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ORIGINAL RESEARCH

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Prognostic role of human papilloma virus status in hypopharyngeal squamous cell carcinoma

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Abstract

Objective: Although the prognostic role of human papilloma virus (HPV) status in oropharyngeal head and neck squamous cell carcinoma (SCC) is well established, growing evidence shows that there may be a prognostic role for HPV status in hypopharyngeal SCC. The objective of this study was to determine the prognostic role of HPV status in hypopharyngeal SCC.

Methods: We performed a retrospective, population-based analysis of 1934 adult patients with HNSCC diagnosed between 2010-2016 and treated with a combination of surgery and/or radiotherapy, with or without chemotherapy, and a subset of 641 patients with hypopharyngeal SCC and known HPV status included in the Surveillance, Epidemiology, and End Results (SEER) Head and Neck with HPV Status Database. Patient data were used to determine the adjusted 2-year cancer-specific survival (CSS) and overall survival (OS) for the entire cohort and the specific subgroup of hypopharyngeal cancer patients with known HPV status.

Results: Of the 1934 hypopharynx SCC cases, HPV status was unknown in 1294 (66.9%), and 167 (8.6%) were HPV positive; among hypopharynx cases with known HPV status, 21.6% were HPV positive. In models adjusting for sex, age, race/ethnicity, marital status and stage, patients with HPV-positive hypopharyngeal tumors had improved CSS compared with patients with HPV-negative tumors (CSS: HR: .57, 95% CI = .38 to .86, P = .008; OS: HR: .49, 95% CI = .34 to .71, P = <.001).

Conclusion: Our findings in a large cohort of hypopharyngeal SCC with known HPV status and cancer-specific survival support the hypothesis that HPV has a prognostic role in hypopharyngeal cancer. Consideration should be given to increased testing for HPV in hypopharyngeal SCC.

Level of Evidence: 4

KEYWORDS

clinical research, head and neck, human papilloma virus, hypopharynx/esophagus

1 | INTRODUCTION

Human papilloma virus (HPV) infection is a well-known risk factor in the development of head and neck squamous cell carcinoma, although risk associated with this infection varies by anatomic tumor site.[1-4] The prognostic role of HPV infection specifically in oropharyngeal head and neck squamous cell carcinoma (HNSCC) is well established,[5-9] and has been incorporated into recent prognostic staging groups.[10] Accordingly, clinical treatment guidelines now include HPV testing for oropharyngeal SCC,[11] and efforts are ongoing to explore whether treatment can be tailored to HPV status.

Limited data exist about the role of HPV in nonoropharyngeal SCC, in part because these cancers are less common. Proportions of HPV or p16 (a surrogate marker for HPV infection) positivity have been estimated at 13% to 24% in hypopharyngeal cancers,[9,12-14] lower than those observed in nonoropharyngeal sites. Existing data regarding the prognostic value of HPV or p16 status[9,12,13,15-19] in hypopharyngeal SCC is conflicting. A recent large study of US Veterans suggested that there may be a prognostic role for p16 status in nonoropharyngeal SCC, including patients with hypopharyngeal cancers,[13] although the sample size for that analysis was small.

The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program has collected data on the HPV status of patients with head and neck squamous carcinoma diagnosed between 2010 and 2016, representing the largest known US database of HPV status that includes cancer-specific survival for patients with hypopharyngeal cancers. The aim of this study was to investigate whether HPV status has a prognostic role in patients with hypopharyngeal squamous cell carcinoma.

2 | MATERIALS AND METHODS

2.1 | Study population

We performed a population-based analysis of patients included in the Surveillance, Epidemiology, and End Results (SEER) Head and Neck with HPV Status Database. Patients who were over 18 with a pathologically confirmed diagnosis of invasive squamous cell carcinoma, available cause-specific survival and staging, nonoverlapping primary tumor sites, and nonmetastatic disease, whose treatment included any standard therapy (including any surgery and/or radiation) were selected (eFigure 1). We selected patients treated with standard therapies because untreated patients or patients treated with a nonstandard therapy, such as chemotherapy alone, likely have poor overall prognosis due to unmeasured noncancer factors that may obscure the relationship between HPV status and survival. Given that survival outcomes included cancer death related to this diagnosis, our sample included patients with this cancer diagnosis indicated as the first of two or more cancer diagnoses.

