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HPV Status and Survival in Non-Oropharyngeal Squamous Cell Carcinoma of the Head and Neck

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Abstract. *Background/Aim: HPV-mediated oropharyngeal squamous cell carcinoma is associated with an increased survival. The prognostic value of HPV status for other primary sites is unclear. We aimed to assess the effect of HPV status on overall survival in patients with non-oropharyngeal head and neck squamous cell carcinoma (non-OPSCC) using the National Cancer Database (NCDB). Patients and Methods: Adults with non-OPSCC [gum, lip, floor of mouth, tongue (excluding base), hypopharynx, nasopharynx, other pharynx] and known HPV status were included in our study. Associations between HPV status, primary site, patient characteristics and overall survival (OS) were assessed. Results: HPV positivity was associated with a better OS compared to HPV-negative patients (HR=0.83, 95%CI=0.74-0.93, p<0.001). Female gender, gum, lip, nasopharynx primaries, and private insurance predicted for improved OS. Conclusion: HPV positivity and female gender are good prognostic factors in non-OPSCC. Routine HPV testing should be considered for HPV positive non-OPSCC, as well as studies evaluating de-escalation of treatment if this association is confirmed.*

The prevalence of human papillomavirus (HPV)-associated malignancies of the head and neck is constantly increasing (1), with these patients likely to have less exposure to tobacco or alcohol, which are considered as traditional risk factors associated with squamous cell carcinoma of the head and neck (HNSCC) (2). Instead, HPV-mediated HNSCC is associated more with extensive sexual exposures and marijuana use (2) and has a different genetic profile compared to HPV-negative HNSCC (3). HPV (particularly genotype 16) has a stronger association with oropharyngeal squamous cell carcinoma (OPSCC) and, though prevalence varies based on the detection method, it has been reported between 40-80% in North America (1, 4-6). Reportedly, 5-20% of non-oropharyngeal squamous cell carcinomas of the head and neck (non-OPSCC) in North America are HPV-positive, but a higher prevalence has been reported in other regions (1, 3, 5-7).

Clinically, HPV positivity has been associated with an improved overall survival (OS) in OPSCC (5, 8-11). The National Comprehensive Cancer Network (NCCN) currently only recommends routine measurement of HPV status in known or suspected OPSCC (12), as the prognostic implications of HPV status and gender in non-OP HNSCC have been unclear. Several studies have shown no prognostic benefit of HPV in non-OPSCC (5, 10, 11, 13). However, one study has demonstrated that p16 expression by immunohistochemistry (IHC) is associated with increased survival in non-OPSCC (14).

Due to improved prognosis, several studies evaluating treatment de-escalation in HPV positive OPSCC are currently ongoing, and results so far have shown no reduction in OS with de-escalation (15, 16). The purpose of this study was to evaluate the effect of HPV positivity on overall survival in non-OPSCC.

Patients and Methods

Inclusion criteria and variables. Data were extracted from the National Cancer Database (NCDB) to determine the effect of HPV status on OS in patients ≥18 years old with all stages of non-

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Key Words: HPV, prognosis, head and neck neoplasms, carcinoma, squamous cell, non-oropharyngeal.

Table I. *Patient characteristics by HPV status*.

