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Human Papillomavirus Genotype and Oropharynx Cancer Survival in the United States

Marc T. Goodman, **Mona Saraiya**, **Trevor D. Thompson**, **Martin Steinau**, **Brenda Y. Hernandez**, **Charles F. Lynch**, **Christopher W. Lyu**, **Edward J. Wilkinson**, **Thomas Tucker**, **Glenn Copeland**, **Edward S. Peters**, **Sean Altekruse**, and **Elizabeth R. Unger**

Cancer Prevention and Control Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA (Goodman); Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA (Saraiya, Thompson, Watson); Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA (Steinau, Unger); University of Hawaii Cancer Center, University of Hawaii, Honolulu, HI (Hernandez); Department of Epidemiology, College of Public Health, The University of Iowa, Iowa City, IA (Lynch); Battelle Memorial Institute, Durham, NC (Lyu); Department of Pathology, Immunology, and Laboratory Medicine, College of Medicine, University of Florida, Gainesville, FL (Wilkinson); Department of Epidemiology, College of Public Health, University of Kentucky, Lexington, KY (Tucker); Michigan Department of Community Health, Lansing, MI (Copeland); Department of Epidemiology, School of Public Health, Louisiana State University Health Sciences Center, New Orleans, LA (Peters); Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, MD (Altekruse)

Abstract

Correspondence to: Marc T. Goodman, PhD, MPH, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Suite 1S37, Los Angeles, CA 90048, marc.goodman@cshs.org, Ph.: (310) 423-6188. (Alternate) Mona Saraiya, MD, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, 4770 Buford Hwy, MS F-76, Atlanta GA 30341, Ph.: 770 488 4293; msaraiya@cdc.gov.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Background—The presence of human papillomavirus (HPV) DNA in oropharyngeal squamous cell cancer (OPSCC) tissue appears to be a strong predictor of improved prognosis, but this observation has not been explored in a population-based sample with generalizable findings.

Methods—Follow-up data from a large sample of OPSCC patients identified through six population-based cancer registries in the US was used to characterize the association of tumor HPV status with survival.

Results—HPV DNA was detected in tumor tissue from 71% (378/529) of the OPSCC patients. A total of 65% of patients with HPV16-associated tumors survived 5-years compared to 46% of patients with other HPV-types and 28% of patients with HPV-negative tumors (p log-rank test <0.0001). The OPSCC patients with detectable HPV16 DNA had a 62% reduced hazard of death at 5-years, and patients with other HPV types had a 42% reduced hazard of death at 5-years compared to HPV-negative patients. Compared to non-Hispanic Whites, Blacks with OPSCC had a 2.5-fold greater risk of death at 5-years after adjustment for HPV-status and other prognostic variables. Both surgery and radiation therapy were associated with a reduced 5-year risk of death, but no evidence was found for an interaction between HPV-status and radiotherapy or surgery on survival time.

Conclusions—Data from this US study suggest that HPV16-positive OPSCC patients survive longer than HPV-negative patients regardless of treatment, highlighting the prognostic importance of HPV-status for this malignancy. Optimal treatment regimens for OPSCC could be tailored to each patient's HPV-status and prognostic profile.malignancy.

Keywords

Cancer of the oropharynx; human papillomavirus; archived tissue; cancer registry; survival

1. Introduction

The incidence of oropharyngeal squamous cell cancer (OPSCC), including malignancies in the palatine and lingual tonsils, the posterior 1/3 (base) of the tongue, the soft palate, and the posterior pharyngeal wall has been increasing in many parts of the world [1]. The potential etiologic role of human papillomavirus (HPV) infection in head and neck squamous cell cancers has been recognized for more than three decades [2]. Since that time, a number of studies [3–6], including our own [7], have established the presence of HPV in the majority of OPSCC. HPV16 is the predominant genotype in OPSCC, detected in 84% of all HPV-positive patients in our population sample, similar to that found in other investigations.

The epidemiology of HPV-positive and HPV-negative OPSCC is distinct. Although the precise modes of transmission of oral HPV infection are incompletely understood, a sexual route likely predominates with vertical transmission and auto-inoculation much less common possibilities [8]. HPV-negative OPSCC patients are generally older at diagnosis than patients with HPV-positive malignancies, are more likely to be female, and to report a history of tobacco smoking and alcohol drinking [9]. We [7] and others [10–12] have also noted a reduced prevalence of HPV-associated OPSCCs among non-Hispanic Black patients compared to White patients. Although the incidence of tobacco-related head and neck

cancers has decreased in the US with population reductions in tobacco smoking prevalence, HPV-associated OPSCC rates have increased significantly during the past few decades [6].

