population with a high rate of HIV, risk factors for presenting with advanced disease were primary

TABLE 2. Unadjusted and Adjusted ORs of Characteristics Associated With Advanced Oral Cancer at Presentation

Variable	Crude OR (95% CI)	C-Statistic, Univariable Model	Adjusted OR (95%CI) C-Statistic 0.6669
Male sex	2.17 (1.12 to 4.23)	0.5679	1.60 (0.77 to 3.29)
HIV positive	1.0 (0.61 to 1.61)	0.5126	—
Age (per year)	1.02 (0.997 to 1.041)	0.5559	1.01 (0.99 to 1.03)
District			
Central, Kweneng, and Ghanzi	2.24 (1.24 to 4.04)	0.5959	2.37 (1.28 to 4.39)
Site			
Hidden site	3.32 (1.52 to 7.25)	0.5785	2.98 (1.29 to 6.89)

Abbreviation: OR, odds ratio.

anatomical site of oral cancer and residing in a low socioeconomic area with little access to care.

Approximately two thirds of patients presented with advanced-stage oral cancer. This is significantly higher than the global estimate of 50%.[6-25] This finding is similar to that of oral cancer in Brazil[26] and a report of head and neck cancers in Botswana.[20] Late presentation is likely multifactorial[27,28] and related to lack of awareness and limited access to health care, which is associated with poor socioeconomic circumstances encountered more frequently in developing countries than in developed countries.[29]

Oral cancer was more common in men than women, similar to previous oral cancer findings.[30-32] This may result from high rates of smoking and alcohol consumption in men compared with women.[33,34] We were unable to analyze this association in our cohort because of lack of data on smoking and alcohol consumption. However, in Botswana, smoking and alcohol consumption are more prevalent among males than females,[35] suggesting possible correlation. The current study showed that males were also more likely to present with advanced disease, similar to previously reported findings.[28] This may be because men are reluctant to seek medical care,[28] and women are more well-informed about oral cancer compared with men.[36]

Living in a district with little access to care was a risk factor for presenting with advanced disease. Similar findings have been previously identified as a risk factor in head and neck squamous cell carcinoma,[37,38] colorectal cancer,[39] melanoma,[40] and breast cancer[41] as well as in recent systematic review.[42] Central and South East districts had the highest cases of oral cancers, and the Central district reported higher cases of advanced-stage oral cancer compared with the South East. However, we were unable to evaluate individual access to care because these data were not available in our study.

We also found that lesions originating from the lip and salivary gland presented earlier than other oral subsites. This is contrary to previous findings in which these sites are associated with late disease presentation in Ireland.[43] Studies in Taiwan and Brazil, however, showed that cancers of the lip are more likely to present at an early stage.[44] This discrepancy could be due to differences in culture. It supports our hypothesis that lesions that alter facial esthetics are more easily noticed by patients. They may also be stigmatizing than hidden lesions hence being presented at an early stage. It could also be that any form of disfigurement causes concern, and although patients are aware of sores in the oral cavity, they may not realize that they are cancerous.

Our results show that HIV status was not associated with timing of presentation of oral cancer, consistent with previous findings in neighboring South Africa.[45] HIV infection causes immune suppression and promotes carcinogenesis and thus may increase the risk of advanced oral cancer. However, because of robust antiretroviral treatment and HIV care in Botswana, the risk of oral cancer may be lessened in immunocompromised individuals.[46] Furthermore, close follow-up of patients with HIV by primary caregivers not only ensures virological control of HIV[47] but also may encourage health awareness and promote early diagnosis. Unfortunately, our study was unable to assess the characteristics of the clinical visits.

As in many sub-Saharan African countries, the HIV clinics in Botswana comprise among the most robust components of the medical infrastructure. Yet, despite the potential for identifying head and neck cancer earlier in those with HIV than those without, we found no difference in stage of presentation by HIV status. This finding suggests that additional access to care not specifically designed to assess for these lesions may not be sufficient to identify head and neck cancers at earlier stages in such settings.

A strength of our study was the capture of cases from across Botswana, providing data from a range of socioeconomic backgrounds. However, limitations include the inability to fully characterize the effect of patient health-related behaviors such as smoking and alcohol consumption, comorbidities, socioeconomic status, and negligence of hidden lesions. Because we were unable to prospectively interview our cohort, future studies are needed to evaluate these factors.

In conclusion, disparities in oral cancer stage at presentation in Botswana were related to access to care and oral cancer primary site. This study affirms the need to conduct a prospective study with a qualitative component to understand patient experiences, including identifying factors associated with care-seeking behavior and how to implement intervention efforts. Additional infrastructure and informational campaigns may be warranted to encourage routine oral examination and improve access to health care facilities in some districts. This infrastructure could be extended to HIV and non-HIV clinics to incorporate oral cancer screening as part of routine care. This may, in turn, increase public awareness on oral cancer and assist efforts to reduce oral cancer-related health costs and mortality.

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S.G. and R.G. contributed equally to this work.

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