		Total (n=13,908)	HPV status		*p*-Value†
			HPV+ (n=2,576)	HPV– (n=11,332)	
Gender	Male	9005 (64.7%)	1918 (21.3%)	7087 (78.7%)	<0.001
	Female	4903 (35.2%)	658 (13.4%)	4245 (86.6%)	
Age	≤40	780 (5.6%)	148 (19%)	632 (81%)	<0.001
	41-50	1858 (13.4%)	423 (22.8%)	1435 (77.2%)	
	51-60	4005 (28.8%)	919 (22.9%)	3086 (77.1%)	
	61-70	3814 (27.4%)	726 (19%)	3088 (81%)	
	71-80	2220 (16.0%)	267 (12%)	1953 (88%)	
	81-90	1231 (8.9%)	93 (7.6%)	1138 (92.4%)	
Race (6-levels)	White	11900 (85.6%)	2268 (19.1%)	9632 (80.9%)	0.001
	Black	1213 (8.7%)	179 (14.8%)	1034 (85.2%)	
	American Indian	41 (0.3%)	5 (12.2%)	36 (87.8%)	
	Asian	495 (3.6%)	73 (14.8%)	422 (85.2%)	
	Pacific Islander	41 (0.3%)	8 (19.5%)	33 (80.5%)	
	Other	101 (0.7%)	13 (12.9%)	88 (87.1%)	
Spanish origin	Non-Hispanic	12856 (95.4%)	2402 (18.7%)	10454 (81.3)	0.029
	Hispanic	625 (4.6%)	95 (15.2%)	530 (84.8%)	
Charlson-deyo score	0	10830 (77.9%)	2028 (18.7%)	8802 (81.3%)	0.482
	1	2359 (17.0%)	417 (17.7%)	1942 (82.3%)	
	2+	719 (5.2%)	131 (18.2%)	588 (81.8%)	
Treatment	Chemo	318 (2.3%)	74 (23.3%)	244 (76.7%)	<0.001
	Surgery	5294 (38.1%)	668 (12.6%)	4626 (87.4%)	
	RT	660 (4.7%)	150 (22.7%)	510 (77.3%)	
	SCT	152 (1.1%)	23 (15.1%)	129 (84.9%)	
	CRT	2876 (20.7%)	833 (29%)	2043 (71%)	
	SRT	1700 (12.2%)	264 (15.5%)	1436 (84.5%)	
	SCRT	1918 (13.8%)	377 (19.7%)	1541 (80.3%)	
	No treatment	792 (5.7%	146 (18.4%)	646 (81.6%)	
	Unknown treatment	198 (1.4%)	41 (20.7%)	157 (79.3%)	
Insurance	Not insured	769 (5.5%)	148 (19.2%)	621 (80.8%)	<0.001
	Medicaid	1424 (10.2%)	247 (17.3%)	1177 (82.7%)	
	Medicare	5583 (40.1%)	813 (14.6%)	4770 (85.4%)	
	Other	476 (3.4%)	91 (19.1%)	385 (80.9%)	
	Private insurance	5656 (40.7%)	1277 (22.6%)	4379 (77.4%)	
Primary site	Floor of mouth	1461 (10.5%)	228 (15.6%)	1233 (84.4%)	<0.001
	Gum and other mouth	3512 (25.3%)	495 (14.1%)	3017 (85.9%)	
	Hypopharynx	1878 (13.5%)	353 (18.8%)	1525 (81.2%)	
	Lip	467 (3.4%)	35 (7.5%)	432 (92.5%)	
	Nasopharynx	1244 (8.9%)	402 (32.3%)	842 (67.7%)	
	Other pharynx	678 (4.9%)	260 (38.3%)	418 (61.7%)	
	Other tongue	4668 (33.6%)	803 (17.2%)	3865 (82.8%)	
AJCC clinical stage	1	3057 (26.9%)	376 (12.3%)	2681 (87.7%)	<0.001
	2	2071 (18.2%)	296 (14.3%)	1775 (85.7%)	
	3	1826 (16.0%)	392 (21.5%)	1434 (78.5%)	
	4 not further classified	242 (2.1%)	48 (19.8%)	194 (80.2%)	
	4A	3398 (30.0%)	734 (21.6%)	2664 (78.4%)	
	4B	480 (4.2%)	105 (21.9%)	375 (78.1%)	
	4C	310 (2.7%)	64 (20.6%)	246 (79.4%)	

chemo: Chemotherapy; RT: radiation therapy; SCT: surgery and chemo; CRT: chemo and RT; SRT: surgery and RT; SCRT: surgery, chemo and RT; AJCC: American Joint Committee on Cancer. †*p*-Value from Chi-square test of association.

OPSCC [gum, lip, floor of mouth, tongue (excluding base), hypopharynx, nasopharynx, and other pharynx (excluding oropharynx)] diagnosed from 2010 to 2013 (n=59,563). Patient demographics, including age, sex and race were included. Patients were excluded if HPV status was unknown. Data on smoking status, alcohol use and HPV detection technique are not recorded in the NCDB; therefore, were not included in the analysis.

