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Outcomes Of Human Papillomavirus-Associated Head And Neck Cancers

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An In-Depth National Study Examining the Prognostic Effects of the Human Papillomavirus based on Cancer Sub-site
&
the Effects of Patient Sex and Age on Human Papillomavirus-Associated Head and Neck Cancers

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

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Abstract

A STUDY ON THE PROGNOSTIC EFFECTS OF HUMAN PAPILLOMAVIRUS AT HEAD AND NECK CANCER SUBSITES, & THE EFFECTS OF PATIENT SEX & AGE ON HPV-ASSOCIATED HEAD & NECK CANCERS.

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Head and neck cancers are the 6th most common solid cancer in the world. Human papillomavirus (HPV) infections are now accepted to be a previously unrecognized causative agent for head and neck squamous cell carcinomas (HNSCCs). However, research surrounding HPV's effect at non-oropharynx sub-site is limited. There is also mixed literature over the prognostic effect of patient sex and age on overall survival in HNSCCs. We sought to utilize the National Cancer Database from 2004-2013 to evaluate the outcomes of the aforementioned objectives. Univariate and multivariate survival analyses were conducted with chi-square tests, Kaplan-Meier estimates, log-rank tests, and Cox proportional hazards multivariable modeling.

The main findings of the study were:

1. HPV-positive status was associated with survival at 4 tumor subsites: oral cavity (hazard ratio [HR], 0.76; 95% CI, 0.66-0.87), oropharynx (HR, 0.44; 95% CI, 0.41-0.47), hypopharynx (HR, 0.59; 95% CI, 0.45-0.77), and larynx (HR, 0.71; 95%

CI, 0.59-0.85). The HPV status was the greatest factor in survival outcome between the HPV-positive and -negative cohorts at the oropharynx subsite (77.6% vs 50.7%; survival difference, 26.9%; 95% CI, 25.6%-28.2%) and hypopharynx subsites (52.2% vs 28.8%; survival difference, 23.4%; 95% CI, 17.5%-29.3%). For the nasopharynx (HR, 1.03; 95% CI, 0.75-1.42) and sinonasal tract (HR, 0.63; 95% CI, 0.39-1.01) subsites, HPV-positive status was not an independent prognostic factor.

2. Though there were no significant differences in OS between the sexes in OP HPV-associated cancers, female sex was associated with worse OS in OP HPV- cancers (HR: 1.15; 95% CI 1.04–1.28, $p = 0.004$), whereas it was associated with improved OS in OC HPV-associated and HPV- cancers (HPV-associated: HR: 0.71; 95% CI 0.50–0.99, $p = 0.048$; HPV-: HR: 0.87; 95% CI 0.78–0.95, $p = 0.004$).

3. A younger age was independently associated with an improved OS in both OC and OPSCCs (OC- HR: 0.580; $p<0.001$; OP- HR: 0.556; $p<0.001$). Within the OPSCC group, age, however, still plays a secondary role to the effect of HPV (HPV-high risk serotype and young age significantly diminishes the chance of death by approximately 60% and 44% when compared to HPV-negative and old age respectively).

In conclusion, HPV positivity was associated with improved survival in 4 subsites (oropharynx, hypopharynx, oral cavity, and larynx), and the largest survival difference was noted in the oropharynx and hypopharynx subsites. In the nasopharynx and sinonasal tract subsites, HPV positivity had no association with OS. The effect of sex on OS in OC and OP SCC appears to vary based on tumor location and HPV status. Patients <40 years old have an improved OS compared to matched older controls.

As clinicians, when treating individual head and neck patients, it is important to consider all aspects of the patient and their disease (its cancer sub-site, HPV-positivity status, sex and age) to optimize overall survival for our head and neck cancer patients.

Acknowledgements

I would first like to thank my thesis advisor, Dr. Ben Judson of the Section of Otolaryngology, Department of Surgery at Yale University School of Medicine. The door to Dr. Judson's office was always open whenever I ran into a trouble spot or had a question about my research. He consistently allowed this research to be my own work but steered me in the right the direction whenever he thought I needed it. Thank you for being a supportive and wonderful mentor.

I would also like to acknowledge the William U. Gardner Memorial Student Research Fellowship at Yale University School of Medicine. The financial support made this research and thesis possible, and I am gratefully indebted to the foundation and school for the continued support for providing research opportunities for medical students.

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Hong "Linda" Li

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Introduction

Head and neck cancers are the 6th most common solid cancer in the world, with over 60,000 new cases a year.[1] Human papillomavirus (HPV) infections are now accepted to be a previously unrecognized causative agent for head and neck squamous cell carcinomas (HNSCC).[2] In the case of oropharyngeal squamous cell carcinomas (OPSCC), there has been as much as a 225% increase in HPV+ cancers between 1988 and 2004,[3] and up to 70% of new cases are caused by HPV.[2,4,5] HPV+ OPSCC patients generally use less tobacco and alcohol, and are more likely to be younger than their HPV- counterparts.[3,4] HPV+ status has a significant beneficial impact on prognosis, with one study reporting a 25% increase in survival at 3 years.[6] HPV+ OPSCC responds more positively to radiotherapy, which may possibly be related to defects in double-strand break repair.[7–9] This striking improvement has led to calls for de-intensification of treatment,[10] which are currently being investigated.[11–13]

OPSCCs are now hypothesized to behave distinctly compared to HNSCCs at other sites. HPV DNA has been discovered in tumors from other head and neck sites such as cancers of the oral cavity (OC).[14–16] A recent study found that HPV-associated non-OPSCCs display a distinct immune microenvironment and clinical behavior compared to HPV-associated OPSCCs.[17]

HPV's effects at Different Cancer Sub-sites

Investigation into non-OPSCC sub-sites, such as in the hypopharynx, nasopharynx, oral cavity, larynx, and sinonasal cavity, is relatively scarce. The literature that surrounds these other sub-sites is controversial. Studies revealed that HPV is present in these other sub-sites, albeit is estimated to be 5 times less prevalent in non-OPSCC than in OPSCC.[15,18–21] A 2016 study compared the gene expression and DNA methylation profiles between HPV in non-OPSCC sites and OPSCC, and found them to be identical, leading authors to conclude that HPV can drive carcinogenesis in non-OPSCC.[17] Interestingly, the same study concluded that HPV-driven non-OPSCC have a distinct tumor microenvironment compared to that of OPSCC. Few studies have looked at the role of HPV at each individual non-OPSCC sub-site. Tumors of some sub-sites, particularly nasopharyngeal, are rare, and so accurately characterizing the prognostic effect of HPV has been difficult.

HPV-associated HNSCCs in Women

Despite HPV infection being common in both men and women, the incidence of HPV-associated OPSCCs is more than two-fold higher among men than women.[22] This sex-specific finding raises questions regarding possible differences in the biological presentation of the cancer between men and women. To date, few studies have alluded to the sex-related differences in the prognosis for OPSCCs and other HNSCCs. One retrospective, multi-institutional study[23] found sex to be a significant prognostic factor for overall survival (OS) in OPSCCs even after accounting for HPV status. Interestingly, the

same study found that in non-OPSCCs, sex did not have any prognostic significance for OS.

HPV-associated HNSCCs in Young Patients

With an epidemiological shift in HNSCC pathogenesis to a virally-mediated disease, the average HNSCC patient has also changed. HPV-positive HNSCC patients are more likely to be white, male, have a higher socioeconomic status, and have had minimal exposure to tobacco and alcohol.[24–26] Furthermore, HPV-positive patients tend to be between 4 and 10 years younger than their HPV-negative counterparts.[24] It is an generally accepted that HPV-positive HNSCC has been shown to have better survival than HPV-negative cancers, [6,27–29] and, thus, a recent SEER study has shown an improvement in HNSCC prognosis in 2002-2006 compared to 1992 to 1996. This improvement held in all age groups, except for those over the age of 75.[30]

As the average age of HNSCC patients falls,[31] it is important to clarify differences in survival in order to better inform patients of their prognosis, and to better inform treatment plans. The existing literature has shown mixed results. Some have shown no difference in survival between younger and older patient,[32–35] while some have shown a more favorable prognosis for younger patients.[36–38]

Statement of Purpose

The purpose of this research is to provide an in-depth understanding of the outcomes of HPV-associated head and neck cancers through the use of a national, large sample obtained from the National Cancer Database (NCDB).

In particular, the 3 main objectives of research are:

- *Objective 1: Examine the **prognostic effect of HPV at all six HNSCC sub-sites***
- *Objective 2: Determine the effect of **patient sex** (male vs. female) on the overall survival of HPV-associated and non-associated of OP and OCSCCs*
- *Objective 3: Determine the effect of **patient age** (<40 years old vs. 40+ year olds) on the overall survival of HPV-associated and non-associated OP and OCSCCs*

It is our hope that the results of this study will further elucidate HPV's role and importance as a prognostic tool at different head and neck sub-sites, and the role of patient sex and patient age within HPV-associated HNSCCs which ultimately may help inform treatment decisions and reduce the future burden of HNSCC.

Methods

Data

Data were extracted from the NCDB from 2010 to 2014. The NCDB is a joint project of the Commission on Cancer (CoC) and the American Cancer Society.[39] Cases are recorded from over 1500 accredited hospitals in the United States and Puerto Rico. The database represents over 70% of incidences of cancer in the United States. Each hospital that participates in the registry is responsible for submitting and tracking patient and tumor level data on patients with malignant neoplastic diseases. Data was analyzed accordingly to achieve the three research objectives (Figure 1).

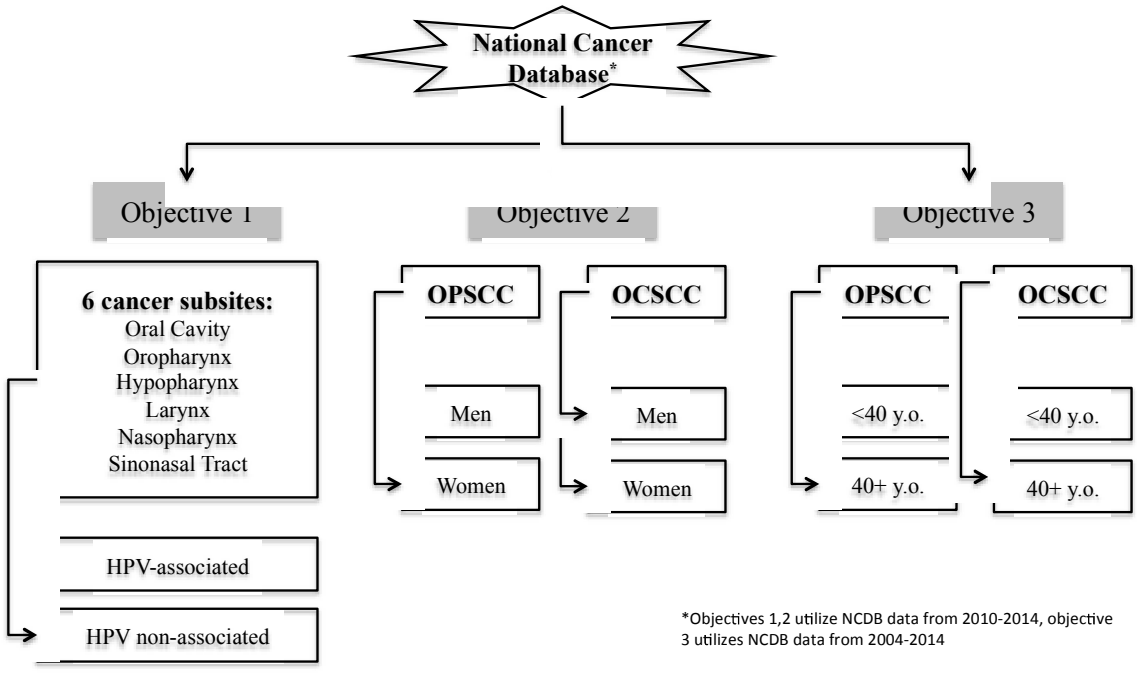

Figure 1. Overview of the data analytics plan of the NCDB for fulfillment of each research objective

Patient Population, Cancer Sub-sites and Histology Definitions

Our study population includes patients whose primary malignancy was diagnosed as squamous cell carcinoma of the head and neck. The following Internal Classification of Disease for Oncology, Third Edition (ICD-O-3) histology codes were used for squamous cell carcinoma M8070-8073 and the following topography codes were used for oropharynx: C09.0-09.1, C09.8-09.9 (tonsil) C10.0, C10.2-10.4 (other oropharynx) and C-01.9 (base of tongue), for oral cavity cancer: C00.0-00.9 (lip), C02.0-02.4, C02.8-02.9 (other/unspecified parts of the tongue), C03.0-03.1, C03.9 (gum), C04.0-04.1, C04.8-04.9 (floor of mouth), C05.0-05.1, C05.8-05.9 (palate), C06.0-06.2, C06.8-06.9 (other/unspecified parts of the mouth), for nasopharynx: C11.0-11.3, C11.8, C11.9 (nasopharynx), for hypopharynx: C12.9 (pyriform sinus) and C13.0-13.2, C13.8, C13.9 (hypopharynx), for sinonasal tract: C30.0, C30.1 (nasal cavity and middle ear) and C31.0-31.3, C31.8, C31.9 (accessory sinuses) and for larynx: C32.0-32.3, C32.8, C32.9 (larynx).

HPV Status Definition

HPV status was available for cases diagnosed from 2010 to 2014 and was categorized as negative, positive for low-risk HPV types, positive for high-risk HPV types (HPV 16 and/or 18), and HPV status unknown. Patients were classified as ‘HPV+’ (HPV-associated) if they tested positive for high-risk HPV types, and ‘HPV-’ (HPV non-associated) if they received a negative HPV test. Patients with low-risk HPV types or unknown HPV status were excluded.

Patient Population Analysis

We examined patient demographic and tumor data (age at diagnosis, race, Charleson/Deyo score, primary tumor site, American Joint Commission on Cancer (AJCC) T and N classification, tumor grade, primary treatment type, insurance status, median income quartiles, treatment facility type and location, and rural/urban classification of patient's primary county of residence). Patients were excluded if they were younger than 18 years old, if AJCC TNM classification was unknown, or if primary treatment type was unknown. Primary treatment type was classified into the following groups: no treatment, radiation only, chemotherapy only, surgery only, radiation and chemotherapy, surgery and radiation, and surgery, radiation and chemotherapy.

Statistical Analysis

Data analyses were performed using SPSS 19.0 (IBM Corp., Armonk, NY). The comparison of mean age at diagnosis was analyzed using the Student's t-test. Proportional distribution of race, primary tumor site, T and N classification, lymph node metastasis, primary treatment type, insurance status, median income quartiles, treatment facility type and location, and rural/urban classification of patient's primary country of residence were compared using chi-squared tests. T-tests and chi-squared tests as described above were used to compare the distribution of characteristics between HPV+ and HPV- patients.

Survival analysis was performed using Kaplan-Meier (KM) analysis. An unadjusted Cox proportional hazards regression model was used for multivariable survival analysis. Age, sex, race, T and N classification, Charleson/Deyo score, HPV status, primary treatment type, insurance status and median income were entered a priori into the model. A two-sided p-value <0.05 was considered statistically significant.

Specifics to Objective 1: Classification of HPV's Association to Survival

We utilized three tests to derive HPV's association to improved survival among patients with HNSCC – 1) 5-year unadjusted survival rate, 2) KM survival curve analysis and 3) an unadjusted Cox proportional hazards regression model. Sub-sites where HPV-positivity was found to have an association to improved outcome in the Cox model were further classified into "strong" or "moderate" association based on the size of the difference of 5-year unadjusted survival rates between HPV+ and HPV- cohorts. A difference of greater than >20% survival was classified as "strong" and a difference <20% was classified as "moderate".

Specifics to Objective 3: Propensity Score Matching (PSM)

To balance the difference in basic clinical characteristics between young (<40 year old) and old (40+ years old) patients, we performed PSM. We performed matching on sex, race, primary treatment type, income, insurance status, AJCC T and N stage, Charlson/Deyo comorbidity index score, HPV status and primary tumor site (OC vs OP). Matching was conducted at a 1:1 ratio. After verifying that the standardized mean

difference between matched groups was satisfactory, KM 10-year OS survival curves and a Cox proportional hazards regression model were used for the matched dataset.

Exemption Statement

Our study is exempt from review by the Yale Human Research Protection Program because it uses a pre-existing, de-identified public database.