Aside from differences in etiology, patients with HPV-associated OPSCC demonstrate an improved prognosis compared to patients with non-HPV-associated malignancies. In a recent meta-analysis of survival differences in HPV-associated head and neck squamous cell cancer, O'Rorke et al. [9] reported a 50% improvement in overall survival in HPV-positive compared with HPV-negative OPSCC patients. In the largest of these pooled studies, a randomized control trial including 323 stage 3–4 OPSCC patients undergoing radiotherapy [13], a 58% reduction in the risk of death was found in participants with HPV-positive tumors compared to patients with HPV-negative tumors.

While previous studies of the association of HPV with survival in OPSCC patients are compelling [10,12–28] most investigations have been small (<100 patients), with limited follow-up time and less use of sensitive laboratory methods for HPV detection. In addition, many of the more recent studies used data from clinical trials in which OPSCC patients were selected based on stage, eligibility for specific treatments, and other factors that reduce the generalizability of the findings. The objective of this analysis was to use follow-up data from a large population-based sample of OPSCC patients identified through cancer registries in the US to characterize the association of tumor HPV status with survival.

2. Materials and Methods

2.1. Cancer Tissue Specimens

A systematic review of OPSCC patients diagnosed from 1994 to 2005 was performed as part of the Centers for Disease Control Cancer Registry Sentinel Surveillance System [7]. The patients were selected from 6 participating registries, including four central cancer registries in Florida, Kentucky, Louisiana, and Michigan and two Surveillance, Epidemiology, and End Results program (SEER [http://seer.cancer.gov/]) cancer registry-based residual tissue repositories in Hawaii and Iowa. All of these registries routinely collect information on the diagnosis, tumor characteristics, first-course surgery of the primary cancer site, and radiation therapy. Each registry maintains vital status follow-up for all individuals who are diagnosed with cancer in their defined geographic region. Data are collected primarily from hospitals, pathology laboratories, surgical centers, and radiation facilities. The following anatomic regions (by ICD-O-3 codes) were included: C01.9 and C02.4 (base of the tongue and lingual tonsil); C09.0, C09.1, C09.8, and C09.9 (tonsil); C14.0, C14.2, C14.8, C02.8, C10.2, C10.8, and C10.9 (other oropharynx) [29]. Cases were restricted to squamous cell carcinomas (defined as ICD-O-3 histology codes 8050–8084, 8120–8131), the most common type of oropharyngeal cancer. All death certificate-only and autopsy-only cases were excluded. Tumor tissues from 557 patients matching these criteria were typed for HPV [7], but specimens from the Los Angeles cancer registry were not included in this report because they lacked follow-up data. The remaining 537 cases were representative of all cases from participating cancer registries with regard to sex and age, but with over-representation by non-Whites (Supplement). We further excluded two patients missing follow-up data (vital status/date of last contact). One archived, formalin–fixed paraffin-embedded tissue sample, representative of the primary tumor, was selected by the submitting pathology laboratory. If

tissue from the primary tumor was unavailable, a sample from a metastatic lesion in a lymph node was accepted because HPV prevalence is usually maintained in OPSCC–positive lymph nodes [30]. Each participating state and CDC received approval from their institutional review boards for the study; CDC approved the overall study.

2.2 DNA Extraction and HPV Typing

All laboratory methods were described previously [31]. Six consecutive 5-μm sections were cut from each selected tissue block; special precautions were used to avoid cross-contamination. The first and last sections were stained with hematoxylin and eosin and reviewed by a study pathologist (ERU) to confirm the presence of viable tumor tissue. DNA was extracted from two 5-μm sections by using high temperature–assisted tissue lysis [32] and further purification was carried out by automated extraction by using Chemagic MSM1 (PerkinElmer, Waltham, MA, USA). HPV types were determined from 2 commercial assays using an algorithm which was evaluated earlier for this application [33,34]. First, all DNA extracts were tested for HPV using the Linear Array HPV Genotyping Assay (Linear Array; Roche Diagnostics, Indianapolis, IN, USA) and a HPV-52-specific PCR to resolve ambiguous positive results from the XR probe of the Linear Array HPV test [35]. Samples that had negative or inadequate linear array results (negative for HPV and cellular β-globin controls) were retested with the INNO-LiPA HPV Genotyping Assay (Innogenetics, Gent, Belgium). HPV status was recorded for HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 which were considered to have a ‘high risk’ (HR) for oncogenic potential [36]; as well as 6, 11, 26, 40, 42, 43, 44, 53, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 73, 74, 81, 82, 83, 84, IS39, 89, and unknown types (HPV X) which were considered ‘low risk’ (LR) with little or no known oncogenic potential. Samples inadequate in both assays were excluded.