Data source. The National Cancer Database (NCDB) is a joint project of the American Cancer Society and the Commission on Cancer of

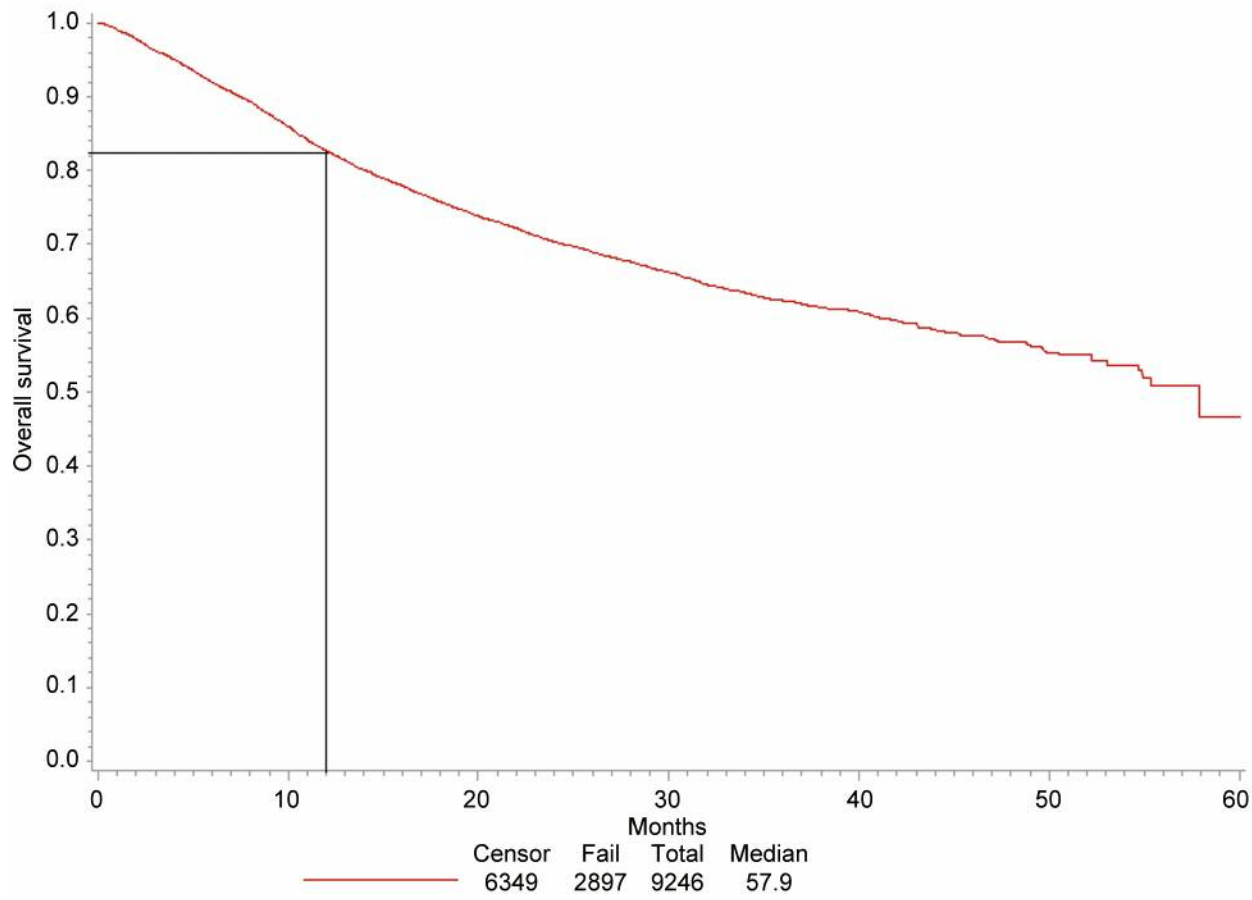

Figure 1. *Kaplan–Meier estimates for overall survival (60 months).*

the American College of Surgeons. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance oncology dataset that currently captures 70% of all newly diagnosed malignancies in the US annually. The data used in the study are derived from a de-identified NCBD file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed here, or the conclusions drawn from these data by the investigators.