SEER site codes were used to identify oropharyngeal, nasopharyngeal, and hypopharyngeal cancers. Tumor HPV status was determined through submission per the SEER CS Collaborative Stage Data Collection System, version 02.02-02.05 schemas. HPV status was determined using the applicable Collaborative Stage site-specific factor 10 for each disease site schema throughout the data collection period.[20] HPV status included any testing done on surgical specimens (HPV in situ hybridization [ISH], tissue PCR, ISH for E6/7 RNA, real time-PCR for E6/7 RNA) and excluded blood or serology testing. Of note, individuals with only a p16 immunohistochemistry (IHC) marker are were reported as unknown HPV status.[21]

Demographic variables were obtained, including age (continuous), sex (male/female), marital status (married/not married/unknown), race/ethnicity (White, Black, Hispanic, Asian/Pacific islander, and other/unknown), overall stage per AJCC 7 (as determined by TNM status), and treatment modality (surgery, radiation, surgery/radiation, surgery/chemotherapy, or surgery/radiation/chemotherapy).

Patient survival time was calculated using time from diagnosis to death (classified as head and neck cancer related or not) or November 2016, whichever came first. Using this information, we determined the unadjusted 2-year cancer-specific survival (CSS) and overall survival (OS) for the entire hypopharyngeal SCC cohort and Kaplan-Meier estimates with log-rank tests were used to evaluate differences in survival by HPV status.

We then performed the analysis in the specific subgroup of hypopharyngeal cancer patients with known HPV status. In the hypopharyngeal SCC subgroup, unadjusted cox regression models were used to test for associations between patient characteristics and survival, including HPV status, age, sex, marital status, race/ethnicity, stage, and treatment modality.

Cox regression models was used to examine the relationship between HPV status and CSS and OS after adjusting for age, sex, race/ethnicity, marital status, and stage. Then we performed a competing risks analysis (with nonhead and neck cancer death as our competing outcome) using the cumulative incidence function[22] and plotted cumulative incidence curves to confirm our survival findings, testing for differences in the curves using the Pepe-Mori method.[23]

Two-sided *P* values with an α level < .05 were applied to all statistical tests. The statistical analysis was performed R v3.3 (R Core Team, Vienna, Austria). The Mount Sinai Hospital Institutional Review Board determined that the study was exempt.

TABLE 1 Characteristics and survival of SEER hypopharyngeal SCC patients

	Overall	HPV−	HPV+	HPV unknown	*P* value
Hypopharynx SCC patients [N (%)]	1934 (8.3)	473 (24.4)	167 (8.6)	1294 (66.9)	–
2 year cancer-specific survival (95% CI)	64.0 (61.6, 66.5)	68.6 (63.8, 73.8)	79.1 (72.1, 86.7)	60.8 (57.9, 63.8)	**<.001**[a]
2 year overall survival (95% CI)	57.2 (54.8, 59.7)	61.8 (56.9, 67.1)	78.1 (71.1, 85.9)	53.5 (50.7, 56.5)	**<.001**[a]

Abbreviations: CI, confidence interval; HPV, human papillomavirus; SCC, squamous cell carcinoma.

[a]*P* value for log-rank (Mantel Cox) test. α = .05, CI 95% for all tests. Percentages may not add to 100 due to rounding. HPV status determined by any testing done on surgical specimens (HPV in situ hybridization [ISH], tissue PCR, ISH for E6/7 RNA, real time-PCR for E6/7 RNA) and excluded blood or serology testing.

TABLE 2 Characteristics and survival of SEER nonmetastatic hypopharyngeal SCC patients with known HPV status

