RESEARCH ARTICLE

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Prognosis of South Asian Buccal Mucosa Cancer Patients in the United States: Association of Race with Overall Survival

Stephen Joseph Sozio[1]*, Sachin R. Jhawar[2], Shengguo Li[3], Hao Liu[3], Mutlay Sayan[4], Rahul Parikh[1], Anupama Chundury[5], Sung Kim[1]

Abstract

Background: Squamous Cell Carcinoma (SCC) of the buccal mucosa and gingiva accounts for approximately 10% of oral and pharyngeal cancers diagnosed in the United States each year, with a disproportionally higher incidence in individuals of South Asian descent. However, little has been documented regarding trends pertaining to overall survival. Thus, this research serves to identify predictors of survival and determine if overall survival (OS) differs for South Asians compared to other races once they develop non-metastatic buccal mucosa or gingiva squamous cell carcinoma. **Methods:** A population-based, cohort study of patients registered in the National Cancer Database® (NCDB) between the years 2004-2016 was performed. Kaplan-Meyer Survival Curves were executed to examine overall survival, while univariable (UVA) and multivariable analysis (MVA) was performed to determine the effect of multiple variables on OS. **Results:** South Asians had longer median OS at 88.7 months, compared to 58.6 months and 38.3 months for Caucasians and African Americans respectively ($p<0.001$). In UVA, race was highly significant, but when the cohort was selected to include only those who had undergone surgical resection, no statistically significant difference remained. On MVA, lack of surgery, older age, higher grade, higher T and N stage, use of chemotherapy, higher comorbidity scores were associated with worse OS, but race was not significant. **Conclusion:** South Asians in the US with non-metastatic buccal mucosa or gingiva SCC have better OS compared to Caucasians or African Americans, likely due to younger age at diagnosis (median 59 vs. 71 and 62 years old) and more frequent surgical resection (75% vs. 72% and 64%). In MVA, South Asians have similar OS as Caucasians.

Keywords: Survival- race- cancer- squamous cell carcinoma

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Introduction

Squamous Cell Carcinoma (SCC) of the buccal mucosa and gingiva accounts for approximately 10% of oral and pharyngeal cancers diagnosed in the United States each year [1-3]. The incidence of buccal mucosa and gingiva SCC is disproportionately high in South Asian populations throughout the world, attributable in part to their use of Betel nut [3, 4]. Betel nut is often used in combination with tobacco and other spices, and is placed in the oral cavity and vestibule to be chewed and expectorated. Betel nut has mood enhancement and psychostimulatory properties, but also induces tumorigenesis through multiple cellular mechanisms, including through induction of proto-oncogene expression and generation of reactive oxygen species [5-8].

Previously, our group utilized the National Cancer Database® (NCDB) to investigate the incidence of head and neck SCC in different populations living within the United States [3]. We found that the incidence of buccal mucosa SCC in particular, was higher in South Asians than in Caucasians and African-Americans, while other more common cancers (such as oropharynx cancers) were less common in South Asians. We theorized that this paradox was due to frequent use of Betel nut products within the South Asian community [3]. In contrast, little is known regarding the relative prognosis of South Asians in the US once they develop buccal mucosa or gingiva SCC. Because the drivers of this disease may be unique for South Asians, in part due to the use of Betel nut, this study aims to determine if overall survival (OS) differs for South Asians compared to Caucasians and African Americans once they develop non-metastatic buccal

*[1]Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, United States. [2]Department of Radiation Oncology, Ohio State University Comprehensive Cancer Center, Columbus, OH, United States. [3]Department of Biostatistics & Epidemiology, Rutgers School of Public Health, United States.[4]Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA, United States. [5]Department of Radiation Oncology, Loyola University, United States. *For Correspondence: sjs335@cinj.rutgers.edu*

mucosa or gingiva SCC.