2.3. Statistical Analysis

Patient and tumor characteristics were compared according to hierarchical HPV status groups (HPV16-positive, other HR-HPV types, and HPV-negative). Continuous variables are presented as medians, 25th, and 75th percentiles, and discrete variables as frequencies and percentages. Statistical testing was performed using the likelihood ratio chi-square test for discrete variables. The Kruskal-Wallis test was used to test for differences among continuous variables. Survival was censored at five years because some states did not have follow-up data beyond 2009. Five-year survival was complete for 81% of the cases. Five-year survival curves are presented as Kaplan-Meier estimates. Statistical testing for differences in unadjusted survival rates was performed using the log-rank test.

A time-dependent Cox proportional hazards model was used to determine the independent predictors of 5-year overall survival. Age, sex, race/ethnicity, stage, grade, subsite, HPV status, surgery, radiation, and chemotherapy were included as covariates in the survival model. Time-dependent covariates for the treatment variables were used to minimize artificially inflating any beneficial association between treatment and survival. For each of these treatments, patients were considered not treated until the date of treatment. HPV status-radiation and HPV status-surgery interaction terms were tested to determine if the effect of those treatments on survival varied across HPV groups. The linearity assumption

for the continuous age variable was assessed using restricted cubic spline functions. Missing data were imputed for all independent predictors except treatment using the aregImpute function in R. The aregImpute function performs multiple imputation using predictive mean matching. This technique takes all aspects of uncertainty into account by using the bootstrap to approximate the process of drawing predicted values from a full Bayesian predictive distribution. Due to the time-dependent nature of the treatment variables, 85 patients missing treatment status or timing were excluded from the multivariate analysis.

3. Results

High-risk HPV DNA was detected in 71% of the 529 tissue blocks from OPSCC patients included in this analysis (Table 1). The 6 OPSCC patients with LR-HPV types in tumor tissue were not considered further because there were too few for independent analysis. Based on actual counts, including multiple HPV types in a single tumor, the majority (N=322) of the 378 HPV-positive specimens contained HPV16 DNA, with smaller numbers of high-risk HPV33 (N=31), HPV18 (N=14), HPV35 (N=11), HPV31 (N=4), HPV52 (N=4), HPV39 (N=3), and HPV45 (N=2). HPV16-positive patients tended to be younger than patients positive for other HR types or HPV-negative patients (p=0.01) and were more likely to be male (p=0.03). Most patients were non-Hispanic White and these patients were more likely than non-Hispanic Black patients, but less likely than other race-ethnic groups, to have HPV-positive tumors (p for difference between 3 race-ethnicity categories < 0.0001). Regional tumors were the most common stage at presentation and this tendency was greatest among patients who were HPV16-positive. Patients who were HPV-negative were more likely than HPV-positive patients to present at a localized stage. More than half of the HPV-positive patients were diagnosed with poorly differentiated / undifferentiated tumors in contrast to those patients with HPV-negative tumors that were most likely to be moderately differentiated. Nearly 82% of tonsil cancers were HPV-positive compared to 70% of malignancies at the base of the tongue and 48% of other OPSCCs (p for difference < 0.0001). HPV-positive patients, especially patients with tumors that were positive for HPV16, were more likely to have received radiotherapy than were HPV-negative patients (p = 0.01).

Five-year all cause survival decreased with increasing age, and was significantly poorer among non-Hispanic Black patients than non-Hispanic Whites and other race-ethnic groups (Table 2). Stage at diagnosis, but not tumor grade, was inversely associated with survival time. A total of 65% of patients with HPV16 associated tumors survived 5-years compared to 46% of patients with other HR HPV-types and 28% of patients with HPV-negative tumors (p log-rank test comparing HPV16 positive patients to patient positive for other HR types = 0.001; p log-rank test comparing all 3 groups <0.0001) (Table 2; Figure 1, Panel A). Sixty-two percent of patients with tonsil cancer survived 5 years compared to 50% of those with base of tongue cancer and 31% of patients diagnosed with other OPSCC (p log rank test <0.0001) (Figure 1, Panel B).