	Overall	HPV−	HPV+	*P* value
Patients [N (%)]	640 (100)	473 (73.9)	167 (26.1)	
2 year cause-specific survival [% (95%CI)]	71.3 (67.2, 75.6)	68.6 (63.8, 73.8)	79.1 (72.1, 86.7)	**.005**[a]
2 year overall survival (95% CI)	65.9 (61.8, 70.4)	61.8 (56.9, 67.1)	78.1 (71.1, 85.9)	**<.001**[a]
Age				
Mean (SD)	62.8 (9.8)	63.0 (10.0)	62.4 (9.2)	.50[b]
Sex				.73[c]
Male [N (%)]	533 (83.3)	392 (82.9)	141 (84.4)	
Female [N (%)]	107 (16.7)	81 (17.1)	26 (15.6)	
Marital status				.06[c]
Married [N (%)]	299 (46.7)	214 (45.2)	85 (50.9)	
Not married [N (%)]	307 (48.0)	238 (50.3)	69 (41.3)	
Unknown [N (%)]	34 (5.3)	21 (0.04)	13 (7.8)	
Race/ethnicity				**.02**[c]
White [N (%)]	447 (69.8)	318 (67.2)	129 (77.2)	
Black [N (%)]	77 (12.0)	67 (14.2)	10 (6.0)	
Hispanic [N (%)]	56 (8.8)	39 (8.2)	17 (10.2)	
Asian/Pacific islander [N (%)]	49 (7.7)	41 (8.7)	8 (4.8)	
Other/unknown [N (%)]	11 (1.7)	8 (1.7)	3 (1.8)	
Overall stage (AJCC 7)				.37[c]
I [N(%)]	25 (3.9)	22 (4.7)	3 (1.8)	
II [N (%)]	60 (9.4)	47 (9.9)	13 (7.8)	
III [N (%)]	112 (17.5)	82 (17.3)	30 (18.0)	
IVX [N (%)]	21 (3.3)	13 (2.7)	8 (4.8)	
IV A [N (%)]	349 (54.5)	258 (54.5)	91 (54.5)	
IV B [N (%)]	73 (11.4)	51 (10.8)	22 (13.2)	
Treatment modality				.43[c]
Surgery [N (%)]	20 (3.1)	14 (3.0)	6 (3.6)	
Radiation [N (%)]	70 (10.9)	57 (12.1)	13 (7.8)	
Surgery and radiation [N (%)]	39 (6.1)	30 (6.3)	9 (5.4)	
Radiation and chemotherapy [N (%)]	432 (67.4)	310 (65.5)	121 (72.5)	
Surgery and chemotherapy [N (%)]	4 (6.2)	4 (0.8)	0 (0)	
Surgery, radiation and chemotherapy [N (%)]	76 (11.9)	58 (12.3)	18 (10.8)	

Notes: HPV status determined by any testing done on surgical specimens (HPV in situ hybridization [ISH], tissue PCR, ISH for E6/7 RNA, real time-PCR for E6/7 RNA) and excluded blood or serology testing. Percentages may not add to 100 due to rounding.
Abbreviations: HPV, human papillomavirus; SCC, squamous cell carcinoma.
[a] *P* value for log-rank (Mantel Cox) test.
[b] *P* value for one-way ANOVA.
[c] *P* value for Pearson's chi-squared test.

3 | RESULTS

3.1 | Survival estimates in patients with hypopharyngeal SCC by HPV status

There were 1934 adult patients with nonmetastatic HNSCC of the hypopharynx pathologically diagnosed between 2010 and 2016 and treated with surgery and/or radiotherapy, with or without chemotherapy. Overall and cause-specific survival by HPV status (negative, positive, and unknown) are summarized in Table 1 and survival curves are shown in eFigure 2.

Median follow up was 17 months (interquartile range [IQR]: 8, 35). HPV status was unknown in 67% of hypopharynx patients. There were significant differences in cause-specific and overall survival for hypopharynx patients by HPV status (Table 1).

TABLE 3 Unadjusted cancer-specific and overall survival of SEER nonmetastatic hypopharyngeal SCC patients with known HPV status