Materials and Methods

The sample for this study was built from the National Cancer Database® (NCDB), a comprehensive database of oncology patient data compiled from over 1,500 hospital tumor registries throughout the United States, which was collected between the years 2004-2016. In total, this data encompasses approximately 70% of new cancers diagnosed throughout the United States during this time [9]. University IRB approval was not required, as the sample was compiled from a publicly available, de-identified database.

Raw data of those patients diagnosed with gum of mouth, oral cavity, and oropharyngeal SCC was initially extracted from NCDB, as delineated by ICD-O 8070-8076. As those suffering a primary buccal mucosa or gingiva neoplasm are spread among multiple datasets, a single, composite sample was formed to include only patients diagnosed with a buccal mucosa/vestibule or gingiva primary site by utilizing the following ICD-10 codes: C03.0 (Malignant neoplasm of gum), C03.1 (Malignant neoplasm of lower gum), C03.9 (Malignant neoplasm of gum, unspecified), C06.0 (Malignant neoplasm of cheek mucosa), and C06.1 (Malignant neoplasm of vestibule of mouth). Next, data was filtered to include only those of Caucasian, African-American, or South Asian race (defined as being of Pakistani or Indian descent, based on available data in NCDB) who have known follow-up data after the completion of treatment. Lastly, as we only intended to study potentially curable cases, those with metastatic disease at the time of initial diagnosis, as delineated by clinical M score, and those who had undergone treatment with palliative intent, were excluded from the final sample.

Statistical Analysis

After the final dataset of patients with non-metastatic, primary buccal mucosa or gingiva SCC was compiled, Kaplan-Meyer Survival Curves were then built for all races, with OS rates compared utilizing the log rank test. Additionally, descriptive statistics were performed, as well as univariable cox analyses on the following variables: race, age at diagnosis (in 10-year increments), sex, tumor grade, clinical T and N stage, median time from diagnosis to start of treatment, median distance traveled by patient from residence to location of treatment, treatment modalities received (surgery, chemotherapy, and/or radiation therapy), and Charlson Comorbidity Index (CCI, CDCC). Variables which had a p-value < 0.20 on univariable analysis (UVA) were then included in the subsequent multivariable analysis (MVA). Stepwise variable selection based on AIC (Akaike Information Criterion) was utilized to obtain the final model, the results of which were reported. Statistical significance was established at p-value < 0.05. R v.4.1.2 was utilized to conduct the analyses [10].

Results

Descriptive statistics for the entire cohort are illustrated in Table 1. Overall, a total of 426 South Asians, 19,754 Caucasians, and 1,399 African-Americans diagnosed with primary buccal mucosa or gingiva SCC were included in the analysis. South Asians had a considerably younger age at diagnosis (median 59 vs. 71 and 62 years old, respectively; p<0.001) and male predominance (78% vs. 51% and 47%, respectively; p<0.001), when compared to Caucasians or African-Americans. Caucasians had less advanced nodal disease, with more N0 disease and less N2 disease; however, South Asians had fewer Grade 3 tumors. Notably, South Asians more often underwent surgical resection than the other races (75% vs. 72% and 64%, respectively; p<0.001), and received radiation therapy (49.8% vs. 38% and 48.6%, respectively; p<0.001).

Figure 1 illustrates the Kaplan-Meier Survival Curve for OS for patients with buccal mucosa SCC by race. South Asians had longer median survival at 88.7 months,