HPV status was an independent predictor of 5-year all cause survival following multivariate modeling (Table 3). The OPSCC patients with an HPV16 associated malignancy had a 62% reduced hazard of death at 5-years, and patients with other HR HPV types had a 42%

reduced hazard of death at 5-years compared to HPV-negative patients. There was a borderline non-significant reduction in 5-year death among HPV16-positive cancers compared to other HR HPV types (HR: 0.65; 95% CI: 0.41–1.03; p=0.07). Increasing age, non-Hispanic Blacks, and advanced SEER summary stage were associated with increased 5-year risk of death, but no significant differences in the hazard ratios were found by sex or tumor grade.

Non-Hispanic black OPSCC patients had a 2.6-fold greater risk of death after 5-years compared to non-Hispanic White patients after adjustment for other prognostic variables. No significant difference in survival time was found between patients who had cancer at the base of the tongue compared to those with tonsil cancer; however, patients with cancer at other OPSCC sub-sites had a 79% (95% CI: 1.21–2.65) increased 5-year hazard of death compared to patients with tonsil cancer. Surgery and radiation therapy, modeled as time dependent covariates, were associated with reduced 5-year death. However, there was no evidence that treatment benefit varied by HPV status (HPV x radiotherapy interaction p=0.87; HPV x surgery interaction p=0.36) (Table 4). OPSCC patients with HPV16 positive cancers had significantly improved survival compared to patients with HPV-negative cancers irrespective of radiation treatment (Figure 1, Panels C and D).

4. Discussion

A unique contribution of this investigation was the ability to compare survival in OPSCC patients by HPV-type, anatomic subsite, clinical factors, and patient demographics that have not been explored comprehensively in previous studies. Chaturvedi et al. [6] took advantage of the Surveillance, Epidemiology, and End Results (SEER) Program's Residual Tissue Repository Program to examine 271 specimens of OPSCC tissue collected by three cancer registries (Hawaii, Iowa, and Los Angeles, California). Multivariate adjusted all-cause survival was significantly longer for HPV-positive compared with HPV-negative OPSCC patients (HR: 0.31; 95% CI: 0.21–0.46). The Cancer Registry Sentinel Surveillance System extended these findings to include tissue blocks from 537 OPSCC patients identified through participating central cancer registries throughout the US. Consistent with the previous study of HPV-related OPSCC survival in the US [6], we showed a significantly improved prognosis among patients with HPV-positive tumors compared to patients with HPV-negative tumors. Moreover, in the largest systemic review and meta-analysis of HPV-related head and neck cancer survival [9], the pooled hazard ratio for HPV-positive compared to HPV-negative OPSCC patients was 0.47; 95% CI: 0.35–0.62), very similar to our own HPV16 hazard ratio estimate of 0.38 (95% CI: 0.27–0.52).

Although the majority of OPSCC specimens were HPV16 positive, a novel finding was that HPV16-related OPSCC had higher observed five-year survival compared to patients with tumors testing positive for other high-risk HPV types. We reasoned that some of this difference might be attributable to the higher percentage of other HR HPV types relative to HPV16 in anatomic sites with poorer survival, such as the base of the tongue or other OPSCC sites. We found these differences were borderline non-significant after adjusting for subsite and other covariates. However, there may also be biological differences in the

pathogenicity of these tumors. Larger studies are needed to compare HPV-type specific survival within subsite of OPSCC.

A survival advantage for non-Hispanic White head and neck cancer patients compared with Black patients has been noted, but only a few studies have been able to examine the role of HPV as a source for this racial/ethnic difference [37,38]. In a retrospective cohort of University of Maryland patients with stage III/IV squamous cell carcinoma of the head and neck cancer, Settle et al.[37] reported significantly (p log rank test = 0.0006) improved survival for White OPSCC patients compared to Black OPSCC patients, but no such differences by race for survival in patients with other head and neck cancers. In a separate analysis of the TAX 324 phase 3 clinical trial data from stage 3–4 head and neck squamous cell cancer patients, survival was significantly improved in HPV-positive patients compared with HPV-negative patients. Because HPV-positive specimens were found in one (4%) Black patient compared to 66 (34%) White patients, subsite differences in survival by race and HPV-status could not be explored. We found that the significant racial differences in survival among OPSCC patients persisted even after adjustment for HPV-status, age, treatment and other confounders. It is possible that our inability to adjust for tobacco smoking behaviors in these patients may have influenced our results.