Results

Objective 1: HPV's Effects at Different Cancer Sub-sites

Baseline Characteristics

We identified a total of 41,950 patients (16,644 with HPV+, 25,306 with HPV- tumors) with head and neck squamous cell carcinoma in the NCDB between 2010 and 2014 (Figure 2). Baseline patient, hospital, clinical, and treatment characteristics by each sub-site are shown in Table 1- Table 6. In general, HPV+ patients were more likely to be white, younger, male, present with earlier T staging tumors, and have poor differentiation on histology.

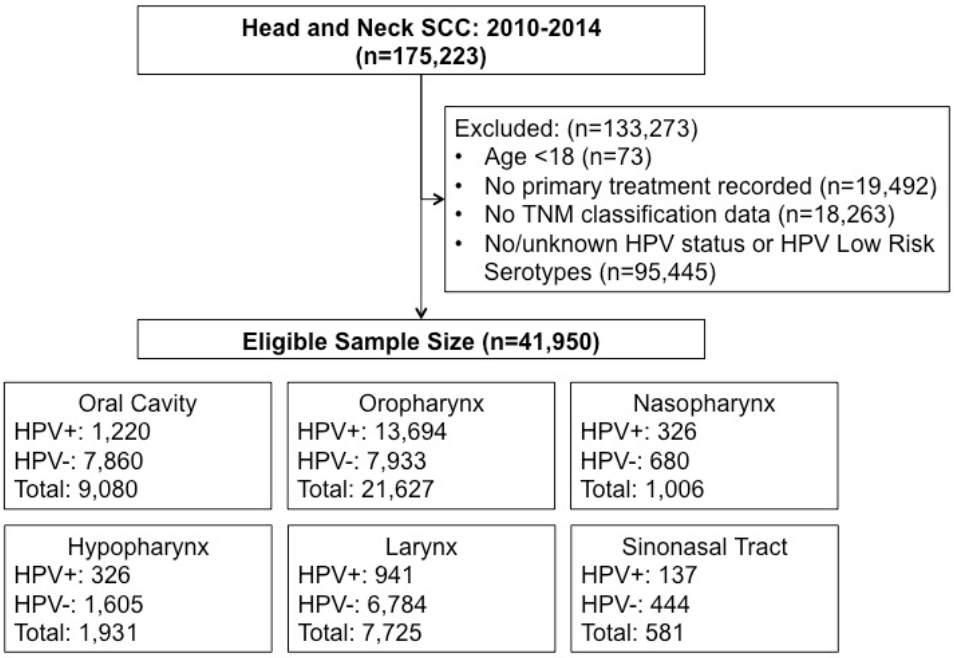

Figure 2. CONSORT flow diagram of patient selection and exclusion.

Survival outcomes analyses

5-year unadjusted survival rates and KM survival curves for each sub-site are shown in Table 7 and Figure 3 respectively. Large survival differences were noted in the oropharynx and hypopharynx between HPV+ and HPV- patients (OP: 77.6% vs. 50.7% (Δ 26.9%, 95 CI 25.6%-28.2%); HP: 52.2% vs. 28.8% (Δ of 23.4%, 95% CI 17.5%-29.3%)) between HPV+ and HPV- patients respectively.

Smaller survival differences were found between HPV+ and HPV- patients in oral cavity, larynx, and sinonasal tract sub-sites (OC: 59.4% vs. 53.1% (Δ 6.3%, 95% CI 3.3%-9.3%); LRX: 57.2% vs. 48.7% (Δ 8.5%, 95% CI 5.1%-11.9%), SNT: 63.1% vs. 45.1% (Δ 18.0%, 95% CI 8.7%-27.3%)). No statistically significant survival difference was noted in the nasopharynx 5-year unadjusted survival rates (NP: 52.5% vs. 58.7% (Δ -6.2%, 95% CI -12.8%-0.4%)).

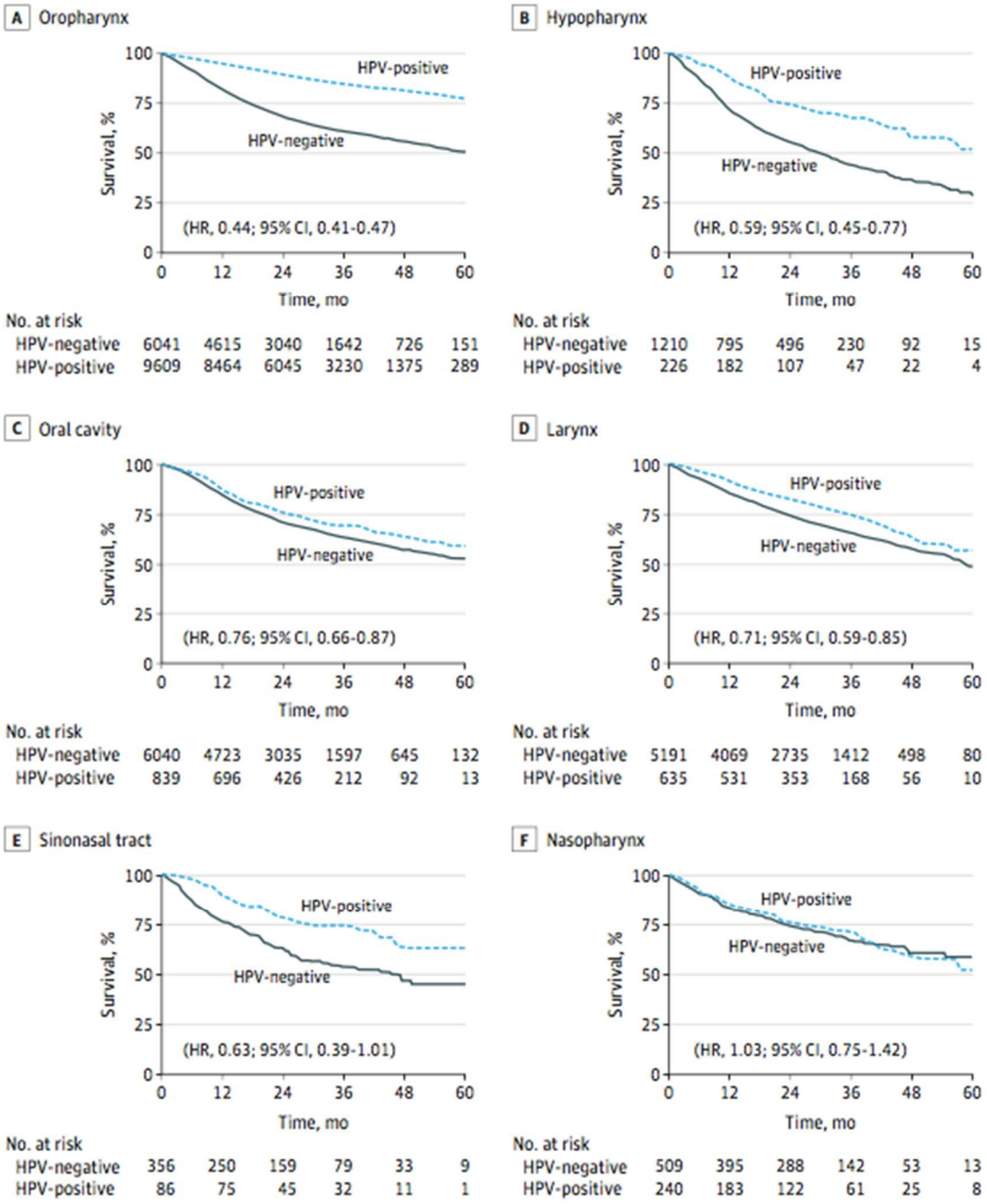

Figure 3. Kaplan-Meier survival curves by HPV status. Unadjusted hazard ratios (HR) for HPV status and its associations with overall survival are shown for each sub-site. HPV-positive status is compared with baseline HPV- status

On multivariate analysis, HPV+ status remained an independent prognostic factor for the oral cavity, oropharynx, hypopharynx, and larynx sub-sites (OC: HR 0.76, 95% CI 0.66-0.87, OP: HR 0.44, 95% CI 0.41-0.47, HP: HR 0.59, 95% CI 0.45-0.77, LRX: HR 0.71, 95% CI 0.59-0.85) after accounting for age, sex, race, Charleson/Deyo comorbidity score, insurance, income, T and N staging, and primary treatment. For the nasopharynx and sinonasal tract sub-sites, HPV+ status was not associated with increased overall survival (NP: HR 1.03, 95% CI 0.75-1.42; SNT: HR 0.63, 95% CI 0.39-1.01).

Other factors associated with survival at each sub-site are shown in Table 8-Table 13. Having any treatment other than chemotherapy alone was associated with improved survival in five of six sub-sites. The HRs ranged between 0.07-0.7 and the 95% CIs did not include unity (1.0) when comparing treatment groups to baseline no treatment. Interestingly, having chemotherapy alone did not improve the hazard of death in five of the six sub-sites (HR ranged between 0.8-1.1 and 95% CI included unity). Having a score of 2 on the Charlson/Deyo score is associated with worse survival at all sub-sites (HRs ranged between 1.4 and 2.1 and 95% CI were larger than unity).

Objective 2: Effects of Sex on HPV OP and OCSCCs

Baseline Characteristics

Our study population (n=30,707) included 13,694 OP HPV-associated; 7,933 OP HPV- cancers; 1,220 OC HPV-associated and 7,860 OC HPV- cancers (Figure 4).

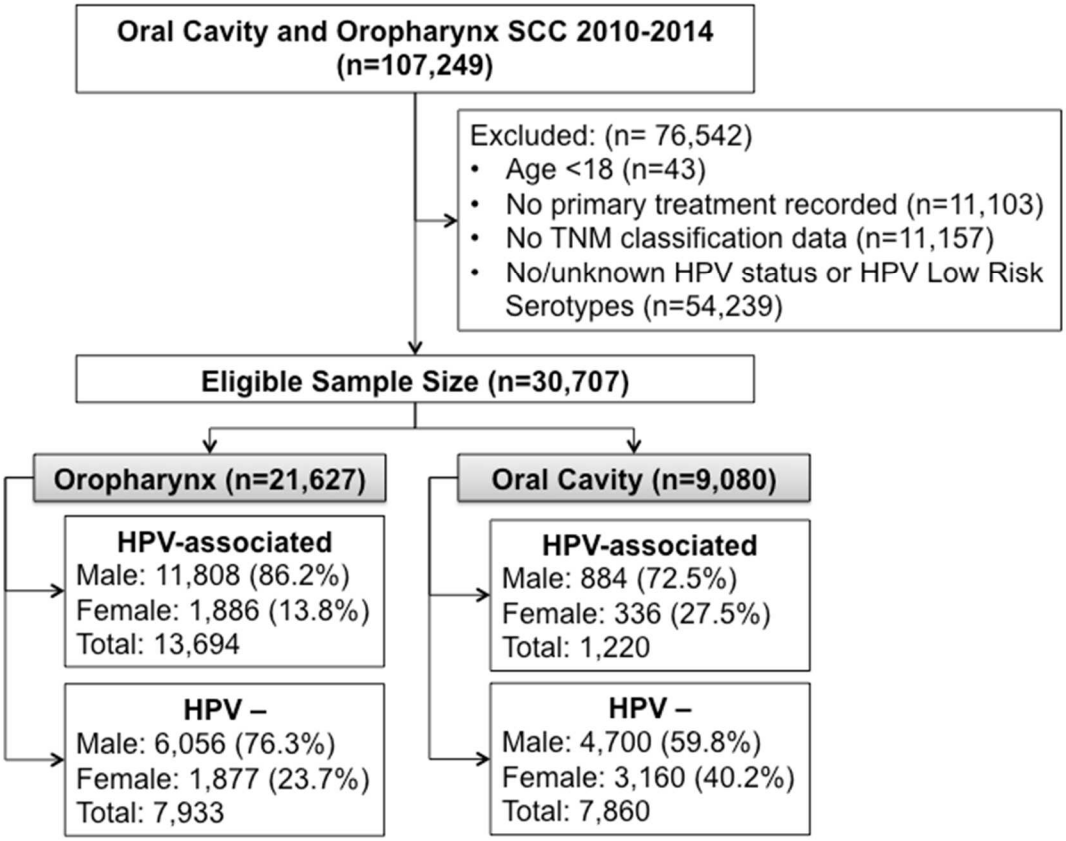

Figure 4. CONSORT diagram of total study population (n=30,707), patient selection and exclusion.

The presence of HPV was correlated with higher proportion of disease burden among men. Among the OP HPV-associated and HPV- cohorts, 86.2% and 76.3% of patients were men respectively. Among the OC HPV-associated and HPV- cohorts, 76.3% and 59.8% were men respectively. Each group was further analyzed for baseline characteristic differences by sex (Table 14 and

Table 15).

Within all four groups, women were on average older at age of diagnosis ($p<0.001$ for each group). Women were generally diagnosed with cancers in earlier T and N clinical classification than men. In OP, this difference was most pronounced in N classification; in OP HPV-associated cancers, 39.4% women vs. 27.2% men had N0-1 cancers ($p<0.001$), in OP HPV- cancers, 50.0% women vs. 39.9% men had N0-1 cancers ($p<0.001$). In OC HPV-associated cancers, 40.1% women had T0-1 cancers vs. 29.8% men and in OC HPV- cancers ($p=0.005$), 42.3% vs. 34.8% in women and men respectively ($p<0.001$). Women in all four groups were more likely to be treated with a modality including surgery (surgery only, surgery and radiation, or surgery and chemo-radiation; $p<0.001$ in each group). For insurance coverage, more women were covered by Medicare than men across all four study populations.

Factors associated with survival in OPSCCs

Kaplan-Meier survival analysis showed no difference in OS between the two sexes in OP HPV-associated cancers ($p=0.64$; Figure 5a). On multivariate analysis, after accounting for age at diagnosis, ethnicity, clinical T and N classification, primary disease site, primary treatment, insurance status and median income, female sex (HR: 0.93; 95% CI 0.79-1.009, $p=0.412$) did not prove to be an independent prognostic factor for OS.

In OP HPV- cancers, men had a statistically significant better OS than women on Kaplan Meier survival analysis ($p=0.035$, Meier survival analysis ($p=0.035$, Figure 5b). In multivariate analysis, female sex (HR: 1.15; 95% CI 1.04-1.28, $p=0.004$) 1.15; 95% CI 1.04-1.28, $p=0.004$) continued to be an independent prognostic factor for worse OS in OP HPV- cancers even

worse OS in OP HPV- cancers even after controlling for other variables (as described previously,

Table 16).

The hazard of death was notably higher for both OP HPV-associated and HPV- cohorts with increasing age, higher T and N classification, cancers at sites other than base of tongue or tonsils and patients with no primary treatment (

Table 16).

Factors associated with survival in OCSCCs

Kaplan-Meier survival analysis showed that among OC cancers, women had better OS than men in both HPV-associated and HPV- cancers ($p=0.049$, $p<0.001$ respectively, Figure 5c,d).

In contrast to the varying prognostic roles of female sex in OPSCCs, in OCSCCs, female sex remained a strong prognostic factor for better OS in both HPV-associated and HPV- cancers (HPV-associated: HR: 0.71; 95% CI 0.0.50-0.99, $p=0.048$; HPV-: HR: 0.87; 95% CI 0.78-0.95, $p=0.004$; Table 17) after controlling for over variables. In OC HPV-associated cancers, age (HR: 1.02; 95% CI 1.00-1.04, $p=0.01$) and black race (HR: 1.88; 95% CI 1.14-3.11, $p=0.013$) were significant predictors of OS in patients. In OC HPV- cancers, age (HR: 1.02; 95% CI 1.02-1.02, $p<0.001$), N classification ($p<0.001$) and having higher median income $63,000+ ((HR: 0.77; 95% CI 0.67-0.88, $p<0.001$), and having treatment (over no treatment; $p<0.001$ for all except chemotherapy only group $p=0.31$) were all significant predictors of OS.