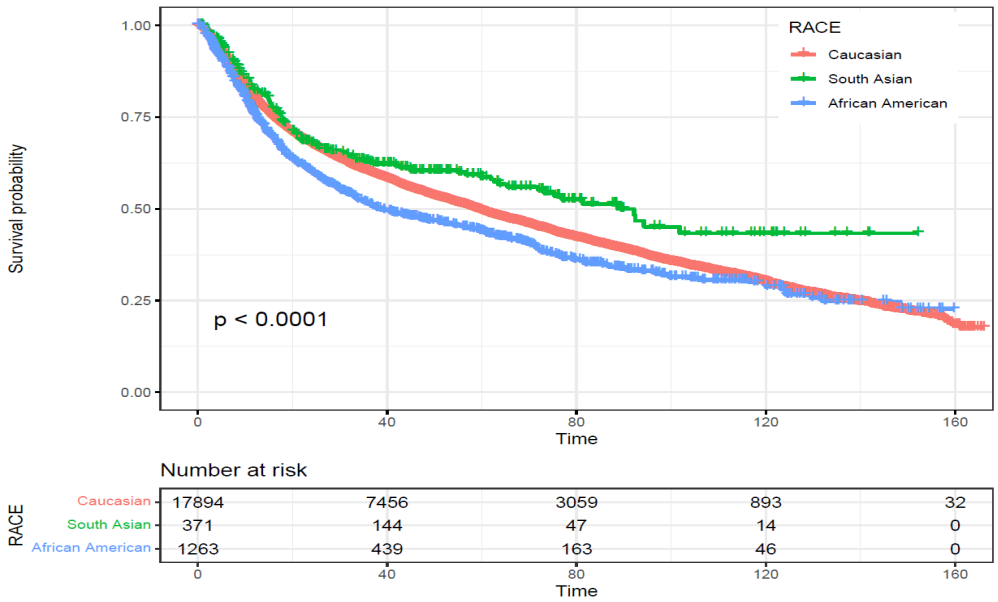

Figure 1. Overall Survival of Buccal Mucosa Patients by Race.

Table 1. Descriptive Statistics of Cohort of Caucasians, African-Americans, and South Asians Treated in the United States for Buccal Mucosa Squamous Cell Carcinoma, as recorded in NCDB between 2004-2016

	Descriptive Statistics			
N	South Asian 426	Caucasian 19754	African-American 1399	p-value
Median age at Diagnosis	59 (IQR 52-67)	71 (IQR 61-80)	62 (IQR 52-74)	<0.001
Sex				<0.001
Male	333 (78.17%)	10126 (51.26%)	665 (47.53%)	
Female	93 (21.83%)	9628 (48.74%)	734 (52.47%)	
Grade				<0.001
1	106 (24.88%)	5687 (28.79%)	355 (25.38%)	
2	214 (50.23%)	8680 (43.94%)	578 (41.32%)	
3	35 (8.22%)	2346 (11.88%)	217 (15.51%)	
4	2 (0.47%)	95 (0.48%)	8 (0.57%)	
Unknown	69 (16.20%	2946 (14.91%)	241 (17.23%)	
Clinical T-Score				<0.001
T0	1 (0.23%)	43 (0.22%)	2 (0.14%)	
T1	79 (18.54%)	4798 (24.29%)	206 (14.72%)	
T2	102 (23.94%)	3785 (19.16%)	234 (16.73%)	
T3	27 (6.34%)	1145 (5.80%)	96 (6.86%)	
T4	117 (27.46%)	5447 (27.57%)	560 (40.03%)	
Unknown	100 (23.47%)	4536 (22.96%)	301 (21.52%)	
Clinical N-Score				<0.001
N0	228 (53.52%)	12735 (64.47%)	719 (51.39%)	
N1	48 (11.27%)	1732 (8.77%)	151 (10.79%)	
N2	82 (19.25%)	2111 (10.69%)	280 (20.01%)	
N3	1 (0.23%)	69 (0.35%)	15 (1.07%)	
Unknown	67 (15.73%)	3107 (15.73%)	234 (16.73%)	
Clinical Extranodal Extension				<0.001
Absent	187 (43.90%)	7979 (40.39%)	480 (34.31%)	
Present	60 (14.08%)	1854 (9.39%)	197 (14.08%)	
Unknown	179 (42.02%)	9921 (50.22%)	722 (51.61%)	
Median Time from Diagnosis to Treatment (weeks)	4.86 (IQR 2.17-7)	4.57 (IQR 2-7)	5.07 (IQR 2.11-8)	<0.001
Surgical Resection				<0.001
No	105 (24.65%)	5574 (28.22%)	505 (36.10%)	
Yes	321 (75.35%)	14148 (71.62%)	891 (63.69%)	
Unknown	0 (0%)	32 (0.16%)	3 (0.21%)	
Radiation				<0.001
No	212 (49.77%)	12031 (60.90%)	707 (50.54%)	
Yes	212 (49.77%)	7563 (38.29%)	680 (48.61%)	
Unknown	2 (0.47%)	160 (0.81%)	12 (0.86%)	
Chemotherapy				<0.001
No	296 (69.48%)	15916 (80.57%)	978 (69.91%)	
Yes	114 (26.76%)	3152 (15.96%)	361 (25.80%)	
Unknown	16 (3.76%)	686 (3.47%)	60 (4.29%)	
CDI Score				<0.001
0	312 (73.24%)	14871 (75.28%)	1022 (73.05%)	
1	92 (21.60%)	3588 (18.16%)	269 (19.23%)	
2	18 (4.23%)	903 (4.57%)	53 (3.79%)	
3	4 (0.94%)	392 (1.98%)	55 (3.93%)	
Median Distance from Primary Residence to Treatment Site (miles)	12.3 (IQR 6.5-23.6)	19.1 (IQR 7.3-50.1)	9.6 (IQR 4.3-29.0)	<0.001
Median Time from Diagnosis to Last Follow-Up or Death (months)	27.0 (IQR 11.7-59.9)	30.8 (IQR 11.9-63.9)	23.0 (IQR 10.1-57.2)	<0.001