Statistical analysis. Counts, proportions and comparisons between HPV statuses (including all sub-types) are presented for patient characteristics and treatment information using the SAS software Version 9.4 (SAS Institute Inc., Cary, NC). Pearson's Chi square test was used for comparison of proportions by HPV status. Overall survival was calculated from the date of diagnosis to date of last contact or death in the participant use file (PUF). OS distributions were estimated using the Kaplan-Meier method, and the differences between groups were compared using a log-rank test. The association between HPV status, treatment information and 60-month survival was evaluated with a multivariate Cox regression analysis including significant variables from the univariate analysis. Hazard ratios (HR), *p*-Values and 95% confidence intervals (95%CI) are presented. A *p*-value of <0.05 was used as a threshold of statistical significance.

Results

Patients with squamous cell carcinoma of the gum, lip, floor of mouth, tongue (excluding base), hypopharynx, nasopharynx and pharynx (excluding oropharynx), as classified by ICD-O-3, with complete data were included. Patients with unknown HPV status were excluded from the study (n=13,909) and data from ≤60 months was evaluated (n=13,908), representing 17.47% of the total cases initially identified. Of the 13,908 patients included, 11,332 patients were HPV negative (81.5%) and 2,576 were positive for HPV (18.5%). The study population comprised of 9,005 (64.7%) males and 4,903 (35.3%) females. The largest proportion of patients were treated with surgery alone (38.1%), followed by 20.7% treated with chemotherapy and radiation (CRT), 13.8% treated with surgery, chemotherapy and radiation therapy (S-CRT), and 12.2% were treated with surgery and radiation therapy (SRT). Oral tongue and gum/other mouth primaries represented 33.6% and 25.3% of the cohort respectively. Table I includes patient characteristics and treatments received