An important strength of this study was our ability to adjust for treatment differences between OPSCC patients. The improved response to radiation therapy in HPV-positive compared to HPV-negative patients with head and neck cancer has been observed by several investigators [6,12,13,15,39]. Our study does not support the notion that HPV-positive OPSCC is more sensitive to radiation therapy than HPV-negative cancers. Biological differences between tumors, such as degree of cellular dysregulation and response to therapy, likely drive the improved prognosis among HPV-positive compared to HPV-negative patients since tobacco use, age, performance status, comorbidities, and other confounders only account for ~9% of the variation in overall survival by HPV-status [40].

This is the largest study conducted to date regarding an association of HPV-status with OPSCC prognosis. The long follow-up time for the OPSCC patients allowed us to evaluate the association of HPV-status on survival after multivariate adjustment for other significant prognostic factors. The population-based design precluded the selection bias associated with randomized control trials. HPV detection techniques were state-of-the-art, using the INNO-LiPA HPV genotyping assay with smaller amplicons to decrease the likelihood that assay performance was reduced by DNA damage in tumor blocks. Detection of HPV DNA in a cross-section study is insufficient to indicate a causal relation with the tumor. Sensitive molecular methods may detect low copy-number HPV that is latent or infecting surrounding normal tissue. Additional markers, such as p16, E6/E7 mRNA, or in situ hybridization to document cellular localization of HPV, have been used to enhance evidence for causation. However, each of these methods has technical limitations, particularly in archival tissues, and does not eliminate uncertainty in the estimates. A further potential limitation of this analysis was the lack of information regarding tobacco smoking and alcohol use among patients that may have affected the hazard ratios. Although the possibility of confounding of the survival estimates by these and other exposures cannot be excluded, O'Rorke et al.[9]

reported that the survival benefits associated with HPV were generally independent of smoking and alcohol histories.

In conclusion, data from this large US study demonstrate that patients with HPV-positive OPSCC survived longer than patients with HPV-negative OPSCC. Defining those subgroups of OPSCC patients with the best survival remains a challenge, but this study adds to the growing evidence that HPV-status is an important prognostic variable for patients diagnosed with this malignancy. Future clinical trials will need to determine optimal treatment regimens that are tailored to each patient's HPV-status and prognostic profile.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Largest study conducted regarding an association of HPV-status with OPSCC prognosis
- Survival was significantly longer for HPV+ compared with HPV− OPSCC patients
- Five-year survival for HPV16+ OPSCC higher compared to other high-risk HPV types
- Racial differences in OPSCC survival persisted after adjustment for HPV-status

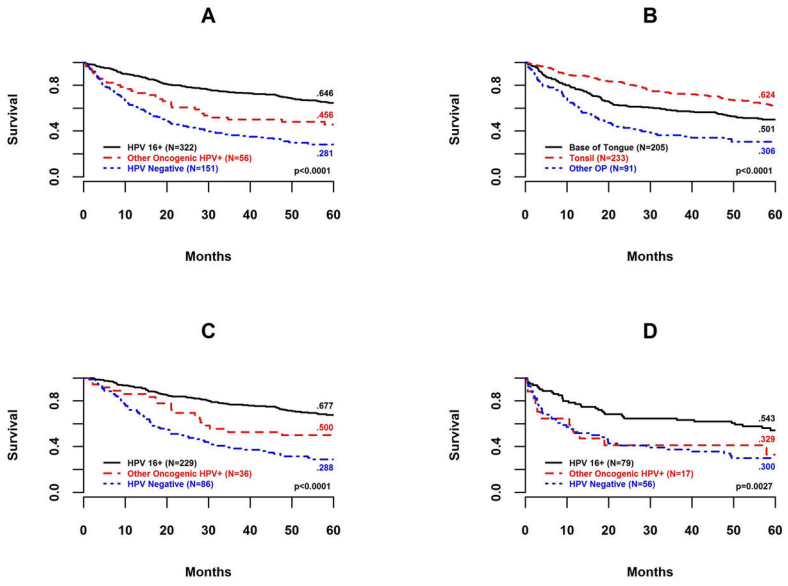

Figure 1.