Table 2. Univariate Cox Analysis of Prognostic Factors Impacting Overall Survival, Illustrated for the Entire Cohort

Univariate Analysis		
Variable	HR (95% CI)	p-value
Race		
African-American vs. White	1.19 (1.10-1.28)	1.43E-05
South Asian vs. White	0.80 (0.68-0.94)	8.29E-03
Age (increments of 10 years)	1.37 (1.35-1.39)	0.00E -07
Sex (Male vs. Female)	0.96 (0.93-1.00)	0.065
Grade		
2 vs. 1	1.39 (1.32-1.46)	0.00E -07
3 vs. 1	1.90 (1.78-2.03)	0.00E -07
4 vs. 1	1.89 (1.47-2.45)	8.00E-07
Clinical T-Stage		
T0 vs. T1	0.99 (0.58-1.67)	0.96
T2 vs. T1	1.66 (1.55-1.77)	0.00E -07
T3 vs. T1	2.43 (2.23-2.65)	0.00E -07
T4 vs. T1	2.61 (2.46-2.77)	0.00E -07
Clinical N-Stage		
N1 vs. N0	1.81 (1.69-1.93)	0.00E -07
N2 vs. N0	2.40 (2.27-2.55)	0.00E -07
N3 vs. N0	5.26 (4.15-6.68)	0.00E -07
Clinical Extranodal Extension		
(Present vs. Absent)	2.25 (2.10-2.41)	0.00E -07
Median Time from Diagnosis to Treatment (weeks)	1.01 (1.010-1.018)	0.00E -07
Surgery (Yes vs. No)	0.59 (0.57-0.61)	0.00E -07
Radiation (Yes vs. No)	1.48 (1.42-1.54)	0.00E -07
Chemotherapy (Yes vs. No)	1.66 (1.58-1.73)	0.00E -07
CDI Score		
1 vs. 0	1.21 (1.15-1.27)	0.00E -07
2 vs. 0	1.61 (1.47-1.78)	0.00E -07
3 vs. 0	1.65 (1.44-1.89)	0.00E -07
Median Distance from Primary Residence to Treatment Site (miles)	1 (0.999-1)	6.85E-05

compared to 58.6 months and 38.3 months for Caucasians and African Americans respectively ($p<0.001$).