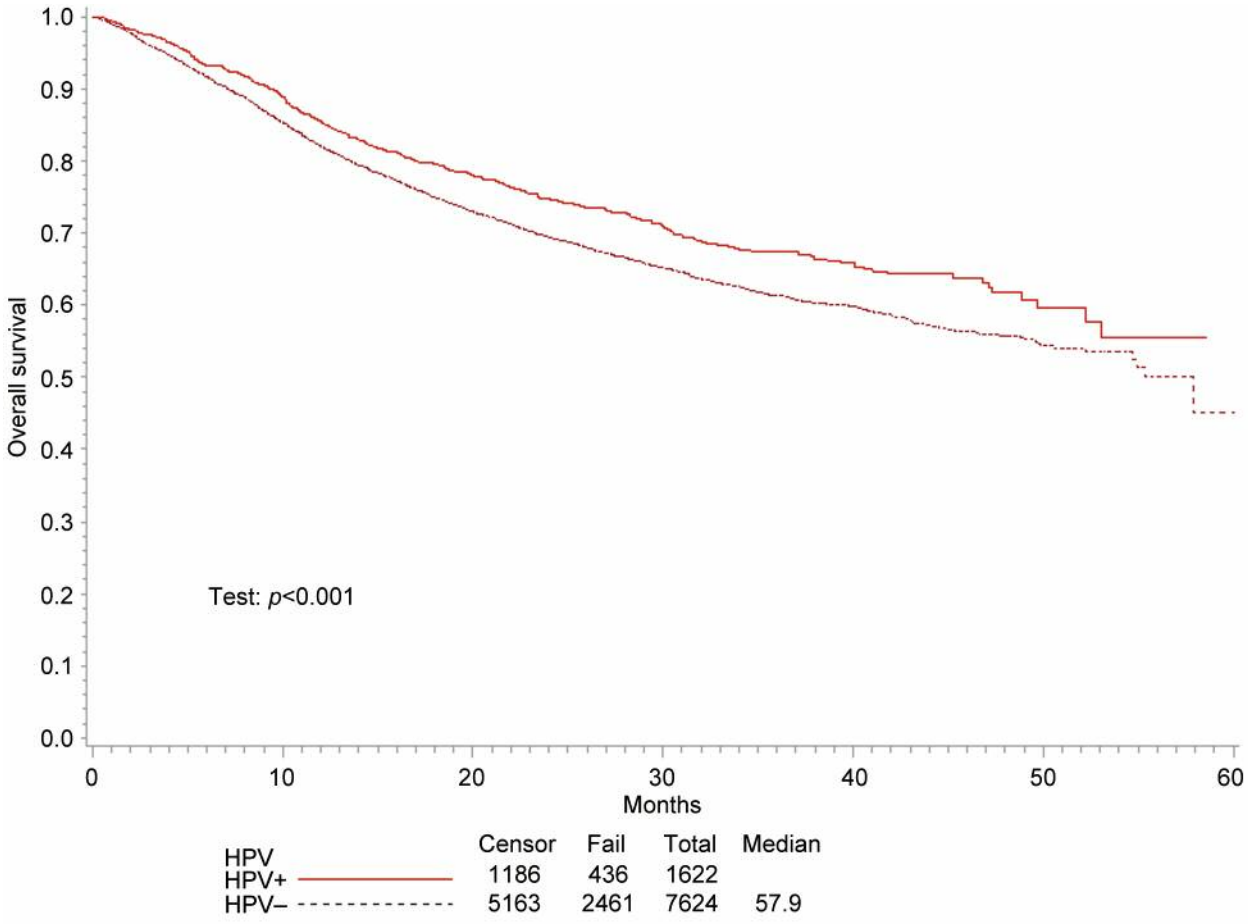

Figure 2. *Kaplan–Meier estimates for overall survival by HPV status.*

compared by HPV status. HPV-positive patients were more likely to be male and white than HPV negative patients. A higher proportion of HPV positive patients were treated with CRT, whereas the majority of HPV negative patients received surgery only.

The probability of one-year survival at all primary sites and stages was 82% (Figure 1). In the univariate analysis, HPV positivity was associated with improved OS (HR=0.80, 95%CI=0.73-0.89, $p<0.001$), as was female sex (HR=0.85, 95%CI=0.79-0.92, $p<0.001$), private insurance (HR=0.54, 95%CI=0.46-0.63, $p<0.001$) and Asian race (HR=0.69, 95%CI=0.54-0.87, $p=0.002$). Improved OS in the univariate analysis was also associated with lip, nasopharynx, and tongue primaries, whereas decreased OS was seen in hypopharynx and other pharynx primaries when compared to the mouth floor. Black race was associated with a worse OS (HR=1.43, 95%CI=1.27-1.61, $p<0.001$). Higher American Joint Committee on Cancer (AJCC) stage and diagnosis at a community cancer program were associated with reduced OS; otherwise the facility type was not associated with OS. Increasing age and higher Charlson-Deyo comorbidity scores were associated with decreased OS.

Kaplan-Meier estimates assessing overall survival by HPV status in all patients (Figure 2) showed an improvement in OS in patients with HPV positive tumors compared to HPV negative tumors. The Kaplan Meier estimates comparing overall survival between HPV negative and HPV positive tumors for each primary site (Figure 3) showed a statistically significant improvement in OS in patients with HPV positive SCC of the hypopharynx and other pharynx, compared to the corresponding HPV negative tumors of the same sites. Patients with HPV positive SCC of the lip had a statistically significantly worse OS compared to HPV negative SCC of the lip. However, this difference was no longer significant in multivariate analyses (HR=1.46, 95%CI=0.64-3.34, $p=0.371$), likely due to the small number of patients with HPV positive SCC (n=35).