Five-Year All-Cause Survival among Squamous Cell Oropharynx Cancer Patients by HPV-Status, Antomic Site, and Radiation Treatment

Panel A. Five-Year All-Cause Survival by HPV Hierarchy among Squamous Cell Oropharynx Cancer Patients

Panel B. Five-Year All-Cause Survival by Anatomic Site among Squamous Cell Oropharynx Cancer

Panel C. Five-Year All-Cause Survival by HPV Hierarchy among Squamous Cell Oropharynx Cancer Patients Treated with Radiation

Panel D. Five-Year All-Cause Survival by HPV Hierarchy among Squamous Cell Oropharynx Cancer Patients not Treated with Radiation

Table 1

Distribution of Patient and Tumor Characteristics by HPV-Positivity Status among Invasive Squamous Cell Oropharynx Cancer Patients

Characteristic	HPV16-positive (n=322)	Other High-Risk HPV−Positive[a] (n = 56)	HPV-Negative (n = 151)	P-Value
Age at Diagnosis				
Lower quartile, median, upper quartile	51.2, 57.5, 64.0	52.8, 59.5, 69.2	54.0, 61.0, 68.0	0.0063
Mean ± standard deviation	58.4 ± 10.8	61.5 ± 12.5	61.6 ± 11.3	
Sex, No. (%)				0.0261
Male	253 (64.2)	37 (9.4)	104 (26.4)	
Female	69 (51.1)	19 (14.1)	47 (34.8)	
Race,[c] No. (%)				<0.0001
Non-Hispanic White	259 (64.9)	37 (9.3)	103 (25.8)	
Non-Hispanic Black	19 (27.9)	15 (22.1)	34 (50.0)	
Other	43 (71.7)	4 (6.7)	13 (21.7)	
Stage,[c] No. (%)				0.0065
Localized	48 (50.0)	9 (9.4)	39 (40.6)	
Regional	209 (67.6)	31 (10.0)	69 (22.3)	
Distant	40 (54.8)	10 (13.7)	23 (31.5)	
Grade,[c] No. (%)				0.0982
Well-Differentiated	15 (42.9)	6 (17.1)	14 (40.0)	
Moderately-Differentiated	112 (56.6)	18 (9.1)	68 (34.3)	
Poorly Differentiated / Undifferentiated	133 (63.0)	24 (11.4)	54 (25.6)	
Site,[c] No. (%)				<0.0001
Base of Tongue	120 (58.5)	24 (11.7)	61 (29.8)	
Tonsil	168 (72.1)	22 (9.4)	43 (18.5)	
Other Oropharynx	34 (37.4)	10 (11.0)	47 (51.6)	
Surgery,[c] No. (%)				0.1713
Yes	122 (66.3)	15 (8.2)	47 (25.5)	
No	183 (58.3)	37 (11.8)	94 (29.9)	
Radiation,[c] No. (%)				0.013
Yes	229 (65.2)	36 (10.3)	86 (24.5)	
No	79 (52.0)	17 (11.2)	56 (36.8)	
Chemotherapy,[c] No. (%)				0.0834
Yes	151 (65.9)	22 (9.6)	56 (24.5)	
No	140 (56.0)	31 (12.4)	79 (31.6)	

[a] Other high-risk types defined as HPV 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

[b] Statistical testing performed using Kruskal-Wallis rank sum test for continuous variables and likelihood ratio test for discrete variables

[c] Numbers do not sum to total due to missing/unknown data

Note: 6 OPSCC patients with LR-HPV types in tumor tissue were not considered in this analysis

Table 2

Unadjusted 5-Year All-Cause Survival by Patient and Tumor Characteristics among Invasive Squamous Cell Oropharynx Cancer Patients

Characteristic	5-Year Survival Percent[a]	P-value[b]
Age		0.0003
<55	58.4	
55–64	56.7	
65+	39.9	
Sex		0.3624
Male	50.6	
Female	56.9	
Race[c]		<0.0001
Non-Hispanic White	56.6	
Non-Hispanic Black	15.2	
Other	62.8	
Stage[c]		<0.0001
Localized	62.0	
Regional	56.0	
Distant	27.9	
Grade[c]		0.4569
Well-Differentiated	51.4	
Moderately-Differentiated	49.4	
Poorly Differentiated / Undifferentiated	57.0	
Site		<0.0001
Base of Tongue	50.1	
Tonsil	62.4	
Other Oropharynx	30.6	
HPV Hierarchy Group		<0.0001
HPV16-Positive	64.6	
Other High-Risk HPV-Positive	45.6	
HPV-Negative	28.1	