UVA of possible prognostic factors for OS (race, age, sex, grade, T & N stage, median time from diagnosis to treatment, whether the patient had surgery, radiation or chemotherapy, comorbidity score, median distance to treatment site) was performed (Table 2). In UVA, South Asians had less risk of death (HR 0.80, 95% CI 0.68-0.94) compared to Caucasians whereas African Americans had higher risk of death compared to Caucasians (HR 1.19, 95% CI 1.10-1.28). Older age (in 10-year increments) conferred higher risk of death, as did higher tumor grade, T stage, N stage, and comorbidity score. Surgical resection conferred less risk of death (HR: 0.59, 0.57-0.61), whereas radiation (HR: 1.48, 95% CI 1.42-1.54) and chemotherapy (HR: 1.66, 95% CI 1.58-1.73) were associated with higher risk of death. Neither sex or median distance from residence to treatment site were significant. To explore the overwhelming benefit of surgical resection, we repeated UVA on patients who had all received surgical resection (Table 3). In this very selected cohort, neither South Asian race (HR = 0.85, 95% CI: 0.70-1.04, p = 0.10 or African-American race (1.106, 95% CI: 0.996-1.228, p = 0.06) had significantly different OS compared to Caucasians.

On MVA, as illustrated in Table 4, the same prognostic factors were analyzed except for median distance from residence to treatment site. In MVA, neither South Asian race (HR 0.86, 95% CI 0.64-1.14, p=0.29) or African American race (HR: 1.12, 95% CI 0.96-1.31, p=0.13) had statistically different OS compared to Caucasians. Surgical resection continued to confer less risk of death (HR: 0.63, 95% CI 0.58-0.69, p=0.0E-07), while radiation therapy now also conferred lower risk of death (HR: 0.89, 95% CI 0.81-0.98, p=0.01). As expected, older age, higher grade, higher T stage, higher N stage, undergoing chemotherapy, and higher comorbidity score were associated with a higher risk of death. Propensity score matching was attempted but impossible due to unsatisfactory balance, based on an assessment using standardized mean differences.

Table 3. Univariate Cox Analysis of Prognostic Factors Impacting Overall Survival, Illustrated for Only Those that Received Surgical Resection

Variable	HR (95% CI)	p-value
Race		
African-American vs. White	1.10 (1.00-1.23)	0.059
South Asian vs. White	0.85 (0.70-1.04)	0.11
Age (increments of 10 years)	1.33 (1.30-1.35)	0.00E -07
Sex (Male vs. Female)	0.99 (0.95-1.04)	0.84
Grade		
2 vs. 1	1.47 (1.38-1.56)	0.00E -07
3 vs. 1	1.98 (1.83-2.14)	0.00E -07
4 vs. 1	1.90 (1.37-2.65)	1.36E-04
Clinical T-Stage		
T0 vs. T1	0.96 (0.43-2.13)	0.91
T2 vs. T1	1.57 (1.45-1.71)	0.00E -07
T3 vs. T1	2.18 (1.94-2.45)	0.00E -07
T4 vs. T1	2.28 (2.11-2.45)	0.00E -07
Clinical N-Stage		
N1 vs. N0	1.63 (1.50-1.78)	0.00E -07
N2 vs. N0	2.30 (2.13-2.47)	0.00E -07
N3 vs. N0	5.51 (3.68-8.24)	0.00E -07
Clinical Extranodal Extension		
(Present vs. Absent)	2.12 (1.94-2.31)	0.00E -07
Median Time from Diagnosis to Treatment (Weeks)	1.01 (1.01-1.01)	3.43E-05
Surgery (Yes vs. No)	N/A	N/A
Radiation (Yes vs. No)	1.31 (1.25-1.38)	0.00E -07
Chemotherapy (Yes vs. No)	1.49 (1.39-1.58)	0.00E -07
CDI Score		
1 vs. 0	1.30 (1.22-1.38)	0.00E -07
2 vs. 0	1.63 (1.46-1.81)	0.00E -07
3 vs. 0	1.78 (1.51-2.10)	0.00E -07
Median Distance from Primary Residence to Treatment Site (miles)	1.00 (1.00-1.00)	0.93