	Cancer-specific survival			Overall survival		
Covariable	**Unadjusted HR**	**95% CI**	***P* value[a]**	**Unadjusted HR**	**95% CI**	***P* value[a]**
HPV status			**.005**			**<.001**
Negative	(1.00)			(1.00)		
Positive	0.56	(0.38, 0.84)		0.48	(0.33, 0.69)	
			.50			.70
Sex						
Male	(1.00)			(1.00)		
Female	0.86	(0.56, 1.33)		1.08	(0.76, 1.53)	
Age (y)	1.01	(1.00, 1.03)	**.09**	1.02	(1.01, 1.04)	**.005**
Marital status			**.004**			**<.001**
Not married	(1.00)			(1.00)		
Married	1.45	(1.04, 2.00)		1.56	(1.18, 2.07)	
Unknown	2.38	(1.36, 4.17)		2.25	(1.36, 3.75)	
Race/Ethnicity			.20			**.005**
White	(1.00)			(1.00)		
Black	1.54	(0.99, 2.40)		1.93	(1.35, 2.77)	
Hispanic	1.25	(0.71, 2.18)		1.11	(0.66, 1.87)	
Asian/Pacific islander	1.59	(0.94, 2.69)		1.54	(0.96, 2.47)	
Other/unknown	1.37	(0.43, 4.30)		1.75	(0.72, 4.27)	
Overall stage (AJCC 7)			**.007**			.09
I	(1.00)			(1.00)		
II	2.51	(0.29, 21.49)		2.14	(0.72, 6.35)	
III	6.71	(0.91, 49.35)		2.27	(0.81, 6.36)	
IVX	7.23	(0.84, 61.87)		2.20	(0.62, 7.79)	
IV A	9.32	(1.30, 66.83)		2.78	(1.03, 7.53)	
IV B	10.49	(1.42, 77.71)		3.71	(1.351, 10.49)	
Treatment modality			.20			**.02**
Surgery	(1.00)			(1.00)		
Radiation	3.56	(0.82, 15.53)		4.48	(1.36, 14.79)	
Surgery and radiation	1.32	(0.26, 6.82)		1.98	(0.55, 7.10)	
Radiation and chemotherapy	2.72	(0.67, 11.01)		2.34	(0.74, 7.33)	
Surgery and chemotherapy	7.16	(0.65, 79.15)		4.93	(0.51, 47.45)	
Surgery, radiation, and chemotherapy	3.01	(0.71, 12.78)		2.40	(0.73, 7.91)	

Abbreviations: CI, confidence interval; HPV, human papillomavirus; HR, hazard ratio; SCC, squamous cell carcinoma.
[a]Using cox proportional hazards models, Wald test. α = .05, CI 95% for all tests. HPV status determined by any testing done on surgical specimens (HPV in situ hybridization [ISH], tissue PCR, ISH for E6/7 RNA, real time-PCR for E6/7 RNA) and excluded blood or serology testing.

3.2 | Baseline characteristics and survival estimates in patients with hypopharyngeal SCC with known HPV status

We then analyzed the subset of 640 patients with hypopharyngeal SCC and known HPV status. Of the 640 hypopharynx patients with known HPV status, 167 (26.1%) were HPV positive. Baseline characteristics (including HPV status, age, sex, race, marital status, stage, and initial treatment) and cause specific and overall survival are summarized in Table 2. There were greater proportions of HPV-positive patients who were White or Hispanic; otherwise there were no significant differences in demographics, tumor stage or treatment by HPV status.

Median follow up in the hypopharynx SCC subgroup with known HPV status was 17 months (IQR: 8, 35). In unadjusted models (Table 3, Figure 1), patients with HPV positivity had improved 2-year cancer-specific survival and overall survival.

In adjusted models (Table 4), patients with HPV-positive hypopharyngeal tumors had improved CSS (HR: .57, 95% CI = .38 to .86, *P* = .008) and OS (HR: .49, 95% CI = .34 to .72, *P* = <.001) compared with patients with HPV-negative tumors. Competing risks analysis also