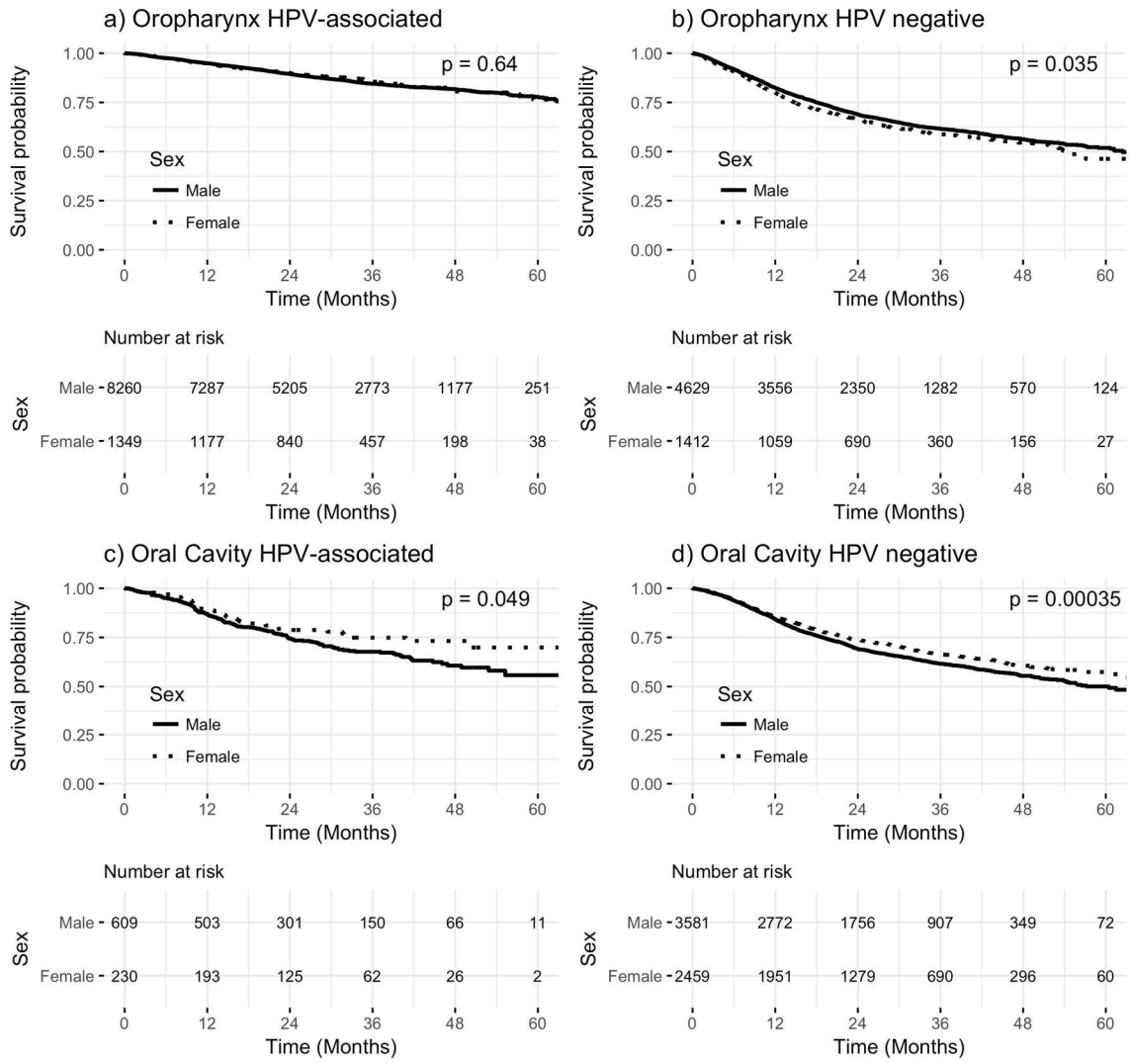

Figure 5. Kaplan-Meier survival and number at risk a) OP HPV-associated: p=0.638, b) OP HPV negative: p=0.035, c) OC HPV-associated: p=0.049, d) OC HPV negative: p<0.001.

Objective 3: Effects of Age on HPV OP and OCSCCs

Patient Characteristics Stratified by Age

After exclusion, we identified 155,359 total patients, of which 3,749 (2.4%) were included in our younger cohort (ages 18 to 39) and 151,610 (97.6%) were included in our older cohort (ages ≥40). The mean age was 33.8 years and 62.3 years for our younger and older cohort, respectively ($p<0.001$). While there was a male predominance in both cohorts, the younger cohort had a significantly larger proportion of females (36.6% vs. 27.2%; $p<0.001$). The younger cohort also had less whites (86.2% vs. 89.1%; $p<0.001$), had higher rates of private insurance (64.2% vs. 42.3%; $p<0.001$), a lower comorbidity burden (CDCC score of 0; 92.5% vs. 80.6%; $p<0.001$), tended to have a higher number of people with an income of over $48,000 a year (58.7% vs. 56.8%; $p=0.036$), and a larger proportion of people living in metro areas (83.5% vs. 81.9%; $p=0.027$) (Table 18).

Oncologically, younger patients were more likely to present with oral cavity cancers (66.20% vs. 44.4%; $p<0.001$) in their early stages (T1: 45.4% vs. 37.1% [$p<0.001$]; N0: 68.1% vs. 59.3% [$p<0.001$]) than their older counterparts, though they were less likely to test positively for high-risk HPV subtypes (7.1% vs .9.7%; $p<0.001$). Younger patients were more likely to undergo surgery (37.5% vs. 26.4%) or surgery with CRT (24.9% vs. 15.2%), but less likely to obtain CRT alone (20.5% vs. 35.7%; $p<0.001$) (Table 19).

As shown in Table 18 and Table 19, after propensity score matching was performed, no differences were seen in any patient characteristic, with the exception of mean age. Post-match, a total of 3,510 patients were matched in each age group (Figure 6).

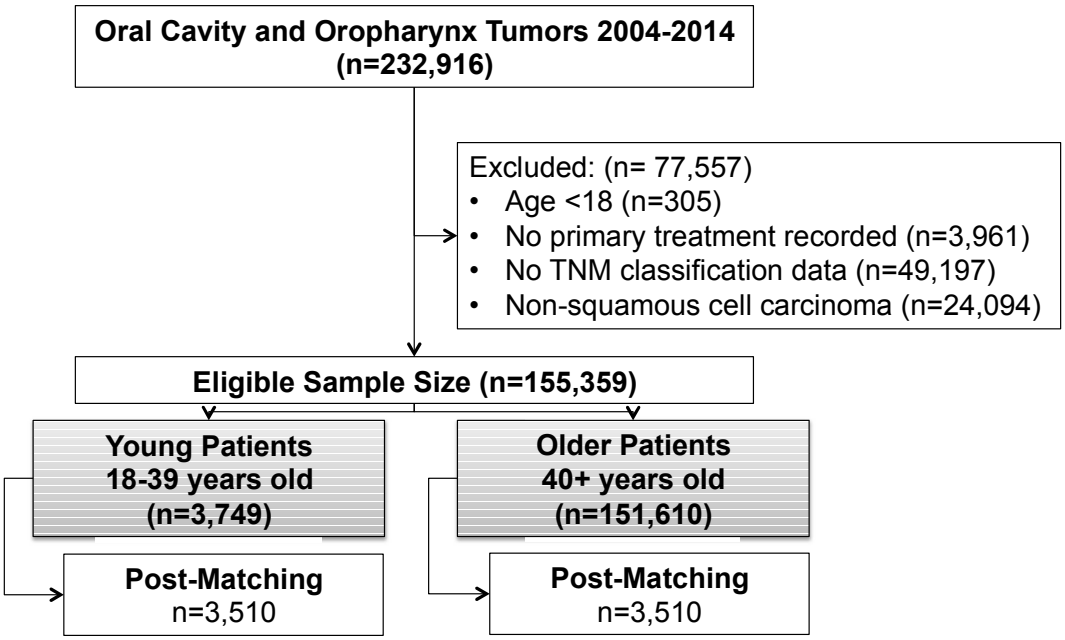

Figure 6. CONSORT diagram of total study population (n=155,358) and post-match sample by age group (n=3,510 in each cohort), patient selection and exclusion.

Primary Sub-site of Tumor

Younger patients were more likely to obtain cancer in a tongue (not base of tongue) sub-site (49.4% vs. 17.7%), while older patients were likely to have a tumor in the base of tongue (23.5% vs. 12.0%) or tonsil (25.4% vs. 19.1%; $p<0.001$). After propensity score matching, these differences were less pronounced, though still statistically significant ($p<0.001$) (Table 20).

Overall Survival Difference by Age

On Kaplan-Meier analysis of the overall study population, the young cohort had better 5-year survival than the older cohort. 5-year survival was 82.8% [SE: 0.8%] for the younger cohort and 72.2% [SE: 0.9%] in the older cohort, Log-Rank $p<0.001$ (Figure 7).

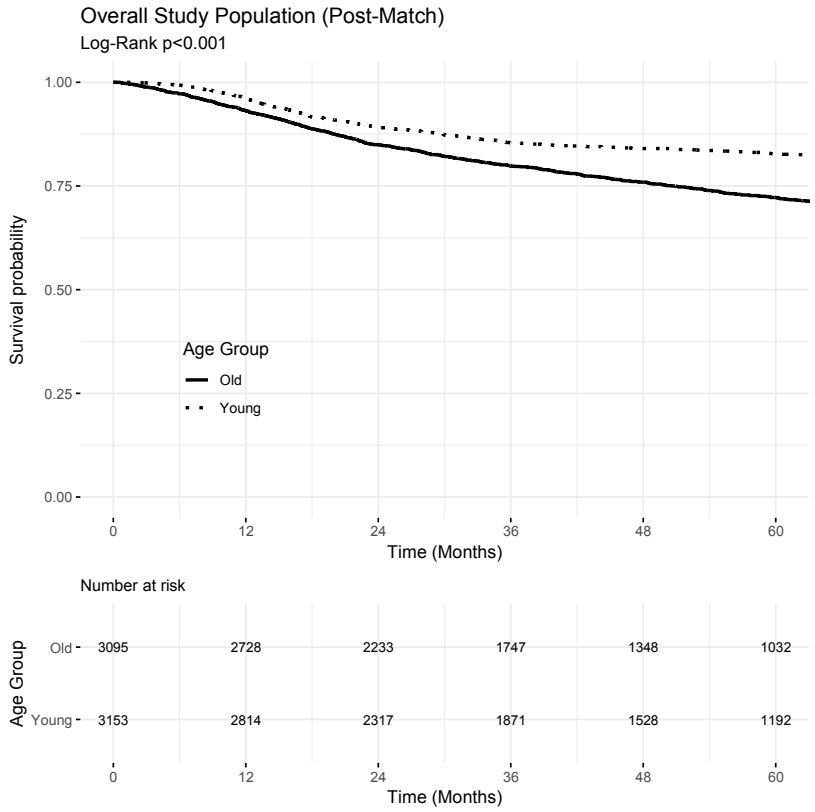

Figure 7. Kaplan-Meier survival curve and number at risk of overall study population (post-Propensity Score Match)

Survival Differences by Age in the Oral Cavity

When looking at the prognostic effect of age at specific oral cavity sub-sites in our matched cohort, we found that the younger cohort was associated with a higher survival than the older cohort in non-base tongue ($p=0.034$) and palatal tumors ($p<0.001$). 5-year survival was 78.2% [SE: 1.2%] for the younger cohort and 74.0% [SE: 1.5%] in the older cohort for tongue (non-base of tongue) sub-sites (Figure 8a). Similarly, 5-year survival was 96.3% [SE: 1.1%] for the younger cohort and 67.4% [SE: 3.5%] in the older cohort for palatal sub-sites (Figure 8c). However, survival did not differ by age in the floor of

mouth sub-sites (young cohort: 5-year survival was 73.9% [SE: 5.6%]; older cohort: 5-year survival was 64.9% [SE: 3.0%]; p=0.314) (Figure 8b).

Upon multivariate cox analysis controlling for sex, race, AJCC T and N stages, HPV status, treatment, and tumor sub-site, we found that a younger age was independently associated with an improved survival (HR: 0.580; p<0.001). Of note, we found that floor of mouth cancers were associated with increased mortality compared to lip tumors (HR: 1.447; p=0.029). RT alone was found to have no improvement in survival when compared to no treatment at all (HR: 0.597; p=0.6639). The full regression may be found Table 21.

Survival Differences by Age in the Oropharynx

When looking at the prognostic effect of age at specific oropharynx subsites in our matched cohort, we found that the younger cohort was associated with a higher survival than the older cohort in tonsillar tumors (p=0.003). 5-year survival was 86.8% [SE: 1.9%] for the younger cohort and 77.3% [SE: 2.5%] in the older cohort for tonsillar tumors (Figure 9b). However, such a survival difference was not noted for base-of-tongue tumors (p=0.330). 5-year survival was 76.4% [SE: 2.7%] for the younger cohort and 73.3% [SE: 3.0%] in the older cohort for tongue tumors (Figure 9a).

In the multivariate cox model, age continued to be associated with a positive prognostic benefit (HR: 0.556; p<0.001). High-risk HPV-positivity was also associated with

improved survival (HR: 0.397; p=0.011). Compared to tumors at the base-of-tongue, tonsillar tumors were associated with increased survival (HR: 0.707; p=0.006). The full regression may be found in Table 21.

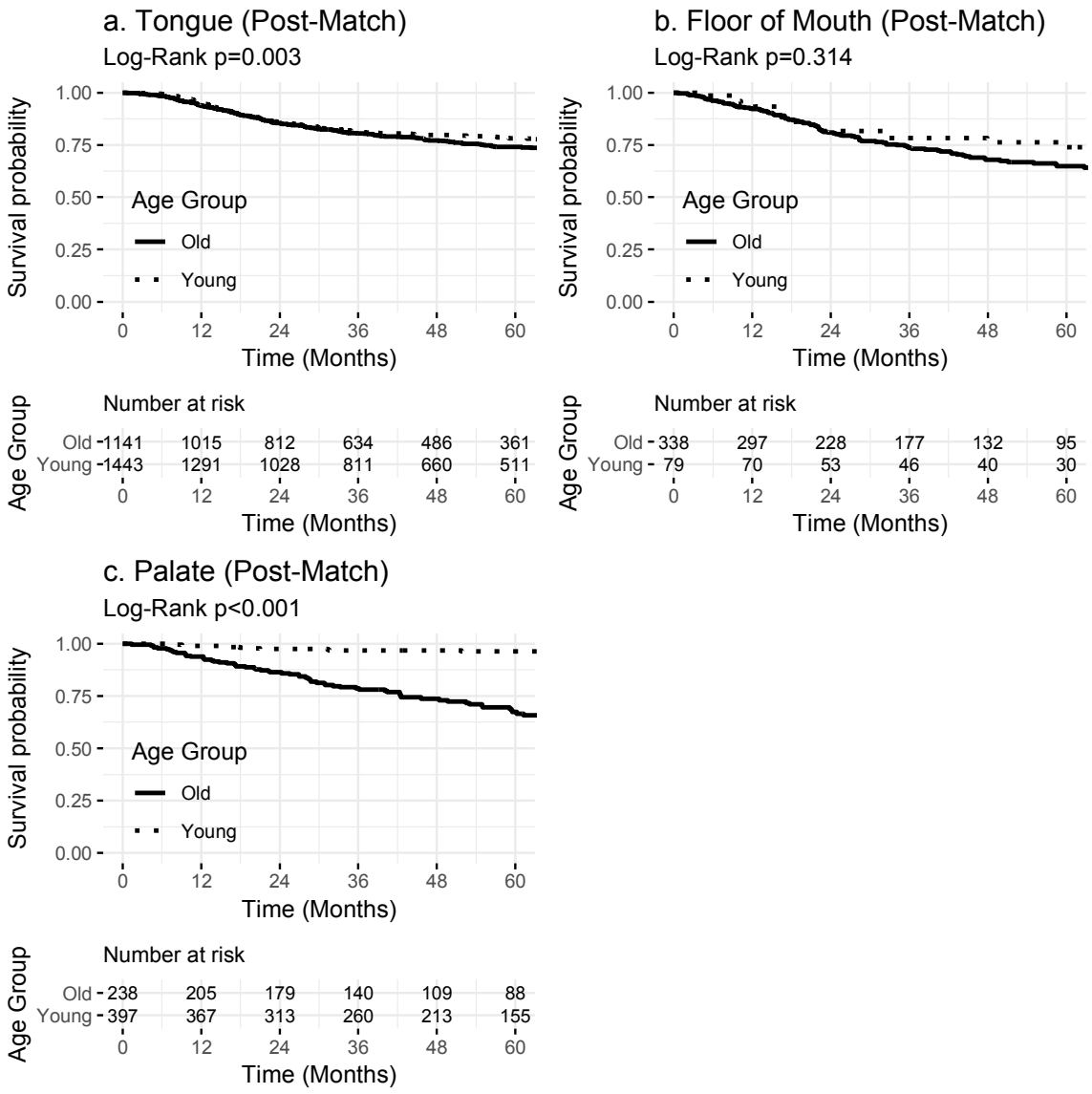

Figure 8. Kaplan-Meier survival curves and number at risk of selected oral-cavity sub-sites post-Propensity Score Match (a) tongue (not base of tongue); (b) floor of mouth; (c) palate