[a] Five-year survival presented as Kaplan-Meier estimates

[b] Statistical testing performed using the log-rank test

[c] Numbers do not sum to total due to missing/unknown data

Table 3

Cox Proportional Hazards Model Predicting 5-year All-Cause Survival among Invasive Squamous Cell Oropharynx Cancer Patients[a]

Characteristic	Wald χ^2	DF	P-value	Hazard Ratio (95% CI)
HPV Hierarchy	35.99	2	<0.0001	
HPV16-Positive vs. HPV-Negative				0.38 (0.27–0.52)
Other High-Risk HPV-Positive vs. HPV-Negative				0.58 (0.36–0.93)
HPV16-Positive vs. Other High-Risk HPV-Positive				0.65 (0.41–1.03)
Age at Diagnosis	9.03	1	0.0027	
Per 5-year increase				1.11 (1.04–1.18)
Sex	1.90	1	0.1683	
Male vs. Female				1.27 (0.90–1.78)
Race/Ethnicity	29.19	2	<0.0001	
Non-Hispanic Black vs. Non-Hispanic White				2.57 (1.78–3.72)
Other vs. Non-Hispanic White				0.76 (0.47–1.24)
SEER Summary Stage	26.90	2	<0.0001	
Regional vs. Local				1.69 (1.08–2.64)
Distant vs. Local				3.68 (2.18–6.23)
Grade	0.64	2	0.7274	
Moderately-Differentiated vs. Well-Differentiated				1.03 (0.56–1.89)
Poorly-Differentiated / Undifferentiated vs. Well-Differentiated				0.91 (0.49–1.70)
Site	9.33	2	0.0094	
Base of Tongue vs. Tonsil				1.14 (0.81–1.61)
Other Oropharynx vs. Tonsil				1.79 (1.21–2.65)
Surgery[b]	9.06	1	0.0026	0.57 (0.39–0.82)
Radiation[b]	4.48	1	0.0342	0.65 (0.44–0.97)
Chemotherapy[b]	<0.01	1	0.9942	1.00 (0.68–1.47)

[a] n = 444 oropharynx cancer patients with 210 events

[b] Surgery, radiation, and chemotherapy were modeled as time-dependent covariates

Table 4

Adjusted Treatment and HPV Hazard Ratios from 5-year All-Cause Survival Models among Invasive Squamous Cell Oropharyngeal Cancer Patients

Characteristic	Hazard Ratio (95% CI)
Radiation[a] (Yes vs. No)	
HPV16-Positive	0.67 (0.40–1.13)
Other High-Risk HPV-Positive	0.52 (0.22–1.27)
HPV-Negative	0.67 (0.40–1.13)
HPV Hierarchy[a]	
Radiation	
HPV16-Positive vs. HPV-Negative	0.37 (0.25–0.55)
Other High-Risk HPV-Positive vs. HPV-Negative	0.52 (0.28–0.97)
No Radiation	
HPV16-Positive vs. HPV-Negative	0.37 (0.22–0.64)
Other High-Risk HPV-Positive vs. HPV-Negative	0.67 (0.32–1.38)
Surgery[b] (Yes vs. No)	
HPV16-Positive	0.73 (0.44–1.19)
Other High-Risk HPV-Positive	0.35 (0.10–1.24)
HPV-Negative	0.47 (0.27–0.82)
HPV Hierarchy[b]	
Surgery	
HPV16-Positive vs. HPV-Negative	0.52 (0.28–0.98)
Other High-Risk HPV-Positive vs. HPV-Negative	0.44 (0.12–1.57)
No Surgery	
HPV16-Positive vs. HPV-Negative	0.34 (0.24–0.49)
Other High-Risk HPV-Positive vs. HPV-Negative	0.59 (0.36–0.99)

[a]Model includes HPV status x radiation interaction (p=0.8651) and adjusts for age, sex, race/ethnicity, SEER summary stage, grade, site, surgery, and chemotherapy

[b]Model includes HPV status x surgery interaction (p=0.3605) and adjusts for age, sex, race/ethnicity, SEER summary stage, grade, site, radiation, and chemotherapy