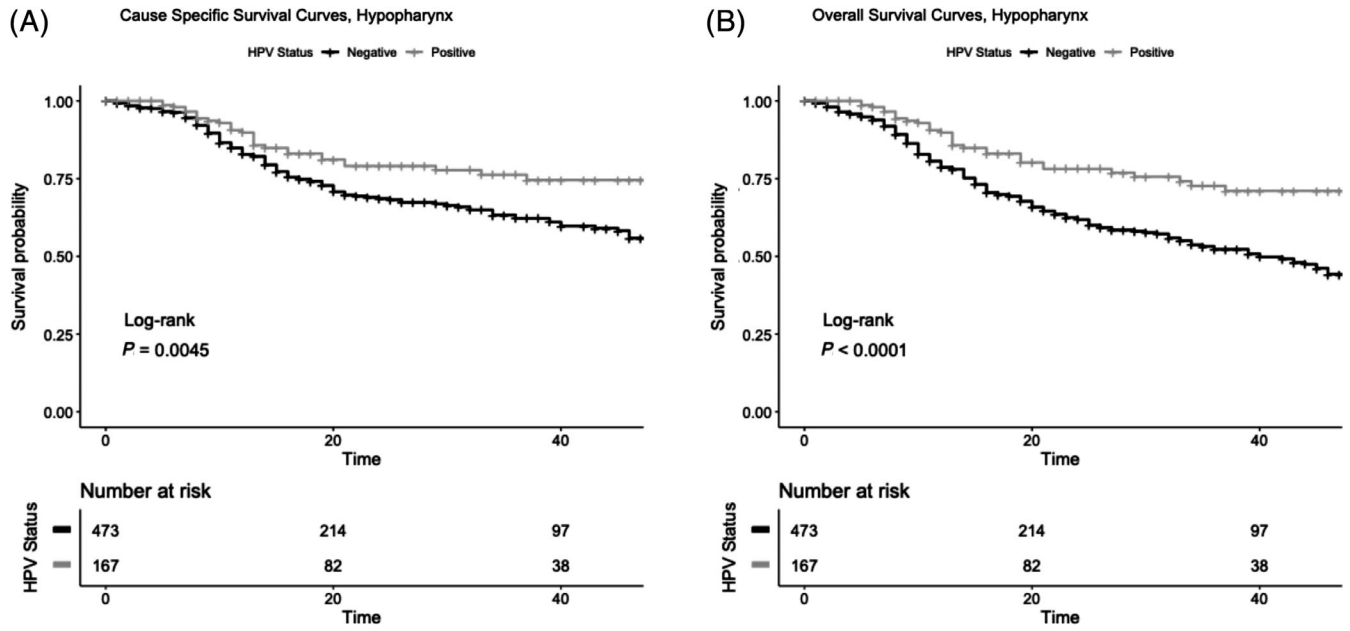


FIGURE 1 Cancer-specific (A) and overall (B) survival of SEER nonmetastatic Hypopharyngeal SCC patients with known HPV status. HPV, human papillomavirus; SCC, squamous cell carcinoma. *P* value for log-rank (Mantel Cox) test. α = .05, CI 95% for all tests. HPV status determined by any testing done on surgical specimens (HPV in situ hybridization [ISH], tissue PCR, ISH for E6/7 RNA, real time-PCR for E6/7 RNA) and excluded blood or serology testing

found that HPV-positive tumors had lower risk of cancer-related death after accounting for noncancer causes of death (*P* = .01, Figure 2).

4 | DISCUSSION

In this large population-based study of patients with treated hypopharyngeal SCC we found that HPV-positive tumors were associated with a better prognosis than HPV-negative tumors. This finding supports consideration for HPV testing among all hypopharyngeal cancers. Additional testing coupled with careful staging are needed prior to interpreting how HPV status may impact management of hypopharyngeal SCC.

Prevalence of HPV or p16 positivity in hypopharyngeal SCC has been estimated to be 13% to 24%,[9,12,14] and our sample included ~9% HPV positive hypopharyngeal cancers among all patients. However, among those with HPV testing, the proportion of HPV-positive tumors was higher in our sample, at ~26%. This suggests that the prevalence of HPV-positivity may be higher than expected in hypopharyngeal SCC, although the large proportion of cases without HPV status and our lack of data regarding the reasons for HPV testing in the cancer cases limits this conclusion. For example, tumors adjacent or with extension to the oropharynx may have been more likely to be tested and it is possible that in a large registry that there may be misclassification of tumor origin. Furthermore, there may be variability in the detection assay results collected by SEER that account for this high prevalence, including non-quantitative PCR, that are less reliable and overestimate clinically significant HPV detection.[24] SEER required tissue HPV testing to establish tumor viral involvement as opposed to p16 IHC assessment, a commonly employed surrogate marker of HPV-associated tumors. P16 has been found to have less concordance with HPV testing in nonoropharyngeal HNSCC sites,[5,9,12,18,25] also potentially explaining these differences. Nonetheless, our results are consistent with a global meta-analysis showing the prevalence of laryngeal/hypopharyngeal high-risk HPV positivity to be ~24%,[14] and these data likely reflect variable detection assays similar to SEER. However, misclassification of p16 positive tumors as HPV 16 positive for oropharyngeal patients was observed in a review of SEER registry data from Iowa,[26] and it is possible that the HPV variable in this dataset includes some tumors that were similarly misclassified. We do not yet know the accuracy of HPV testing in the hypopharynx subset, though SEER continues their quality assurance efforts. Despite this, other recent findings indicating the potential prognostic value of both p16 and HPV support the conclusion that testing both p16 and HPV to determine how hypopharyngeal cancers differ from other head and neck cancers with regard to the prognostic significance of each of these markers is warranted.[12,13]