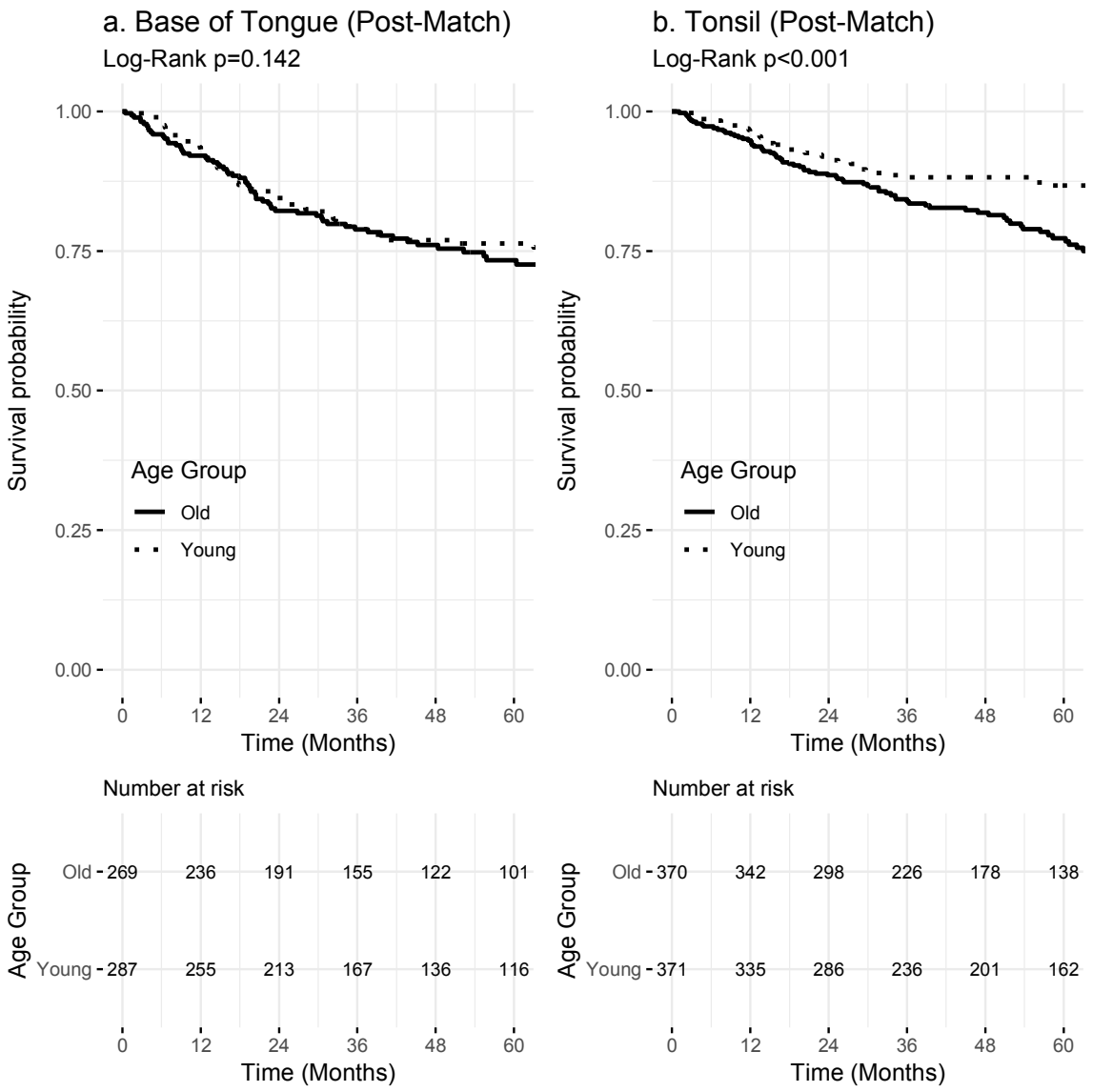

Figure 9. Kaplan-Meier survival curves and number at risk of selected oropharynx sub-sites post-Propensity Score Match (a) base of tongue tumors; (b) tonsil

Discussion

We present the largest and most comprehensive retrospective study examining 1) the role of HPV and its association to overall survival at all head and neck sub-sites, 2) the role of sex and 3) the role of age in HPV-associated oral cavity and oropharynx tumors.

In our study, with respect to objective 1 - we found HPV to have a strong association with overall survival in the oropharynx and hypopharynx, moderate association with improved survival in the oral cavity and larynx, and no effect in the nasopharynx and sinonasal tract.

Given that HNSCCs affect the two sexes disproportionately (80% men)[22], we hypothesized that sex will be a prognostic factor for survival in HNSCCs. With respect to objective 2 - our study found that sex does appear to play a distinct role in predicting OS and that the prognostic value of sex is dependent on HPV status and location of primary tumor.

Finally, as the average age of HNSCC patients falls,[31] we hypothesized that young patients, specifically those between 18-39 years old, would have better OS than older patients (40 years or older). Based on our findings for objective 3, young age indeed is prognostic of better OS in both oral cavity and oropharynx sub-sites. Interestingly, contrary to existing literature,[35,40] even for tumors of the tongue (not base of tongue) sub-site, young patients had better 5-year and 10-year OS.

The following sections of the discussion address each research objective separately followed by a summative section addressing the limitations of this research with respect to the use of the NCDB.

HPV's effects at Different Cancer Sub-sites

The results of our study, suggesting a variance in the magnitude of survival benefit depending on sub-site, provide a foundation for further study. It is unknown why HPV plays a bigger prognostic role in the oropharynx and hypopharynx than in the oral cavity and larynx. Perhaps it is because anatomy and function of each sub-site differs substantially. This theory may partly explain the similarity in HPV's role between the adjacent oropharynx and hypopharynx. Preclinical studies alluded to differences in the micro-tumor environment between OPSCC and non-OPSCC.[17] This may explain the contrast seen between the oral cavity/larynx and oropharynx/hypopharynx sites.

Recent studies have found that mutations in TRAF3 and CYLD occur only in HPV-associated HNSCC[41] and correlate with survival.[42,43] The absence of viral genome integration is also associated with improved survival[44], and was predicted by mutations in TRAF3 or CYLD.[43] Together, these data suggest that HPV carcinogenesis can occur through HPV integration or through maintenance of the HPV episome,[43] and that tumors lacking HPV integration have improved survival. Future studies will be required to determine if laryngeal and oral cavity are more likely to lack mutations in TRAF3/CYLD

and have HPV integration, which could explain why HPV is not associated with as large a survival advantage in these sub-sites.

The sinonasal tract is unique in that it may be at lower risk of exposure to HPV. It is hypothesized that oral HPV infection is transferred by oral sexual contact.[45] However, it is not known if high-risk sexual behavior also affects cancers of the sinonasal tract. A histological analysis of 131 sinonasal carcinomas found high-risk HPV DNA in 21% of tumors.[46] Interestingly, though non-keratinizing squamous cell carcinoma was found to be the most common histologic type, the study also reported multiple tumors that were basaloid, papillary, and adenosquamous variants, and some that contained features of a salivary gland neoplasm. This study, in combination with our results, suggests that sinonasal carcinomas confer distinct biological and clinical characteristics worthy of further investigation.

Though HPV's prognostic role in oropharynx cancers is well established[6], there is now an emerging body of conflicting evidence regarding its role in other sites of the head and neck.[14,16,23,47–50] The majority of studies investigating the prognostic effect of HPV at each non-OPSCC sub-site suffered from small sample sizes and report varied results.[51–53] Many trials have reported the strong association of p16 with improved progression survival, OS, and relapse-free survival in oral cavity, hypopharyngeal, and laryngeal cancers.[14,47–49] Some studies have grouped together all non-OPSCC subtypes, as opposed to delineating the effect by sub-site. The results of such studies range from minimal impact,[16,23] to a substantial increase in survival.[50]

Our data is supported by a recent study by Ko and colleagues that examined the role of HPV at non-OP subsites (oral cavity, hypopharynx, and larynx).[50] The investigators aggregated the three sub-sites and examined the two cohorts based on disease staging (I & II, and III & IV). Favorable prognosis was identified in both groups for HPV+ patients. However, their analysis did not specifically examine the role of HPV at each sub-site by running a multivariate analysis for each sub-site cohort, though KM studies were done by sub-site. Our study more thoroughly examined the effect of HPV as we isolated patient cohorts by sub-site to determine the role of HPV. In this way, we were able to exclude effects of interactions between the primary location of the tumor and HPV status on overall survival.

Though our study and many others have found improved outcomes associated with HPV+ non-OPSCC, two studies exist to the contrary. One recent two-institutional pooled analysis found no survival advantage for patients with larynx, oral cavity, and nasopharynx cancers.[23] Another study utilizing the Danish Head and Neck Cancer Group database comparing advanced p16 and non-p16 tumors in larynx and hypopharynx tumors demonstrated no outcome differences.[16] These contrasting results may be due to a difference in patient population (median age, sex distribution, race, and inclusion criteria) between the aforementioned studies and our own. In addition, their utilization of p16 as a surrogate for HPV status is another factor that differed from our study.

The role of HPV in nasopharynx is still controversial. One study with 90 patients (9 HPV+ cases) found survival benefit with HPV+ tumors,[54] while another recent study with 125 patients (13 HPV+ cases) found no survival benefit with HPV+ tumors.[23] One case series of 45 cases found that HPV+ nasopharyngeal tumors may represent primary oropharyngeal tumors with extension to the nasopharynx site.[55] This is one of the largest studies examining the role of HPV in nasopharyngeal cancers. Though we found no survival benefit associated with HPV+ NP tumor status, given the retrospective and database nature of this study, we were unable to determine the level of primary site misclassification. Historically, the role of the Epstein-Barr virus (EBV) has been well characterized in the pathogenesis of nasopharynx tumors. The role of EBV and its interaction with HPV were outside the scope of our study and not captured by the NCDB; data suggest that EBV-associated nasopharyngeal cancers have improved prognosis compared to virus-negative tumors,[56] which could confound the analysis of the effect of HPV status.

In summary, we identified a variance in the role of HPV and its association with outcomes in head and neck tumors. Though HPV+ status improved disease survival outcomes for four sub-sites, the greatest magnitude of its effect is most noted at the oropharynx and hypopharynx subsites. HPV does not appear to affect the prognosis for the nasopharynx and sinonasal tract sub-sites. Given these results, we recommend routine testing for HPV status in HNSCC at the oropharynx, hypopharynx, oral cavity, and larynx sub-sites.

HPV-associated HNSCCs in Women

HPV status and its importance as a prognostic marker in oropharyngeal SCCs has been well established.[6,57] The prognostic associations of HPV status with other clinical factors such as sex and primary tumor location have not been well investigated. Given that HNSCCs affect the two sexes disproportionately (80% men), we hypothesized that sex will be a prognostic factor for survival in HNSCCs. Our study found that sex does appear to play a distinct role in predicting OS and that the prognostic value of sex is dependent on HPV status and location of primary tumor. This finding is consistent with the idea that HPV-driven cancers in non-OP locations exhibit distinct clinical behavior and possess unique risk factors than HPV-driven cancers in OP.[17,23]

Molecular underpinnings of the HPV infection between the two sexes also vary. One Finnish study examining the clearance of HPV DNA using oral rinses between spouses found earlier virus clearance in men than in women as well as significantly different cumulative clearance rates (5% vs. 0% clearance in men and women respectively over 24 months).[58] In a long-term prospective 6 year study of asymptomatic HPV infections, Syrjänen and colleagues found a 5.5 fold number of viral HPV copies in women than in men who were able to clear the infection.[59] Although similar copy numbers were found between sexes for those with persistent infections, 71% of the HPV DNA was integrated or mixed in women vs. 57% in men. Full integration of the HPV episome into human chromosomes has been shown to be an early event in cervical carcinogenesis,[60,61] though its role in oral mucosal carcinogenesis is still debated. Nonetheless, these studies reflect a

distinction in HPV's molecular behavior between sexes that needs to be further categorized.

Prior studies have been inconclusive on the significance of sex as a prognostic marker for overall survival. A recent two-institution retrospective study found sex to be prognostic in OPSCCs even after accounting for HPV-status.[23] The authors examined 860 patients with OPSCCs (including HPV-associated and HPV- patients) and performed a multivariate regression model. Our study utilizes more targeted patient subgroups that specifically examines the role of sex among HPV-associated or HPV- patients. To our knowledge, our study is the largest study with patients and their HPV status spanning across the entire U.S. As a result, our sample provides the power for the subgroup analyses for the detection of differences in sex. However, due to the nature of the national cancer registry, there is inherent uncertainty to the nature of our data as the quality of the data relies on the accuracy of data entry, diagnosis and treatment at over 1500 hospitals. In comparison, Fakhry et al.'s two-institution study limits their data inaccuracies due to a smaller sample size.

Existing research has shown that women have a significant survival benefit in many cancers outside of the head and neck region.[62] However, for HPV- OPSCCs, we found the opposite where men have better survival than women. This similar trend also exists in patients with bladder cancer.[63,64] The reason for this observed survival advantage is unknown. Preclinical studies support a role for sex hormones as cofactors for HPV-related malignancies[65,66] though other unidentified factors may also be responsible for

this unique sex-specific finding. One study found the progesterone antagonists and nuclease-resistant oligomers containing HPV-16 response element are able to abrogate cell growth and E6/E7 gene transcription.[65] Another study examining HPV-induced laryngeal tumors found estradiol stimulated proliferation while 2-hydroxyestrone was anti-proliferative.[66] Both preclinical studies found hormonal interactions using HPV-associated tumor models, thus this does not fully explain our findings in the HPV- OPSCC cohort. Perhaps there exists an interaction between HPV and sex hormones in the OP sub-site, which improves the survival of women thus equalizing overall survival between the two sexes. Nonetheless, we acknowledge the proximity of the Kaplan-Meier survival curve between the two sexes in the HPV- OPSCC cohort. Given the absence of tobacco and alcohol data, it is possible that the two sexes may have no survival difference in HPV- OPSCCs.

Interestingly, in our OCSCC study population, women were shown to have better survival than men in both the HPV-associated and HPV- group. This finding contrasts with the role that sex plays in OPSCCs and is consistent with the developing hypothesis that OP and non-OP SCCs are distinct cancers. Risk factors for OCSCC are well established: alcohol, tobacco and betel nut chewing.[67,68] Current rates of tobacco usage in the US are lower in women than in men.[69] As a result, a lower overall lifetime exposure to tobacco may partly explain the survival advantage among women in OCSCC. There is a new growing body of research interested in characterizing HPV in non-OP sites. A molecular study of 520 HNSCCs profiling the gene-expression signature of HPV-

associated OP and non-OP sites found there to be two distinct tumor immune microenvironments.[17]

While our study did not directly test for the role of HPV within the OCSCC group, the similarity in risk factors between the HPV-associated and HPV- OCSCC groups infers that HPV may only play a minor prognostic role in OC cancers. A recent study by our group[28] found HPV to be associated with improved survival at the OCSCC subsite, though the survival advantage noted at the oral cavity subsite was not as great as that at the oropharynx subsite.

In our study, we found women were generally diagnosed with earlier T and N staged cancers than men. Earlier detection of cancers would lead to better prognosis.[70] From a health behavior perspective, this finding may be explained by the consistent underutilization of preventative healthcare by men leading to a delay in early diagnosis.[71,72] It has been hypothesized that women have more frequent contact with healthcare professionals due to pregnancy, childcare and hormone replacement therapy as well as women having more interest in health.[71,73]

In summary, the effect of sex on outcomes of OP and OC SCCs appears to vary based on primary tumor location and HPV status. Notably, sex does not appear to affect the prognosis of HPV-associated OPSCCs after accounting for other risk factors. Men with HPV- OPSCCs appear to have a better prognosis for survival than women, though women appear to have a better prognosis in OCSCCs regardless of HPV-status. Given

these results, we recommend further studies to investigate the clinical behavior and the sex-specific pathophysiological biology of HPV-associated HNSCCs and explore opportunities to further eliminate disparities in our patients.