Discussion

Little is known about the natural history of South Asians who develop buccal mucosa or gingiva SCC in the United States. We found that South Asians in the United States with non-metastatic buccal mucosa SCC had better OS than their Caucasian and African American counterparts. The main drivers of this improved survival appear to be younger age at diagnosis and more frequent surgical intervention. While this study cannot isolate why South Asians would present at a much younger age than Caucasians or African Americans (median age at presentation: 59 vs. 71 and 62 years old, respectively), one plausible explanation may be the habitual use of betel nut. On MVA, surgical resection reduced the risk of death dramatically (HR: 0.63, 95% CI 0.58-0.69) and South Asians received surgery more often than Caucasians or African Americans. The finding that surgery would confer a survival advantage in this disease is not surprising, given that surgery remains the gold standard for primary treatment of buccal mucosa and gingiva SCC [11-14]. Compared to Caucasians, South Asians had better OS and African-Americans had worse OS on UVA, but these differences were no longer significant on UVA once the cohort was selected to include only patients receiving surgery, and remained non-significant on MVA.

Because the difference in median survival for buccal mucosa cancers was so striking in favor of South Asians (88.7 months, vs 58.6 months and 38.3 months), we did an exploratory analysis of NCDB data during the same period for other more common head and neck SCCs. When we analyzed oral cavity SCC (excluding buccal mucosa), South Asians had a median OS of greater than 160 months, compared to 75 months for Caucasians and 37.9 months for African Americans. In analyzing oropharynx SCC, South Asians had a median OS of 100.8 months, compared to 97.4 months for Caucasians and 32 months for African Americans. Thus, on first glance, it appears that South Asians have better OS relative to other races for a number of common head and neck SCC. The reason for this intriguing finding is beyond the scope of this study, but certainly worthy of future investigation.

In contrast, African Americans with buccal mucosa or gingiva SCC had worse OS than Caucasians, and had

Table 4. Multivariate Cox Analysis of Prognostic Factors Impacting Overall Survival, Illustrated for the Entire Cohort

	Multivariate Analysis	
Variable	HR (95% CI)	p-value
Race		
African-American vs. White	1.12 (0.96-1.31)	0.13
South Asian vs. White	0.86 (0.64-1.14)	0.29
Age (increments of 10 years)	1.44 (1.39-1.48)	0.00E -07
Sex (Male vs. Female)	1.10 (1.01-1.19)	0.02
Grade		
2 vs. 1	1.26 (1.16-1.38)	4.00E-07
3 vs. 1	1.59 (1.41-1.79)	0.00E -07
4 vs. 1	1.37 (0.79-2.37)	0.26
Clinical T-Stage		
T0 vs. T1	1.87 (0.77-4.54)	0.17
T2 vs. T1	1.45 (1.29-1.62)	0.00E -07
T3 vs. T1	1.92 (1.64-2.24)	0.00E -07
T4 vs. T1	2.10 (1.88-2.35)	0.00E -07
Clinical N-Stage		
N1 vs. N0	1.16 (0.99-1.35)	0.06
N2 vs. N0	1.43 (1.22-1.66)	5.30E-06
N3 vs. N0	2.40 (1.52-3.79)	1.50E-04
Clinical Extranodal Extension		
(Present vs. Absent)	1.35 (1.17-1.55)	4.30E-05
Median Time from Diagnosis to Treatment (weeks)	1.00 (1.00-1.01)	0.00E -07
Surgery (Yes vs. No)	0.63 (0.58-0.69)	0.00E -07
Radiation (Yes vs. No)	0.89 (0.81-0.98)	0.01
Chemotherapy (Yes vs. No)	1.38 (1.24-1.53)	0.00E -07
CDI Score		
1 vs. 0	1.10 (1.00-1.21)	0.04
2 vs. 0	1.40 (1.19-1.65)	4.00E-05
3 vs. 0	1.87 (1.50-2.32)	0.00E -07