Other studies have shown results consistent with our findings. Chung et al.[12] evaluated p16 and HPV status of patients treated on Radiation Therapy Oncology Group (RTOG) 0129, 0234 and 9501 trials, finding that p16-positive hypopharynx SCC patients had improved progression-free survival and a trend toward improved overall survival in a small cohort of 61 patients. Improved overall survival outcomes in HPV-positive hypopharyngeal SCC patients have been observed in single institution or database studies, although these studies do not include cancer-specific outcomes,[16,17,27] were combined with other subsites and/or were limited to patients with locally advanced disease,[28] or included patients with metastatic disease and those who did not receive appropriate therapies.[17] In comparison, our analysis of

TABLE 4 Adjusted cancer-specific and overall survival of SEER nonmetastatic hypopharyngeal SCC patients with known HPV status

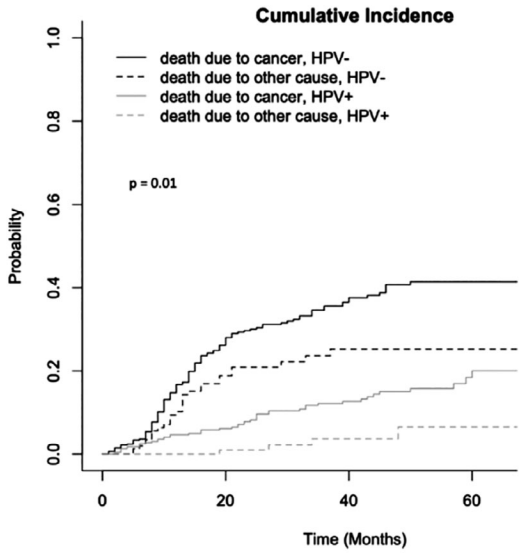
	Cancer-specific survival			Overall survival		
Covariable	**Adjusted HR**	**95% CI**	***P* value[a]**	**Adjusted HR**	**95% CI**	***P* value[a]**
HPV status						
Negative	(1.00)			(1.00)		
Positive	.57	(.38, .86)	**.008**	.49	(.34, .72)	**<.001**
Sex						
Male	(1.00)			(1.00)		
Female	1.05	(.67, 1.65)	.83	1.20	(.83, 1.73)	.34
Age (y)	1.02	(1.01, 1.04)	**.005**	1.03	(1.02, 1.05)	**<.001**
Marital status						
Not married	(1.00)			(1.00)		
Married	1.38	(.98, 1.95)	.06	1.42	(1.05, 1.91)	**.02**
Unknown	3.04	(1.74, 5.33)	**<.001**	2.64	(1.56, 4.44)	**<.001**
Race/ethnicity						
White	(1.00)			(1.00)		
Black	1.46	(.93, 2.29)	.13	1.80	(1.24, 2.61)	**.002**
Hispanic	1.11	(.63, 1.95)	.71	1.01	(.60, 1.71)	.96
Asian/Pacific islander	1.55	(.89, 2.68)	.12	1.36	(.83, 2.21)	.22
Other/unknown	1.00	(.31, 3.21)	.99	1.30	(.52, 3.24)	.57
Overall stage (AJCC 7)						
I	(1.00)			(1.00)		
II	2.16	(.25, 18,55)	.48	1.91	(.64, 5.74)	.25
III	7.02	(.95, 52.04)	.06	2.43	(.86, 6.90)	.10
IV X	7.62	(.89, 65.71)	.06	2.47	(.69, 8.83)	.16
IV A	10.04	(1.34, 72.62)	**.02**	3.14	(1.14, 8.61)	**.03**
IV B	12.59	(1.68, 94.56)	**.01**	4.59	(1.58, 13.30)	**.005**

Abbreviations: CI, confidence interval; HR, hazard ratio; HPV, human papillomavirus; SCC, squamous cell carcinoma.
[a]Using cox proportional hazards models, Wald test. α = .05, CI 95% for all tests. HPV status determined by any testing done on surgical specimens (HPV in situ hybridization [ISH], tissue PCR, ISH for E6/7 RNA, real time-PCR for E6/7 RNA) and excluded blood or serology testing.

cancer-specific outcomes was limited to patients with nonmetastatic disease and those who likely received standard therapy, though our results remain consistent with these other studies. In particular, our study included cancer-specific survival and our findings were consistent with Bryant and colleagues[13] who identified United States Veterans Affairs patients with HNSCC and found that p16 had a prognostic role in nonoropharyngeal cancers including both laryngeal and hypopharyngeal cancers, using competing risks models incorporating smoking and comorbidities. Our findings support their results in a larger, more representative sample including women.