HPV-associated HNSCCs in Young Patients

This study is the largest national study comparing the outcomes of oral cavity and oropharynx SCCs in young patients. As the average age of HNSCC patients falls,[31] we hypothesized that young patients, specifically those between 18-39 years old, would have better OS than older patients (40 years or older). Our study suggests that young age indeed is prognostic of better OS for SCCs at both oral cavity and oropharynx sub-sites. In addition, young patients were also found to have better 5-year and 10-year OS in oral tongue SCCs that their older counterparts.

We used a propensity score match analysis to evaluate the survival difference between the two age groups. Our results strongly suggest that young age is associated with improved survival in both OC and OP SCCs. Currently, there is much debate surrounding the prognostic value and appropriate management of young patients with OCSCCs. Older studies of small samples of young patients have predominantly found worse prognosis and called for more aggressive treatment in young patients with OCSCCs.[74–76] However, more recent studies, though still single-institution or with small sample sizes have found younger patients to have similar or better OS that older patients.[32,36,77–80]

While we were unable to assess locoregional recurrences due to data capture restrictions, a few studies have found young patients to have higher locoregional recurrence rates without any corresponding difference in OS when compared to older patients.[33,40,81]

Pre-matched pair analysis, our sample showed young patients to present with earlier clinical T and N staging (45.4% vs 37.1% in T1 and 68.1% vs. 59.3% in N0). In addition, there were more women among the younger cohort (36.6% vs 27.2%) and young patients were more likely to present with OC tumors. Based on previous findings from our group, women, irrespective of HPV-status, performed better than men at the OC sub-site.[82] These findings, combined, may partially explain the mechanisms underlying age and its prognostic effects on OS at OC and OP sub-sites.

A recent single institution, small UK study (n=50) examining the clinicopathological features of OC and OPSCCs in young patients (<45 years old) matched to older patients found similar disease profile in terms of tumor sub-site distribution and similar conventional risk factors profiles including tobacco and alcohol use between the two age groups.[83] The study also suggests that existing prognostic and treatment paradigms for the treatment of OC and OPSCCs is likely applicable to young patients as well. Our study, in contrast, found varying distributions of tumors between the two age groups. Almost half (49.4%) of our young patient cohort presented with oral tongue cancers (vs. 17.7% in older patients).

Within OCSCCs, we are seeing both a global and US trend of increasing incidence of oral tongue SCCs (OTSCCs) in young adults.[84,85] Though we do not fully understand the mechanism underlying this increase, nonetheless, this has become an increasingly important public health issue. Prognosis of young adults with OTSCCs and their clinical progression remains an area of debate as multiple studies have reported varying (equivalent, worse or better) prognosis when compared to their older counterparts.[86–89] Most recently, Mukdad et al. found that, using a national US registry between 1973-2002, young patients with OTSCCs have improved survival rates.[80] Our study supports this finding as a sub-analysis of the OTSCC sub-site found young patients to have better OS at both 5-years (78.2%) and 10-years (74.1%). As our study only examined NCDB data from 2004-2013, improvements in the treatment of OTSCCs within the last 15 years may explain the higher 5-year and 10-year OS as compared to the Mukdad et al. results (53.7% and 38.4% respectively).

At the OP sub-site, our study continued to find young age to be a prognostic indicator for overall survival. As HPV is now widely believed to play a significant role in OPSCCs, we also accounted for its role in the multivariate regression. A recent study by Lassig et al. found no survival difference between their young and older patient cohorts with OPSCCs.[32] While Lassig's study utilized a similar methodology of matched pair analysis, their sample size of 87 patients per cohort may explain their lack of significant finding. In comparison, our OPSCC cohort included over 700 patients in each age group. Age, however, still plays a secondary role to effect of HPV within the OP sub-site (HPV-high

risk serotype and young age significantly diminishes the chance of death by approximately 60% and 44% when compared to HPV-negative and old age respectively).

Finally, although literature has been inconclusive on the difference in survival between young and older patients in head and neck cancer, evidence from the Lassig study found that young patients are more likely to undergo neck dissection and thus receive more aggressive approach.[32] In a deep-dive analysis (results not shown) of patients with both OC and OP SCCs in the post-matched cohorts, we found that younger patients were statistically significantly more likely to receive a neck dissection compared to the older cohort (OC: 48.7% vs. 45.3% p=0.041; OP 48.6% vs. 40.5% p=0.005). It is unknown whether this more aggressive approach is the cause for the improved OS among young patients in our study as neck dissections together with the surgical resection are bucketed into the 'surgery' treatment group. This is perhaps an interesting topic that warrants further investigation.

Limitations associated with the NCDB

The NCDB database, as a source, has well-documented limitations.[90] We were unable to account for every variable that may influence survival (e.g. alcohol, tobacco use, and other comorbidities), as these data were not captured by NCDB. In addition, the database does not capture other causes of OC and OP cancers that may influence survival. Specifically, studies have shown that patients with cancer from previous leukoplakia[91] or oral mucositis[92] leading to earlier cancer detection is associated with improved survival, where as patients with cancer from immunosuppression[93] tend to have worse survival.

The type of testing (PCR, ISH for HPV DNA vs. p16) for HPV status may vary depending on each institution and reporting agency. Furthermore, the source of the sample may not necessarily derive from the primary site. There are likely low rates of misclassification due to the nature of the registry of the data; however, any misclassification is likely to have been evenly distributed across our four subgroups. Our retrospective study focuses on OS, not cancer-specific survival. The absence of cause-specific survival data in NCDB makes in plausible that other causes of death such as treatment derived toxicities, secondary primary cancer and comorbid cardiovascular, pulmonary and metabolic syndrome causes which are more prominent in men may contribute to the difference in mortality seen between the two sexes. In addition, other general cancer risk factors such as tobacco and alcohol as well as high-risk sex behavior associated with HPV+ transmission[94] may also influence the survival difference seen.

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Figure Captions

Tables

Table 1. Patient Characteristics Among Those with Oropharyngeal SCC by HPV Status

	HPV-		HPV+		
	Count	%	Count	%	P-Value
Average Age (years)	60.95		58.83		<0.001
Sex					<0.001
Male	6056	76.3%	11808	86.2%	
Female	1877	23.7%	1886	13.8%	
Ethnicity					<0.001
White	6733	85.6%	12714	93.7%	
Black	952	12.1%	645	4.8%	
American Indian/Eskimo	20	0.3%	27	0.2%	
Asian/Pacific Islander	119	1.5%	131	1.0%	
Other	43	0.5%	57	0.4%	
Charlson/Deyo Score					<0.001
0	6294	79.3%	11487	83.9%	
1	1246	15.7%	1758	12.8%	
2	393	5.0%	449	3.3%	
Primary Payer					<0.001
Not Insured	494	6.3%	508	3.7%	
Private Insurance/Managed Care	3333	42.8%	8253	60.9%	
Medicaid	943	12.1%	915	6.8%	
Medicare	2871	36.9%	3574	26.4%	
Other Government	150	1.9%	302	2.2%	
Median Income Quartiles: 2008-2012					<0.001
<$38,000	1573	19.9%	1746	12.8%	
$38,000-$47,999	1786	22.6%	2878	21.1%	
$48,000-$62,999	2097	26.6%	3753	27.5%	
$63,000 +	2430	30.8%	5273	38.6%	
Urban/Rural					0.23
Metro	6592	85.2%	11399	85.3%	
Urban	1040	13.4%	1747	13.1%	
Rural	108	1.4%	224	1.7%	
Facility Type					<0.001
Community Cancer Program	690	8.8%	871	6.5%	
Comprehensive Community Cancer Program	2785	35.6%	4315	32.0%	
Academic/Research Program	3469	44.4%	6717	49.7%	
Integrated Network Cancer Program	870	11.1%	1599	11.8%	
Other specified types of cancer programs	0	0.0%	0	0.0%	
Facility Location					<0.001
Northeast	1621	20.7%	2859	21.2%	
South	3158	40.4%	4525	33.5%	
Midwest	1875	24.0%	3689	27.3%	
West	1160	14.8%	2429	18.0%	
Primary Treatment					<0.001
No treatment	376	4.7%	241	1.8%	
Radiation only	694	8.7%	1026	7.5%	
Radiation and chemotherapy	4575	57.7%	8196	59.9%	
Surgery and radiation	334	4.2%	881	6.4%	
Surgery, chemotherapy and radiation	935	11.8%	2368	17.3%	
Surgery only	682	8.6%	727	5.3%	
Chemotherapy only	337	4.2%	255	1.9%	
Clinical T Stage					<0.001
0	22	0.3%	98	0.7%	
1	1649	21.0%	3807	28.0%	
2	2768	35.2%	5604	41.1%	
3	1658	21.1%	2179	16.0%	
4	1560	19.8%	1544	11.3%	
X	208	2.6%	387	2.8%	
Clinical N Stage					<0.001
0	2004	25.3%	1654	12.1%	
1	1341	17.0%	2298	16.8%	
2	4175	52.8%	9111	66.6%	
3	343	4.3%	571	4.2%	
X	47	0.6%	36	0.3%	
Grade					<0.001
Well differentiated	437	7.2%	280	2.8%	
Moderately differentiated	3237	53.1%	4130	40.8%	
Poorly differentiated	2387	39.2%	5606	55.4%	
Undifferentiated, anaplastic	34	0.6%	98	1.0%	

Table 2. Patient Characteristics Among Those with Hypopharyngeal SCC by HPV Status

	HPV-		HPV+		
	Count	%	Count	%	P-Value
Average Age (years)	63.53		61.29		0.005
Sex					0.11
Male	1288	80.2%	274	84.0%	
Female	317	19.8%	52	16.0%	
Ethnicity					<0.001
White	1299	81.2%	293	90.7%	
Black	253	15.8%	23	7.1%	
American Indian/Eskimo	8	0.5%	0	0.0%	
Asian/Pacific Islander	30	1.9%	7	2.2%	
Other	9	0.6%	0	0.0%	
Charlson/Deyo Score					0.07
0	1182	73.6%	257	78.8%	
1	326	20.3%	58	17.8%	
2	97	6.0%	11	3.4%	
Primary Payer					<0.001
Not Insured	79	5.0%	13	4.0%	
Private Insurance/Managed Care	498	31.5%	154	47.5%	
Medicaid	246	15.6%	32	9.9%	
Medicare	725	45.9%	115	35.5%	
Other Government	33	2.1%	10	3.1%	
Median Income Quartiles: 2008-2012					0.01
<$38,000	335	20.9%	41	12.6%	
$38,000-$47,999	378	23.6%	79	24.3%	
$48,000-$62,999	406	25.3%	100	30.8%	
$63,000 +	483	30.1%	105	32.3%	
Urban/Rural					0.17
Metro	1349	85.8%	273	86.4%	
Urban	204	13.0%	35	11.1%	
Rural	20	1.3%	8	2.5%	
Facility Type					0.47
Community Cancer Program	128	8.0%	23	7.1%	
Comprehensive Community Cancer Program	544	34.1%	118	36.5%	
Academic/Research Program	754	47.3%	156	48.3%	
Integrated Network Cancer Program	169	10.6%	26	8.0%	
Other specified types of cancer programs	0	0.0%	0	0.0%	
Facility Location					<0.001
Northeast	375	23.5%	83	25.7%	
South	620	38.9%	113	35.0%	
Midwest	389	24.4%	56	17.3%	
West	211	13.2%	71	22.0%	
Primary Treatment					0.02
No treatment	105	6.5%	12	3.7%	
Radiation only	174	10.8%	41	12.6%	
Radiation and chemotherapy	930	57.9%	201	61.7%	
Surgery and radiation	44	2.7%	9	2.8%	
Surgery, chemotherapy and radiation	131	8.2%	37	11.3%	
Surgery only	132	8.2%	16	4.9%	
Chemotherapy only	89	5.5%	10	3.1%	
Clinical T Stage					0.01
0	2	0.1%	3	0.9%	
1	243	15.2%	49	15.2%	
2	525	32.9%	119	37.0%	
3	414	26.0%	83	25.8%	
4	385	24.2%	58	18.0%	
X	25	1.6%	10	3.1%	
Clinical N Stage					0.003
0	521	32.5%	73	22.5%	
1	239	14.9%	57	17.5%	
2	738	46.0%	174	53.5%	
3	92	5.7%	21	6.5%	
X	14	0.9%	0	0.0%	
Grade					0.14
Well differentiated	77	6.2%	9	3.7%	
Moderately differentiated	702	56.1%	124	51.5%	
Poorly differentiated	465	37.1%	106	44.0%	
Undifferentiated, anaplastic	8	0.6%	2	0.8%	

Table 3. Patient Characteristics Among Those with Oral Cavity SCC by HPV Status

	HPV-		HPV+		
	Count	%	Count	%	P-Value
Average Age (years)	62.40		59.09		<0.001
Sex					<0.001
Male	4700	59.8%	884	72.5%	
Female	3160	40.2%	336	27.5%	
Ethnicity					0.08
White	6870	88.1%	1100	90.8%	
Black	589	7.6%	69	5.7%	
American Indian/Eskimo	22	0.3%	3	0.2%	
Asian/Pacific Islander	254	3.3%	29	2.4%	
Other	65	0.8%	10	0.8%	
Charlson/Deyo Score					0.13
0	6041	76.9%	948	77.7%	
1	1389	17.7%	222	18.2%	
2	430	5.5%	50	4.1%	
Primary Payer					<0.001
Not Insured	368	4.8%	74	6.1%	
Private Insurance/Managed Care	3132	40.5%	565	46.8%	
Medicaid	775	10.0%	120	10.0%	
Medicare	3330	43.1%	417	34.6%	
Other Government	123	1.6%	30	2.5%	
Median Income Quartiles: 2008-2012					0.25
<$38,000	1355	17.3%	184	15.2%	
$38,000-$47,999	1896	24.2%	299	24.6%	
$48,000-$62,999	2113	27.0%	349	28.7%	
$63,000 +	2472	31.5%	382	31.5%	
Urban/Rural					0.04
Metro	6378	83.2%	1028	85.9%	
Urban	1169	15.3%	149	12.4%	
Rural	116	1.5%	20	1.7%	
Facility Type					0.15
Community Cancer Program	462	6.2%	84	7.3%	
Comprehensive Community Cancer Program	2049	27.4%	314	27.4%	
Academic/Research Program	4130	55.2%	642	56.0%	
Integrated Network Cancer Program	838	11.2%	107	9.3%	
Other specified types of cancer programs	0	0.0%	0	0.0%	
Facility Location					0.08
Northeast	1657	22.2%	242	21.1%	
South	2674	35.8%	376	32.8%	
Midwest	1942	26.0%	327	28.5%	
West	1206	16.1%	202	17.6%	
Primary Treatment					<0.001
No treatment	283	3.6%	40	3.3%	
Radiation only	499	6.3%	82	6.7%	
Radiation and chemotherapy	1073	13.7%	331	27.1%	
Surgery and radiation	969	12.3%	137	11.2%	
Surgery, chemotherapy and radiation	1214	15.4%	201	16.5%	
Surgery only	3692	47.0%	403	33.0%	
Chemotherapy only	130	1.7%	26	2.1%	
Clinical T Stage					0.001
0	13	0.2%	4	0.3%	
1	2871	37.7%	380	32.3%	
2	2323	30.5%	378	32.1%	
3	777	10.2%	128	10.9%	
4	1590	20.9%	272	23.1%	
X	48	0.6%	16	1.4%	
Clinical N Stage					<0.001
0	5227	66.7%	618	50.8%	
1	884	11.3%	176	14.5%	
2	1589	20.3%	399	32.8%	
3	71	0.9%	17	1.4%	
X	65	0.8%	7	0.6%	
Grade					<0.001
Well differentiated	1624	23.4%	148	14.8%	
Moderately differentiated	4119	59.3%	565	56.6%	
Poorly differentiated	1188	17.1%	279	28.0%	
Undifferentiated, anaplastic	17	0.2%	6	0.6%	