higher grade tumors, higher clinical T and N stage, and lower rates of surgery than Caucasians or South Asians. Furthermore, during our exploratory look at oral cavity and oropharynx SCC, African Americans had remarkably worse OS compared to Caucasians or South Asians. Our findings seem consistent with current literature, which has found worse OS in African-Americans suffering buccal mucosa SCC when compared to Caucasians, South Asians, and Hispanics living in the United States [15].Other studies of buccal mucosa cancers in African-Americans have attributed this to decreased access to healthcare, more advanced disease upon initial evaluation for treatment, and lack of offering of surgery [15-17]. Interestingly, the median distance from residence to treatment site was closest for African Americans, but failed to confer a survival advantage.

Most of the other findings on MVA were consistent with previous literature. We found that older age, higher tumor grade, higher T and N stage and presence of comorbidities conferred worse OS [18-20]. Both chemotherapy and radiation conferred a worse OS in UVA, with chemotherapy retaining its worse OS upon MVA, which is in line with literature showing that chemotherapy cannot substitute for surgical resection for oral cavity cancers. However, upon MVA, radiation conferred an increased OS, which aligns with current literature that RT improves OS [21, 22].

Previously, our group had found that the incidence of buccal mucosa SCC was disproportionately high in South Asians residing in the United States compared to Caucasians and African Americans, and we theorized that this might be due to Betel nut use. The next logical question was how South Asians fare once they develop the disease, and here we demonstrate that they have improved survival compared to other races. The main reasons behind this appear to be younger age at diagnosis and more frequent surgical resection. Furthermore, improved OS for South Asians with head & neck cancer does not seem isolated to buccal mucosa cancers, but to apply to more common cancers as well. Our findings that South Asians do relatively better with head & neck cancer as well as the reasons for African Americans' consistently worse OS are questions that merit further investigation.

This research does carry certain limitations, particularly

surrounding its retrospective nature. NCDB only accounts for approximately 70% of new cancers diagnosed within the country, thus leaving 30% unaccounted for. Other factors were not available in NCDB for analysis, such as time from initial symptoms of disease to diagnosis, and specifics of surgery, radiation or chemotherapy. NCDB also does not catalog information surrounding disease-specific survival, thus requiring our research to focus on overall survival, which may introduce a potential confounder to the analysis. Additionally, as NCDB is a large database which is aggregated through multiple data collectors across the United States, specific imprecisions may be present within the dataset. Lastly, while increased incidence of buccal mucosa SCC has been well-documented within the South Asian community, little has been published regarding current screening practices for this neoplasm, which could result in lead-time bias.

In conclusions, South Asians residing within the United States who suffer non-metastatic buccal mucosa or gingiva SCC have better OS compared to Caucasians or African Americans, likely attributable to a younger age at diagnosis (median 59 vs. 71 and 62 years old) and more frequent surgical intervention (76% vs. 72% and 65%). However, in MVA, South Asian or African American race vs Caucasians were not significant. Additional prospective research to further explore these findings and their corresponding root causes is warranted.

Author Contribution Statement

Stephen J. Sozio, DO, MBS: Writing- Original and Revision, Study Design; Sachin R. Jhawar, MD: Study design, Writing - Revision; Shengguo Li, PhD: Study design, Statistical analysis; Hao Liu, PhD: Study design, Statistical analysis; Mutlay Sayan, MD: Writing - Revision; Rahul Parikh, MD: Study design, Writing - Revision; Anupama Chundury, MD: Study design, Writing - Revision; Sung Kim, MD: Study design, Writing – Original and Revision, Primary oversight.

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None.

Ethics Statement of Approval

N/A, as analysis was performed on publicly available data. This research was NOT part of a student thesis.

Availability of Data

Sample was obtained from the National Cancer Database (NCDB), a freely accessible dataset available to the public.

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