However, our findings of improved cause-specific and overall survival in HPV-positive hypopharyngeal SCC are inconsistent with smaller studies looking at the role of p16 or HPV in nonoropharyngeal SCC. A study by Wilson et al. evaluated 27 hypopharyngeal patients by retrospective chart review, and found that there was no prognostic significance of p16 status.[15] Other small studies have shown similar results,[18,19,29-31] though most were limited by a small sample size given the lower frequency of HPV positivity in hypopharyngeal SCC. One of the larger studies evaluated cancer-specific survival in pooled outcomes for larynx (62 patients) and hypopharynx (14 patients) cases which found no difference in survival outcomes based on HPV status, although it included only seven HPV+ patients thus limiting the interpretation of the results.[18] Similarly, in the pooled analysis of DAHANCA trials, Lassen and colleagues[9] found no association of p16 status and survival in hypopharyngeal patients, though their sample size was limited to 158 patients with only 21 (13%) being p16 positive. These studies were limited by small sample sizes, and classification by p16 positivity may have identified a different patient group than our study which utilized testing for viral antigens and nucleic acids.

Treatment de-escalation in patients with HPV-related oropharyngeal SCC based on improved prognosis has generated considerable interest with several ongoing trials.[32,33] Although recent studies show that chemotherapy deintensification for HPV-related oropharyngeal SCC has not been successful,[34,35] efforts to deintensify radiation or surgery in oropharyngeal SCC[33] continue. Conversely, treatment escalation in patients with non-HPV-related oropharyngeal SCC patients is also being explored.[36] This framework may translate to cancers of the hypopharynx in an effort to reduce therapy-related morbidity, though



Number at risk				
HPV+	473	214	97	25
HPV-	167	82	38	14

FIGURE 2 Cumulative incidence of death due to cancer and non-cancer-related death in SEER nonmetastatic Hypopharyngeal SCC patients with known HPV status. HPV, human papillomavirus; SCC, squamous cell carcinoma. *P* value for log-rank (Mantel Cox) test. α = .05, CI 95% for all tests. HPV status determined by any testing done on surgical specimens (HPV in situ hybridization [ISH], tissue PCR, ISH for E6/7 RNA, real time-PCR for E6/7 RNA) and excluded blood or serology testing

careful consideration of incorporating broad HPV testing and other clinical factors is required prior to exploring treatment modification in hypopharyngeal SCC.

4.1 | Limitations

Strengths of this study include the large sample size and representativeness of the patient population such that it is generalizable to the US population. However, our findings must be viewed in light of several limitations. First, the lack of smoking or other comorbidity data limit the interpretation of our findings. However, SEER does include cause of death information that allows us to account for mortality not related to head and neck cancer so we performed a competing risks analysis to account for noncancer mortality. Second, detailed treatment information on chemotherapy and radiotherapy is not available, nor are data regarding comorbidities that may influence treatment selection, thus we cannot interpret our data with respect to HPV status predicting response to treatment though treatment selection has been shown to be of importance in patients with hypopharyngeal cancer.[37] In addition, as discussed above, there may be classification errors (both in exact tumor site and HPV status), which is why we believe our findings ultimately support exploration of testing for both p16 and HPV status to determine the prognostic significance of both of these factors. The addition of p16 status to the SEER registry would provide additional important information. Our findings also suggest greater influence of HPV status with longer follow up, and a future analysis should be performed for later time points once the SEER data have matured to a greater extent. Lastly, caution must be used when considering treatment modification based on registry data, and these findings cannot support modification of current diagnostic or therapeutic practices without further validation.

5 | CONCLUSION

Our findings in a large cohort of hypopharyngeal HNSCC with known HPV status and cancer-specific outcomes support the hypothesis that HPV has a prognostic role hypopharyngeal cancer. Consideration should be given to increased testing for HPV in hypopharyngeal HNSCC.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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