Table 4. Patient Characteristics Among Those with Larynx SCC by HPV Status

	HPV-		HPV+		
	Count	%	Count	%	P-Value
Average Age (years)	64.12		59.58		0.003
Sex					<0.001
Male	5309	78.3%	661	70.2%	
Female	1475	21.7%	280	29.8%	
Ethnicity					0.00
White	5602	83.2%	812	87.2%	
Black	958	14.2%	102	11.0%	
American Indian/Eskimo	20	0.3%	6	0.6%	
Asian/Pacific Islander	102	1.5%	8	0.9%	
Other	49	0.7%	3	0.3%	
Charlson/Deyo Score					0.39
0	4785	70.5%	684	72.7%	
1	1509	22.2%	193	20.5%	
2	490	7.2%	64	6.8%	
Primary Payer					<0.001
Not Insured	366	5.5%	58	6.2%	
Private Insurance/Managed Care	2175	32.6%	376	40.5%	
Medicaid	853	12.8%	107	11.5%	
Medicare	3164	47.5%	374	40.3%	
Other Government	109	1.6%	14	1.5%	
Median Income Quartiles: 2008-2012					0.31
<$38,000	1499	22.2%	193	20.6%	
$38,000-$47,999	1798	26.6%	242	25.8%	
$48,000-$62,999	1678	24.8%	258	27.5%	
$63,000 +	1789	26.4%	244	26.0%	
Urban/Rural					0.17
Metro	5613	84.7%	760	82.4%	
Urban	914	13.8%	143	15.5%	
Rural	102	1.5%	19	2.1%	
Facility Type					0.09
Community Cancer Program	658	9.8%	75	8.7%	
Comprehensive Community Cancer Program	2512	37.4%	358	41.3%	
Academic/Research Program	2855	42.5%	360	41.5%	
Integrated Network Cancer Program	687	10.2%	74	8.5%	
Other specified types of cancer programs	0	0.0%	0	0.0%	
Facility Location					0.24
Northeast	1604	23.9%	223	25.7%	
South	2575	38.4%	310	35.8%	
Midwest	1653	24.6%	206	23.8%	
West	880	13.1%	128	14.8%	
Primary Treatment					<0.001
No treatment	451	6.6%	40	4.3%	
Radiation only	1897	28.0%	247	26.2%	
Radiation and chemotherapy	2279	33.6%	364	38.7%	
Surgery and radiation	604	8.9%	63	6.7%	
Surgery, chemotherapy and radiation	455	6.7%	79	8.4%	
Surgery only	913	13.5%	130	13.8%	
Chemotherapy only	185	2.7%	18	1.9%	
Clinical T Stage					0.001
0	7	0.1%	2	0.2%	
1	2120	32.8%	227	25.4%	
2	1639	25.3%	262	29.3%	
3	1694	26.2%	260	29.1%	
4	968	15.0%	135	15.1%	
X	39	0.6%	7	0.8%	
Clinical N Stage					<0.001
0	4589	67.9%	535	57.0%	
1	640	9.5%	101	10.8%	
2	1369	20.2%	273	29.1%	
3	98	1.4%	22	2.3%	
X	65	1.0%	7	0.7%	
Grade					<0.001
Well differentiated	820	15.6%	81	11.1%	
Moderately differentiated	3282	62.4%	447	61.1%	
Poorly differentiated	1142	21.7%	200	27.4%	
Undifferentiated, anaplastic	17	0.3%	3	0.4%	

Table 5. Patient Characteristics Among Those with Sinonasal Tract SCC by HPV Status

	HPV-		HPV+		
	Count	%	Count	%	P-Value
Average Age (years)	65.02		60.66		0.298
Sex					0.07
Male	284	64.0%	99	72.3%	
Female	160	36.0%	38	27.7%	
Ethnicity					0.24
White	353	80.2%	118	86.8%	
Black	62	14.1%	9	6.6%	
American Indian/Eskimo	4	0.9%	1	0.7%	
Asian/Pacific Islander	18	4.1%	7	5.1%	
Other	3	0.7%	1	0.7%	
Charlson/Deyo Score					0.87
0	336	75.7%	103	75.2%	
1	78	17.6%	23	16.8%	
2	30	6.8%	11	8.0%	
Primary Payer					0.04
Not Insured	21	4.8%	4	2.9%	
Private Insurance/Managed Care	156	35.8%	60	43.8%	
Medicaid	31	7.1%	17	12.4%	
Medicare	223	51.1%	53	38.7%	
Other Government	5	1.1%	3	2.2%	
Median Income Quartiles: 2008-2012					0.15
<$38,000	104	23.6%	22	16.1%	
$38,000-$47,999	105	23.8%	42	30.7%	
$48,000-$62,999	121	27.4%	42	30.7%	
$63,000 +	111	25.2%	31	22.6%	
Urban/Rural					0.27
Metro	357	82.8%	117	88.6%	
Urban	68	15.8%	14	10.6%	
Rural	6	1.4%	1	0.8%	
Facility Type					0.68
Community Cancer Program	33	7.7%	7	5.3%	
Comprehensive Community Cancer Program	120	28.1%	41	31.1%	
Academic/Research Program	220	51.5%	70	53.0%	
Integrated Network Cancer Program	54	12.6%	14	10.6%	
Other specified types of cancer programs	0	0.0%	0	0.0%	
Facility Location					0.17
Northeast	82	19.2%	33	25.0%	
South	185	43.3%	47	35.6%	
Midwest	88	20.6%	23	17.4%	
West	72	16.9%	29	22.0%	
Primary Treatment					0.85
No treatment	31	7.0%	6	4.4%	
Radiation only	52	11.7%	16	11.7%	
Radiation and chemotherapy	92	20.7%	32	23.4%	
Surgery and radiation	80	18.0%	30	21.9%	
Surgery, chemotherapy and radiation	72	16.2%	20	14.6%	
Surgery only	104	23.4%	29	21.2%	
Chemotherapy only	13	2.9%	4	2.9%	
Clinical T Stage					0.011
0	2	0.5%	0	0.0%	
1	107	24.7%	30	22.7%	
2	54	12.4%	30	22.7%	
3	73	16.8%	26	19.7%	
4	198	45.6%	45	34.1%	
X	0	0.0%	1	0.8%	
Clinical N Stage					0.99
0	352	79.3%	106	77.9%	
1	28	6.3%	9	6.6%	
2	51	11.5%	16	11.8%	
3	2	0.5%	1	0.7%	
X	11	2.5%	4	2.9%	
Grade					0.01
Well differentiated	53	14.6%	4	3.3%	
Moderately differentiated	166	45.9%	62	51.7%	
Poorly differentiated	138	38.1%	52	43.3%	
Undifferentiated, anaplastic	5	1.4%	2	1.7%	

Table 6. Patient Characteristics Among Those with Nasopharyngeal SCC by HPV Status

	HPV-		HPV+		
	Count	%	Count	%	P-Value
Average Age (years)		56.27		56.21	<0.001
Sex					0.25
Male	466	68.5%	235	72.1%	
Female	214	31.5%	91	27.9%	
Ethnicity					<0.001
White	458	67.4%	283	87.6%	
Black	99	14.6%	22	6.8%	
American Indian/Eskimo	3	0.4%	0	0.0%	
Asian/Pacific Islander	111	16.3%	17	5.3%	
Other	9	1.3%	1	0.3%	
Charlson/Deyo Score					0.80
0	554	81.5%	266	81.6%	
1	96	14.1%	43	13.2%	
2	30	4.4%	17	5.2%	
Primary Payer					0.25
Not Insured	51	7.6%	18	5.6%	
Private Insurance/Managed Care	327	49.0%	180	55.7%	
Medicaid	91	13.6%	34	10.5%	
Medicare	185	27.7%	86	26.6%	
Other Government	14	2.1%	5	1.5%	
Median Income Quartiles: 2008-2012					0.18
<$38,000	136	20.0%	48	14.7%	
$38,000-$47,999	157	23.1%	87	26.7%	
$48,000-$62,999	171	25.2%	89	27.3%	
$63,000 +	215	31.7%	102	31.3%	
Urban/Rural					0.01
Metro	588	88.8%	267	84.0%	
Urban	72	10.9%	44	13.8%	
Rural	2	0.3%	7	2.2%	
Facility Type					0.41
Community Cancer Program	49	8.1%	30	9.8%	
Comprehensive Community Cancer Program	219	36.3%	96	31.3%	
Academic/Research Program	267	44.3%	148	48.2%	
Integrated Network Cancer Program	68	11.3%	33	10.7%	
Other specified types of cancer programs	0	0.0%	0	0.0%	
Facility Location					0.61
Northeast	121	20.1%	62	20.2%	
South	228	37.8%	106	34.5%	
Midwest	142	23.5%	84	27.4%	
West	112	18.6%	55	17.9%	
Primary Treatment					0.17
No treatment	45	6.6%	11	3.4%	
Radiation only	36	5.3%	22	6.7%	
Radiation and chemotherapy	506	74.4%	248	76.1%	
Surgery and radiation	9	1.3%	4	1.2%	
Surgery, chemotherapy and radiation	34	5.0%	23	7.1%	
Surgery only	12	1.8%	2	0.6%	
Chemotherapy only	38	5.6%	16	4.9%	
Clinical T Stage					0.01
0	1	0.1%	1	0.3%	
1	205	30.3%	73	22.6%	
2	140	20.7%	72	22.3%	
3	149	22.0%	62	19.2%	
4	161	23.8%	109	33.7%	
X	20	3.0%	6	1.9%	
Clinical N Stage					0.001
0	175	25.8%	79	24.3%	
1	163	24.0%	88	27.1%	
2	233	34.3%	136	41.8%	
3	102	15.0%	19	5.8%	
X	6	0.9%	3	0.9%	
Grade					<0.001
Well differentiated	21	4.2%	5	2.1%	
Moderately differentiated	119	23.9%	72	30.8%	
Poorly differentiated	280	56.3%	150	64.1%	
Undifferentiated, anaplastic	77	15.5%	7	3.0%	

Table 7. 5-year unadjusted survival rates by HPV status and cancer sub-site

Sub-site	HPV+	HPV-	Difference in survival (95%CI)
Oropharynx	77.6%	50.7%	26.9% (25.6%-28.2%)
Hypopharynx	52.2%	28.8%	23.4% (17.5%-29.3%)
Oral Cavity	59.4%	53.1%	6.3% (3.3%-9.3%)
Larynx	57.2%	48.7%	8.5% (5.1%-11.9%)
Sinonasal tract	63.1%	45.1%	18% (8.7%-27.3%)
Nasopharynx	52.5%	58.7%	-6.1% (-12.8%-0.4%)

Table 8. Cox Proportional Hazards Regression Analysis for Patients with Oropharyngeal SCC

	HR (95% CI)
Mean Age	1.01 (1.01-1.02)
Sex	
Men	1
Women	1.09 (1.00-1.19)
Ethnicity	
White	1
Black	1.05 (0.94-1.17)
American Indian/Eskimo	0.40 (0.13-1.25)
Asian/Pacific Islander	0.68 (0.47-0.97)
Other	1.06 (0.58-1.92)
T Stage	
T0	1
T1	1.76 (0.65-4.73)
T2	2.71 (1.01-7.25)
T3	4.45 (1.66-11.9)
T4	6.43 (2.40-17.2)
TX	3.29 (1.20-8.98)
N Stage	
N0	1
N1	0.87 (0.77-0.99)
N2	1.10 (0.99-1.21)
N3	1.84 (1.58-2.15)
NX	1.25 (0.82-1.91)
Charleson/Deyo Score	
0	1
1	1.35 (1.24-1.48)
2	1.62 (1.41-1.86)
HPV Status	
HPV-	**1**
HPV High Risk	**0.44 (0.41-0.47)**
Insurance Status	
Not Insured	1
Private Insurance/Managed Care	0.57 (0.49-0.66)
Medicaid	1.12 (0.96-1.31)
Medicare	0.97 (0.83-1.13)
Other Government	0.99 (0.76-1.29)
Median Income Quartiles: 2008-2012	
<$38,000	1
$38,000-$47,999	0.89 (0.80-0.98)
$48,000-$62,999	0.81 (0.73-0.90)
$63,000 +	0.69 (0.62-0.77)
Treatment Group	
No treatment	1
Radiation only	0.41 (0.34-0.50)
Radiation and chemotherapy	0.26 (0.22-0.30)
Surgery and radiation	0.19 (0.14-0.24)
Surgery, chemotherapy and radiation	0.26 (0.22-0.31)
Surgery only	0.32 (0.26-0.40)
Chemotherapy Only	1.04 (0.86-1.25)

Table 9. Cox Proportional Hazards Regression Analysis for Patients with Hypopharyngeal SCC

	HR (95% CI)
Mean Age	1.02 (1.01-1.03)
Sex	
Men	1
Women	0.94 (0.77-1.16)
Ethnicity	
White	1
Black	1.13 (0.91-1.40)
American Indian/Eskimo	0.83 (0.26-2.63)
Asian/Pacific Islander	0.44 (0.18-1.08)
Other	1.21 (0.29-4.93)
T Stage	
T0	1
T1	1.48 (0.19-11.0)
T2	2.23 (0.30-16.4)
T3	3.14 (0.42-23.1)
T4	4.33 (0.58-31.9)
TX	1.65 (0.19-13.6)
N Stage	
N0	1
N1	1.31 (1.01-1.69)
N2	1.48 (1.21-1.82)
N3	3.09 (2.22-4.31)
NX	10.1 (3.58-28.9)
Charleson/Deyo Score	
0	1
1	1.06 (0.88-1.29)
2	1.42 (1.04-1.95)
HPV Status	
HPV-	**1**
HPV High Risk	**0.59 (0.45-0.77)**
Insurance Status	
Not Insured	1
Private Insurance/Managed Care	0.57 (0.40-0.82)
Medicaid	0.80 (0.55-1.15)
Medicare	0.73 (0.50-1.06)
Other Government	0.57 (0.30-1.05)
Median Income Quartiles: 2008-2012	
<$38,000	1
$38,000-$47,999	0.89 (0.71-1.12)
$48,000-$62,999	0.93 (0.74-1.17)
$63,000 +	0.73 (0.58-0.93)
Treatment Group	
No treatment	1
Radiation only	0.50 (0.34-0.72)
Radiation and chemotherapy	0.27 (0.20-0.37)
Surgery and radiation	0.17 (0.09-0.32)
Surgery, chemotherapy and radiation	0.23 (0.15-0.34)
Surgery only	0.29 (0.19-0.45)
Chemotherapy Only	0.84 (0.56-1.25)

Table 10. Cox Proportional Hazards Regression Analysis for Patients with Oral Cavity SCC

	HR (95% CI)
Mean Age	1.02 (1.02-1.02)
Sex	
Men	1
Women	0.85 (0.78-0.93)
Ethnicity	
White	1
Black	0.99 (0.84-1.15)
American Indian/Eskimo	1.12 (0.50-2.52)
Asian/Pacific Islander	0.95 (0.73-1.23)
Other	0.55 (0.31-0.99)
T Stage	
T0	1
T1	0.41 (0.17-1.01)
T2	0.72 (0.29-1.75)
T3	0.98 (0.40-2.40)
T4	1.14 (0.46-2.77)
TX	1.10 (0.41-2.94)
N Stage	
N0	1
N1	1.49 (1.30-1.70)
N2	1.62 (1.44-1.81)
N3	1.94 (1.38-2.73)
NX	1.23 (0.78-1.93)
Charleson/Deyo Score	
0	1
1	1.08 (0.96-1.21)
2	1.47 (1.24-1.74)
HPV Status	
HPV-	**1**
HPV High Risk	**0.76 (0.66-0.87)**
Insurance Status	
Not Insured	1
Private Insurance/Managed Care	0.80 (0.65-0.98)
Medicaid	1.31 (1.05-1.62)
Medicare	1.04 (0.85-1.28)
Other Government	1.09 (0.75-1.58)
Median Income Quartiles: 2008-2012	
<$38,000	1
$38,000-$47,999	0.88 (0.77-1.00)
$48,000-$62,999	0.94 (0.83-1.07)
$63,000 +	0.81 (0.71-0.92)
Treatment Group	
No treatment	1
Radiation only	0.50 (0.39-0.64)
Radiation and chemotherapy	0.44 (0.35-0.54)
Surgery and radiation	0.33 (0.26-0.41)
Surgery, chemotherapy and radiation	0.44 (0.35-0.55)
Surgery only	0.38 (0.31-0.46)
Chemotherapy Only	0.89 (0.66-1.21)

Table 11. Cox Proportional Hazards Regression Analysis for Patients with Larynx SCC

	HR (95% CI)
Mean Age	1.03 (1.02-1.03)
Sex	
Men	1
Women	0.81 (0.71-0.91)
Ethnicity	
White	1
Black	1.04 (0.91-1.20)
American Indian/Eskimo	0.58 (0.18-1.82)
Asian/Pacific Islander	0.86 (0.55-1.34)
Other	0.45 (0.18-1.10)
T Stage	
T0	1
T1	1.03 (0.14-7.36)
T2	1.73 (0.24-12.4)
T3	2.18 (0.30-15.6)
T4	2.98 (0.41-21.4)
TX	3.23 (0.42-24.7)
N Stage	
N0	1
N1	1.29 (1.09-1.53)
N2	1.72 (1.51-1.96)
N3	3.28 (2.46-4.37)
NX	2.29 (1.55-3.38)
Charleson/Deyo Score	
0	1
1	1.10 (0.98-1.24)
2	1.58 (1.33-1.86)
HPV Status	
HPV-	**1**
HPV High Risk	**0.71 (0.59-0.85)**
Insurance Status	
Not Insured	1
Private Insurance/Managed Care	0.99 (0.78-1.24)
Medicaid	1.34 (1.05-1.71)
Medicare	1.10 (0.87-1.39)
Other Government	0.93 (0.56-1.53)
Median Income Quartiles: 2008-2012	
<$38,000	1
$38,000-$47,999	1.03 (0.89-1.18)
$48,000-$62,999	1.01 (0.87-1.16)
$63,000 +	0.86 (0.74-1.00)
Treatment Group	
No treatment	1
Radiation only	0.34 (0.28-0.42)
Radiation and chemotherapy	0.34 (0.28-0.41)
Surgery and radiation	0.24 (0.18-0.31)
Surgery, chemotherapy and radiation	0.32 (0.25-0.41)
Surgery only	0.33 (0.26-0.42)
Chemotherapy Only	0.93 (0.71-1.22)

Table 12. Cox Proportional Hazards Regression Analysis for Patients with Sinonasal SCC

	HR (95% CI)
Mean Age	1.04 (1.02-1.05)
Sex	
Men	1
Women	0.79 (0.55-1.14)
Ethnicity	
White	1
Black	1.51 (0.97-2.35)
American Indian/Eskimo	2.30 (0.67-7.83)
Asian/Pacific Islander	1.57 (0.78-3.14)
Other	*
T Stage	
T0	1
T1	*
T2	*
T3	*
T4	*
TX	*
N Stage	
N0	1
N1	2.12 (1.16-3.86)
N2	1.30 (0.76-2.22)
N3	0.88 (0.11-6.91)
NX	0.88 (0.31-2.47)
Charleson/Deyo Score	
0	1
1	1.35 (0.86-2.09)
2	2.14 (1.24-3.69)
HPV Status	
HPV-	**1**
HPV High Risk	**0.63 (0.39-1.01)**
Insurance Status	
Not Insured	1
Private Insurance/Managed Care	1.24 (0.48-3.20)
Medicaid	3.16 (1.13-8.81)
Medicare	1.30 (0.48-3.50)
Other Government	0.73 (0.07-6.73)
Median Income Quartiles: 2008-2012	
<$38,000	1
$38,000-$47,999	0.93 (0.58-1.48)
$48,000-$62,999	1.27 (0.80-2.02)
$63,000 +	1.01 (0.61-1.66)
Treatment Group	
No treatment	1
Radiation only	0.17 (0.08-0.39)
Radiation and chemotherapy	0.24 (0.11-0.50)
Surgery and radiation	0.11 (0.05-0.26)
Surgery, chemotherapy and radiation	0.15 (0.06-0.34)
Surgery only	0.23 (0.11-0.49)
Chemotherapy Only	0.11 (0.03-0.36)

*Insufficient sample size in category for calculation

Table 13. Cox Proportional Hazards Regression Analysis for Patients with Nasopharyngeal SCC

	HR (95% CI)
Mean Age	1.03 (1.02-1.05)
Sex	
Men	1
Women	0.85 (0.61-1.17)
Ethnicity	
White	1
Black	1.06 (0.67-1.68)
American Indian/Eskimo	1.30 (0.16-10.2)
Asian/Pacific Islander	0.63 (0.36-1.10)
Other	*
T Stage	
T0	1
T1	0.17 (0.02-1.37)
T2	0.19 (0.02-1.53)
T3	0.25 (0.03-1.98)
T4	0.43 (0.05-3.31)
TX	0.26 (0.03-2.32)
N Stage	
N0	1
N1	0.76 (0.50-1.17)
N2	1 (0.68-1.45)
N3	1.49 (0.92-2.39)
NX	1.23 (0.44-3.46)
Charleson/Deyo Score	
0	1
1	1.18 (0.81-1.73)
2	1.73 (1.03-2.89)
HPV Status	
HPV-	**1**
HPV High Risk	**1.03 (0.75-1.42)**
Insurance Status	
Not Insured	1
Private Insurance/Managed Care	0.41 (0.24-0.70)
Medicaid	0.61 (0.33-1.12)
Medicare	0.57 (0.31-1.02)
Other Government	1.23 (0.39-3.85)
Median Income Quartiles: 2008-2012	
<$38,000	1
$38,000-$47,999	0.83 (0.54-1.29)
$48,000-$62,999	0.93 (0.61-1.42)
$63,000 +	0.70 (0.46-1.07)
Treatment Group	
No treatment	1
Radiation only	0.27 (0.12-0.61)
Radiation and chemotherapy	0.20 (0.11-0.34)
Surgery and radiation	0.07 (0.00-0.57)
Surgery, chemotherapy and radiation	0.29 (0.13-0.63)
Surgery only	0.68 (0.23-2.00)
Chemotherapy Only	1.09 (0.57-2.08)

*Insufficient simple size for calculation

Table 14. Patient characteristics among those with oropharyngeal squamous cell carcinoma based on sex and HPV status

	Oropharynx HPV-associated					Oropharynx HPV -				
	Male		Female			Male		Female		
	Count	%	Count	%	p-value	Count	%	Count	%	p-value
Mean age	58,69		59,65		<0.001	60,74		61,66		<0.001
Ethnicity					0.006					0.32
White	10997	94.0%	1717	91.9%		5167	86.0%	1566	84.2%	
Black	538	4.6%	107	5.7%		709	11.8%	243	13.1%	
American Indian/Eskimo	22	0.2%	5	0.3%		13	0.2%	7	0.4%	
Asian/Pacific Islander	103	0.9%	28	1.5%		87	1.4%	32	1.7%	
Other	45	0.4%	12	0.6%		32	0.5%	11	0.6%	
Charlson/Deyo Score					<0.001					0.72
0	9957	84.3%	1530	81.1%		4817	79.5%	1477	78.7%	
1	1486	12.6%	272	14.4%		942	15.6%	304	16.2%	
2	365	3.1%	84	4.5%		297	4.9%	96	5.1%	
AJCC Clinical Staging										
T Staging					<0.001					0.002
T0	85	0.7%	13	0.7%		16	0.3%	6	0.3%	
T1	3225	27.4%	582	31.1%		1221	20.3%	428	23.0%	
T2	4834	41.1%	770	41.2%		2097	34.9%	671	36.0%	
T3	1925	16.4%	254	13.6%		1319	22.0%	339	18.2%	
T4	1354	11.5%	190	10.2%		1180	19.7%	380	20.4%	
TX	326	2.8%	61	3.3%		170	2.8%	38	2.0%	
N Staging					<0.001					<0.001
N0	1336	11.3%	318	16.9%		1410	23.4%	594	31.7%	
N1	1874	15.9%	424	22.5%		997	16.5%	344	18.3%	
N2	8023	68.1%	1088	57.8%		3298	54.6%	877	46.8%	
N3	522	4.4%	49	2.6%		293	4.9%	50	2.7%	
NX	33	0.3%	3	0.2%		37	0.6%	10	0.5%	
M Staging					0.812					0.013
M0	11042	97.7%	1763	98.0%		5435	95.4%	1718	96.7%	
M1	265	2.3%	36	2.0%		264	4.6%	58	3.3%	
Primary Site					<0.001					0.005
Base of Tongue	4845	41.0%	611	32.4%		2543	42.0%	745	39.7%	
Tonsil	6258	53.0%	1150	61.0%		2615	43.2%	796	42.4%	
Other OP	705	6.0%	125	6.6%		898	14.8%	336	17.9%	
Insurance Status					<0.001					<0.001
Not Insured	437	3.7%	71	3.8%		383	6.4%	111	6.0%	
Private Insurance/Managed Care	7264	62.2%	989	52.9%		2601	43.8%	732	39.5%	
Medicaid	753	6.4%	162	8.7%		703	11.8%	240	13.0%	
Medicare	2940	25.2%	634	33.9%		2121	35.7%	750	40.5%	
Other Government	290	2.5%	12	0.6%		132	2.2%	18	1.0%	
Median Income Quartiles 2008-2012					0.002					0.043
<$38,000	1472	12.5%	274	14.6%		1184	19.7%	389	20.9%	
$38,000-$47,999	2443	20.8%	435	23.1%		1335	22.2%	451	24.2%	
$48,000-$62,999	3265	27.7%	488	25.9%		1606	26.7%	491	26.4%	
$63,000 +	4588	39.0%	685	36.4%		1900	31.5%	530	28.5%	
Urban/Rural 2013					0.190					0.27
Metro	9826	85.3%	1573	84.8%		5053	85.5%	1539	84.0%	
Urban	1488	12.9%	259	14.0%		775	13.1%	265	14.5%	
Rural	200	1.7%	24	1.3%		80	1.4%	28	1.5%	
Facility Type					0.214					0.346
Community Cancer Program	743	6.4%	128	7.0%		531	8.9%	159	8.6%	
Comprehensive Community Cancer Program	3719	31.8%	596	32.7%		2153	36.0%	632	34.3%	
Academic/Research Program	5810	49.7%	907	49.8%		2618	43.8%	851	46.2%	
Integrated Network Cancer Program	1407	12.0%	192	10.5%		671	11.2%	199	10.8%	
Other specified types of cancer programs	0	0.0%	0	0.0%		0	0.0%	0	0.0%	
Facility Location					0.110					0.130
East	2440	20.9%	419	23.0%		1223	20.5%	398	21.6%	
South	3915	33.5%	610	33.5%		2454	41.1%	704	38.2%	
Midwest	3196	27.4%	493	27.0%		1408	23.6%	467	25.4%	
West	2128	18.2%	301	16.5%		888	14.9%	272	14.8%	
Treatment Group					<0.001					<0.001
No treatment	210	1.8%	31	1.6%		286	4.7%	90	4.8%	
Radiation only	868	7.4%	158	8.4%		508	8.4%	186	9.9%	
Radiation and Chemo	7185	60.8%	1011	53.6%		3571	59.0%	1004	53.5%	
Surgery and Radiation	726	6.1%	155	8.2%		240	4.0%	94	5.0%	
Surgery, Chemotherapy and Radiation	2027	17.2%	341	18.1%		725	12.0%	210	11.2%	
Surgery only	572	4.8%	155	8.2%		464	7.7%	218	11.6%	
Chemotherapy Only	220	1.9%	35	1.9%		262	4.3%	75	4.0%	

Table 15. Patient characteristics among those with oral cavity squamous cell carcinoma based on sex and HPV status

	Oral Cavity HPV-associated					Oral Cavity HPV -				
	Male		Female			Male		Female		
	Count	%	Count	%	p-value	Count	%	Count	%	p-value
Mean age	58,85		59,72		<0.001	61,35		63,95		<0.001
Ethnicity					0.502					0.512
White	804	91.6%	296	88.9%		4093	87.7%	2777	88.7%	
Black	44	5.0%	25	7.5%		371	7.9%	218	7.0%	
American Indian/Eskimo	2	0.2%	1	0.3%		15	0.3%	7	0.2%	
Asian/Pacific Islander	20	2.3%	9	2.7%		151	3.2%	103	3.3%	
Other	8	0.9%	2	0.6%		39	0.8%	26	0.8%	
Charlson/Deyo Score					0.11					0.92
0	689	77.9%	259	77.1%		3607	76.7%	2434	77.0%	
1	165	18.7%	57	17.0%		837	17.8%	552	17.5%	
2	30	3.4%	20	6.0%		256	5.4%	174	5.5%	
AJCC Clinical Staging										
T Staging					0.005					<0.001
T0	4	0.5%	0	0.0%		8	0.2%	5	0.2%	
T1	251	29.3%	129	40.1%		1579	34.6%	1292	42.3%	
T2	277	32.4%	101	31.4%		1409	30.8%	914	29.9%	
T3	96	11.2%	32	9.9%		506	11.1%	271	8.9%	
T4	216	25.2%	56	17.4%		1039	22.7%	551	18.1%	
TX	12	1.4%	4	1.2%		29	0.6%	19	0.6%	
N Staging					0.003					<0.001
N0	420	47.5%	198	59.5%		3001	64.0%	2226	70.7%	
N1	130	14.7%	46	13.8%		552	11.8%	332	10.5%	
N2	313	35.4%	86	25.8%		1038	22.2%	551	17.5%	
N3	15	1.7%	2	0.6%		57	1.2%	14	0.4%	
NX	6	0.7%	1	0.3%		38	0.8%	27	0.9%	
M Staging					0.939					0.004
M0	833	97.9%	313	97.8%		4339	97.7%	2959	98.6%	
M1	18	2.1%	7	2.2%		102	2.3%	41	1.4%	
Insurance Status					0.09					<0.001
Not Insured	51	5.8%	23	6.9%		236	5.1%	132	4.2%	
Private Insurance/Managed Care	420	48.1%	145	43.5%		1935	41.9%	1197	38.5%	
Medicaid	90	10.3%	30	9.0%		515	11.1%	260	8.4%	
Medicare	286	32.8%	131	39.3%		1850	40.0%	1480	47.6%	
Other Government	26	3.0%	4	1.2%		85	1.8%	38	1.2%	
Median Income Quartiles 2008-2012					0.22					0.010
<$38,000	137	15.6%	47	14.0%		843	18.0%	512	16.3%	
$38,000-$47,999	206	23.4%	93	27.8%		1171	25.0%	725	23.0%	
$48,000-$62,999	264	30.0%	85	25.4%		1250	26.7%	863	27.4%	
$63,000 +	272	30.9%	110	32.8%		1426	30.4%	1046	33.2%	
Urban/Rural 2013					0.510					0.072
Metro	741	85.2%	287	87.8%		3799	82.8%	2579	83.9%	
Urban	114	13.1%	35	10.7%		708	15.4%	461	15.0%	
Rural	15	1.7%	5	1.5%		81	1.8%	35	1.1%	
Facility Type					0.507					0.967
Community Cancer Program	64	7.6%	20	6.6%		274	6.1%	188	6.3%	
Comprehensive Community Cancer Program	239	28.3%	75	24.8%		1226	27.3%	823	27.6%	
Academic/Research Program	466	55.2%	176	58.1%		2487	55.3%	1643	55.0%	
Integrated Network Cancer Program	75	8.9%	32	10.6%		507	11.3%	331	11.1%	
Other specified types of cancer programs	0	0.0%	0	0.0%		0	0.0%	0	0.0%	
Facility Location					0.990					0.026
East	178	21.1%	64	21.1%		995	22.1%	662	22.2%	
South	278	32.9%	98	32.3%		1660	36.9%	1014	34.0%	
Midwest	240	28.4%	87	28.7%		1149	25.6%	793	26.6%	
West	148	17.5%	54	17.8%		690	15.4%	516	17.3%	
Treatment Group					<0.001					<0.001
No treatment	29	3.3%	11	3.3%		163	3.5%	120	3.8%	
Radiation only	56	6.3%	26	7.7%		282	6.0%	217	6.9%	
Radiation and Chemo	269	30.4%	62	18.5%		717	15.3%	356	11.3%	
Surgery and Radiation	100	11.3%	37	11.0%		573	12.2%	396	12.5%	
Surgery, Chemotherapy and Radiation	146	16.5%	55	16.4%		806	17.1%	408	12.9%	
Surgery only	264	29.9%	139	41.4%		2072	44.1%	1620	51.3%	
Chemotherapy Only	20	2.3%	6	1.8%		87	1.9%	43	1.4%	

Table 16. Cox proportional hazards regression analysis for patients with oropharyngeal squamous cell carcinoma

	Oropharynx HPV-associated		Oropharynx HPV -	
	HR (95% CI)	P	HR (95% CI)	P
Mean age	1.02 (1.01-1.03)	<0.001	1.01 (1.00-1.02)	<0.001
Ethnicity				
White	1.00		1.00	
Black	0.86 (0.67-1.10)	0.25	1.14 (1.01-1.30)	0.03
American Indian/Eskimo	0.61 (0.15-2.47)	0.49	0.22 (0.03-1.58)	0.13
Asian/Pacific Islander	0.52 (0.24-1.10)	0.09	0.75 (0.50-1.14)	0.19
Other	0.63 (0.15-2.52)	0.51	1.29 (0.67-2.49)	0.44
Sex				
Men	**1.00**		**1.00**	
Women	**0.93 (0.79-1.09)**	**0.412**	**1.15 (1.04-1.28)**	**0.004**
Charlson/Deyo Score				
0	1.0		1.0	
1	1.42 (1.23-1.65)	<0.001	1.31 (1.17-1.46)	<0.001
2	1.97 (1.56-2.48)	<0.001	1.49 (1.25-1.77)	<0.001
AJCC Clinical Staging				
T Staging				
T0	1.00		1.00	
T1	2.61 (0.64-10.5)	0.18	1.31 (0.32-5.30)	0.70
T2	4.24 (1.05-17.0)	0.04	1.93 (0.48-7.79)	0.35
T3	6.47 (1.60-26.1)	0.01	3.26 (0.81-13.1)	0.10
T4	9.92 (2.45-40.0)	0.00	4.35 (1.08-17.5)	0.04
TX	3.93 (0.93-16.4)	0.06	2.65 (0.64-10.9)	0.18
N Staging				
N0	1.00		1.00	
N1	0.81 (0.64-1.01)	0.07	0.95 (0.82-1.10)	0.53
N2	1.14 (0.95-1.37)	0.14	1.10 (0.98-1.24)	0.09
N3	2.06 (1.58-2.67)	<0.001	1.76 (1.45-2.15)	<0.001
NX	0.73 (0.29-1.83)	0.51	1.47 (0.91-2.36)	0.11
Primary Site				
Base of Tongue	1.00		1.00	
Tonsil	1.03 (0.91-1.16)	0.63	0.87 (0.79-0.96)	0.01
Other OP	1.48 (1.21-1.81)	<0.001	1.15 (1.02-1.30)	0.02
Insurance Status				
Not Insured	1.00		1.00	
Private Insurance/Managed Care	0.53 (0.41-0.68)	<0.001	0.61 (0.51-0.72)	<0.001
Medicaid	1.04 (0.78-1.38)	0.77	1.11 (0.93-1.34)	0.23
Medicare	0.99 (0.76-1.30)	0.98	0.94 (0.78-1.13)	0.55
Other Government	0.96 (0.63-1.46)	0.85	0.96 (0.67-1.36)	0.83
Median Income Quartiles 2008-2012				
<$38,000	1.00		1.00	
$38,000-$47,999	0.89 (0.75-1.06)	0.21	0.9 (0.79-1.02)	0.11
$48,000-$62,999	0.78 (0.65-0.93)	0.01	0.83 (0.73-0.94)	0.01
$63,000 +	0.65 (0.54-0.77)	<0.001	0.73 (0.64-0.83)	<0.001
Treatment Group				
No treatment	1.00		1.00	
Radiation only	0.34 (0.24-0.48)	<0.001	0.44 (0.35-0.54)	<0.001
Radiation and Chemo	0.22 (0.16-0.29)	<0.001	0.27 (0.23-0.33)	<0.001
Surgery and Radiation	0.16 (0.10-0.24)	<0.001	0.20 (0.14-0.28)	<0.001
Surgery, Chemotherapy and Radiation	0.21 (0.15-0.29)	<0.001	0.29 (0.23-0.35)	<0.001
Surgery only	0.21 (0.14-0.32)	<0.001	0.37 (0.29-0.47)	<0.001
Chemotherapy Only	1.08 (0.76-1.54)	0.64	0.94 (0.76-1.18)	0.64

Table 17. Cox proportional hazards regression analysis for patients with oral cavity squamous cell carcinoma

	Oral Cavity HPV-associated		Oral Cavity HPV -	
	HR (95% CI)	P	HR (95% CI)	P
Mean age	1.02 (1.00-1.04)	0.010	1.02 (1.02-1.02)	<0.001
Ethnicity				
White	1.00		1.00	
Black	1.88 (1.14-3.11)	0.013	0.93 (0.79-1.09)	0.41
American Indian/Eskimo	*		1.18 (0.52-2.64)	0.68
Asian/Pacific Islander	1.60 (0.64-4.00)	0.312	0.93 (0.71-1.22)	0.63
Other	0.65 (0.09-4.78)	0.678	0.54 (0.30-0.99)	0.05
Sex				
Men	**1.00**		**1.00**	
Women	**0.71 (0.50-0.99)**	**0.048**	**0.87 (0.78-0.95)**	**0.004**
AJCC Clinical Staging				
T Staging				
T0	1.00		1.00	
T1	0.36 (0.07-1.65)	0.189	0.45 (0.14-1.43)	0.18
T2	0.61 (0.13-2.80)	0.529	0.79 (0.25-2.49)	0.70
T3	0.90 (0.19-4.21)	0.903	1.07 (0.34-3.38)	0.90
T4	1.33 (0.29-5.98)	0.707	1.19 (0.37-3.73)	0.76
TX	0.67 (0.11-4.00)	0.666	1.36 (0.39-4.70)	0.63
N Staging				
N0	1.00		1.00	
N1	1.07 (0.70-1.63)	0.743	1.54 (1.34-1.77)	<0.001
N2	1.08 (0.75-1.55)	0.651	1.72 (1.52-1.94)	<0.001
N3	0.88 (0.26-2.93)	0.836	2.12 (1.49-3.03)	<0.001
NX	1.30 (0.17-9.88)	0.795	1.19 (0.75-1.89)	0.45
Insurance Status				
Not Insured	1.00		1.00	
Private Insurance/Managed Care	0.74 (0.42-1.32)	0.319	0.81 (0.65-1.00)	0.06
Medicaid	1.82 (0.96-3.43)	0.064	1.27 (1.00-1.60)	0.043
Medicare	1.32 (0.72-2.41)	0.355	1.04 (0.83-1.30)	0.72
Other Government	0.83 (0.31-2.19)	0.713	1.17 (0.78-1.76)	0.44
Median Income Quartiles 2008-2012				
<$38,000	1.00		1.00	
$38,000-$47,999	1.38 (0.88-2.17)	0.160	0.84 (0.73-0.96)	0.02
$48,000-$62,999	1.49 (0.96-2.33)	0.075	0.90 (0.79-1.03)	0.14
$63,000 +	1.37 (0.87-2.16)	0.169	0.77 (0.67-0.88)	<0.001
Treatment Group				
No treatment	1.00		1.00	
Radiation only	0.56 (0.25-1.23)	0.151	0.49 (0.37-0.63)	<0.001
Radiation and Chemo	0.42 (0.22-0.82)	0.011	0.44 (0.35-0.55)	<0.001
Surgery and Radiation	0.23 (0.10-0.50)	<0.001	0.33 (0.26-0.43)	<0.001
Surgery, Chemotherapy and Radiation	0.59 (0.30-1.15)	0.127	0.42 (0.33-0.53)	<0.001
Surgery only	0.48 (0.24-0.94)	0.033	0.37 (0.29-0.45)	<0.001
Chemotherapy Only	1.18 (0.49-2.82)	0.710	0.84 (0.61-1.16)	0.31

Table 18. Patient characteristics by age (pre- and post-Propensity Score Match)

	Pre-Propensity Score Match							Post-Propensity Score Match						
	18-39yo			40+yo				18-39 years old			40+ years old			
	Mean	Count	Column (%)	Mean	Count	Column (%)	*p-value*	Mean	Count	Column (%)	Mean	Count	Column (%)	*p-value*
Patient Age (years)	33.8			62.3			<0.001	32.5			57.8			<0.001
Sex							<0.001							0.81
Male		2,378	63.4%		110,343	72.8%			1,980	56.4%		1,970	56.1%	
Female		1,371	36.6%		41,267	27.2%			1,530	43.6%		1,540	43.9%	
Race							<0.001							0.052
White		3,180	86.2%		133,631	89.1%			2,977	86.5%		3,007	87.7%	
Black		285	7.7%		12,777	8.5%			238	6.9%		241	7.0%	
American Indian/Eskimo		12	0.3%		396	0.3%			14	0.4%		5	0.1%	
Asian/Pacific Islander		172	4.7%		2,410	1.6%			164	4.8%		126	3.7%	
Other		42	1.1%		797	0.5%			49	1.4%		49	1.4%	
Primary Payer							<0.001							<0.001
Not Insured		381	10.2%		7,985	5.3%			296	8.4%		290	8.3%	
Private Insurance/Managed Care		2,407	64.2%		64,180	42.3%			2,483	70.7%		2,510	71.5%	
Medicaid		599	16.0%		13,675	9.0%			466	13.3%		369	10.5%	
Medicare		158	4.2%		57,655	38.0%			131	3.7%		231	6.6%	
Other Government		49	1.3%		3,134	2.1%			49	1.4%		34	1.0%	
Insurance Status Unknown		155	4.1%		4,981	3.3%			85	2.4%		76	2.2%	
Charlson/Deyo Score							<0.001							0.052
0		3,467	92.5%		122,153	80.6%			3,246	92.5%		3,252	92.6%	
1		234	6.2%		22,863	15.1%			222	6.3%		235	6.7%	
2		48	1.3%		6,594	4.3%			42	1.2%		23	0.7%	
Median Income Quartiles 2008-2012							0.036							0.841
<$38,000		644	17.4%		28,122	18.8%			531	15.1%		554	15.8%	
$38,000-$47,999		885	23.9%		36,544	24.4%			820	23.4%		830	23.6%	
$48,000-$62,999		984	26.6%		39,799	26.6%			932	26.6%		912	26.0%	
$63,000 +		1,188	32.1%		45,154	30.2%			1,227	35.0%		1,214	34.6%	
Urban/Rural							0.027							0.514
Metro		3,039	83.5%		120,145	81.9%			2,908	84.5%		2,872	83.5%	
Urban		538	14.8%		23,669	16.1%			481	14.0%		509	14.8%	
Rural		61	1.7%		2,957	2.0%			54	1.6%		60	1.7%	

Table 19. Clinical, tumor characteristics by age (pre- and post-Propensity Score Match)

	Pre-Propensity Score Match					Post-Propensity Score Match				
	18-39 years old		40+ years old			18-39 years old		40+ years old		
	Count	Column (%)	Count	Column (%)	*p-value*	Count	Column (%)	Count	Column (%)	*p-value*
Primary Sub-site					<0.001					0.775
Oral Cavity	2,482	66.2%	67,385	44.4%		2,728	77.7%	2,718	77.4%	
Oropharynx	1,267	33.8%	84,225	55.6%		782	22.3%	792	22.6%	
Clinical T Stage					<0.001					0.937
0	5	0.2%	413	0.3%		14	0.4%	13	0.4%	
1	1,388	45.4%	44,008	37.1%		1,930	55.0%	1,909	54.4%	
2	1,171	38.3%	49,610	41.9%		1,183	33.7%	1,209	34.4%	
3	428	14.0%	21,641	18.3%		336	9.6%	327	9.3%	
4	63	2.1%	2,829	2.4%		47	1.3%	52	1.5%	
Clinical N Stage					<0.001					0.909
0	1,928	68.1%	63,470	59.3%		2,676	76.2%	2,669	76.0%	
1	457	16.1%	21,940	20.5%		445	12.7%	456	13.0%	
2	331	11.7%	16,074	15.0%		300	8.5%	304	8.7%	
3	117	4.1%	5,614	5.2%		89	2.5%	81	2.3%	
Tumor Size					<0.001					0.126
Microscopic focus or foci only	31	0.9%	822	0.7%		35	1.1%	32	1.0%	
< 1 cm	603	18.4%	16,453	13.0%		821	25.2%	815	25.1%	
> 1 cm, < 2 cm	929	28.3%	30,074	23.8%		1,119	34.4%	1,070	32.9%	
> 2 cm, < 3 cm	708	21.6%	31,478	24.9%		654	20.1%	694	21.3%	
> 3 cm, < 4 cm	455	13.9%	23,131	18.3%		344	10.6%	356	10.9%	
> 4 cm, < 5 cm	278	8.5%	14,084	11.1%		160	4.9%	196	6.0%	
> 5cm	274	8.4%	10,118	8.0%		118	3.6%	87	2.7%	
HPV Status					<0.001					0.399
HPV Negative	505	13.5%	15,448	10.2%		423	12.1%	476	13.6%	
Low Risk Strains	16	0.4%	782	0.5%		14	0.4%	12	0.3%	
High Risk Strains	266	7.1%	14,705	9.7%		183	5.2%	174	5.0%	
Unknown	2,962	79.0%	120,675	79.6%		2,890	82.4%	2,848	81.2%	
Primary Treatment					<0.001					0.583
No treatment	64	1.7%	5,749	3.8%		54	1.5%	58	1.7%	
Radiation only	68	1.8%	10,282	6.8%		61	1.7%	78	2.2%	
Radiation and Chemotherapy	767	20.5%	54,197	35.7%		339	9.7%	357	10.2%	
Surgery and Radiation	437	11.7%	14,154	9.3%		515	14.7%	488	13.9%	
Surgery and Chemo-radiation	935	24.9%	23,017	15.2%		534	15.2%	515	14.7%	
Surgery only	1,406	37.5%	40,064	26.4%		2,007	57.2%	2,014	57.4%	
Chemotherapy Only	72	1.9%	4,147	2.7%		-	0.0%	-	0.0%	

Table 20. Tumor by oral cavity/oropharynx sub-site by age (pre- and post-Propensity Score Match)

	Pre-Propensity Score Match					Post-Propensity Score Match				
	18-39 years old		40+ years old			18-39 years old		40+ years old		
	Count	Column (%)	Count	Column (%)	*p-value*	Count	Column (%)	Count	Column (%)	*p-value*
Primary Oral Cavity/Oropharynx Sub-site					<0.001					<0.001
Lip	187	5.0%	6,141	4.1%		219	6.2%	251	7.2%	
Base of Tongue	449	12.0%	35,571	23.5%		313	8.9%	297	8.5%	
Tongue (excluding base)	1,851	49.4%	26,817	17.7%		1,632	46.5%	1,314	37.4%	
Gum	79	2.1%	6,783	4.5%		63	1.8%	154	4.4%	
Floor of Mouth	109	2.9%	11,448	7.6%		83	2.4%	374	10.7%	
Palate	70	1.9%	6,128	4.0%		439	12.5%	272	7.7%	
Mouth-Other	186	5.0%	10,068	6.6%		292	8.3%	353	10.1%	
Tonsil	715	19.1%	38,495	25.4%		410	11.7%	422	12.0%	
Other-Oropharynx	103	2.7%	10,159	6.7%		59	1.7%	73	2.1%	

Table 21. Cox proportional hazards regression analysis by age grouping in oral cavity and oropharynx tumors

		Oral Cavity		Oropharynx	
		HR	***P-value***	**HR**	***P-value***
Age Grouping					
	40+ years old	1.00		1.00	
	18-39 years old	0.58	<0.001	0.556	<0.001
Sex					
	Male	1.00		1.00	
	Female	0.912	0.17	1.161	0.22
HPV Status					
	HPV Negative	1.00		1.00	
	HPV Low Risk	0.962	0.957	0.826	0.795
	HPV High Risk	0.81	0.512	0.397	0.011
	HPV Unknown	1.089	0.47	0.767	0.201
Primary Treatment Group					
	No treatment	1.00		1.00	
	Radiation only	0.878	0.639	0.399	0.007
	Radiation and Chemotherapy	0.597	0.032	0.364	<0.001
	Surgery and Radiation	0.368	<0.001	0.346	0.001
	Surgery and Chemo-radiation	0.474	0.001	0.351	<0.001
	Surgery only	0.222	<0.001	0.394	0.001
Clinical T Staging					
	1	1.00		1.00	
	2	3.458	<0.001	1.65	0.001
	3	5.056	<0.001	3.111	<0.001
	4	7.554	<0.001	4.175	<0.001
Clinical N Staging					
	0	1.00		1.00	
	1	1.534	<0.001	0.906	0.528
	2	1.395	0.018	0.849	0.339
	3	2.337	0.001	1.792	0.002
Oral Cavity Sub-site					
	Lip	1.00		-	
	Tongue (excluding base)	1.283	0.099	-	
	Gum	1.415	0.104	-	
	Floor of Mouth	1.447	0.029	-	
	Palate	0.871	0.44	-	
	Mouth- Other	1.127	0.483	-	
Oropharynx Sub-site					
	Base of Tongue	-		1.00	
	Tonsil	-		0.707	0.006
	Oropharynx-Other	-		1.224	0.266
Race					
	White	1.00		1.00	
	Black	0.87	0.291	1.506	0.018
	American Indian/Eskimo	0.858	0.793	0.874	0.767
	Asian/Pacific Islander	0.871	0.44	0.94	0.917
	Other	0.927	0.788	-	-