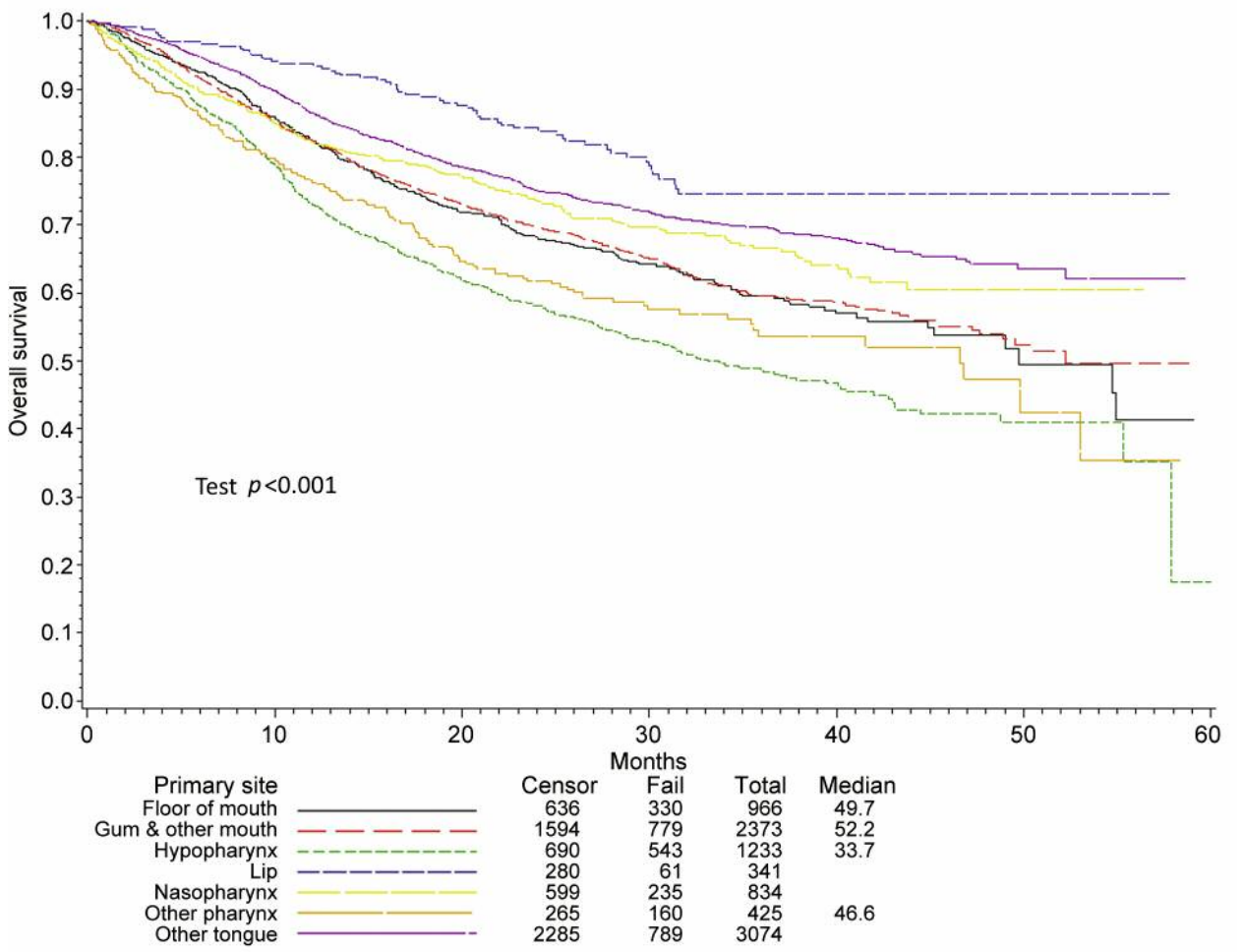

Figure 3. *Kaplan Meier estimates for overall survival by HPV status and primary sites.*

In the multivariate analysis presented in Table II, the association between HPV positivity and improved OS remained significant (HR=0.83, 95%CI=0.74-0.93, p=0.002) after adjusting for covariates. Other predictors associated with improved OS include female sex (HR=0.87, 95%CI=0.79-0.95, p=0.002), private insurance (HR=0.63, 95%CI=0.53-0.76, p<0.001), and any form of treatment compared to no treatment.

Primary sites associated with improved OS compared to floor of mouth included gum/other mouth (HR=0.85, 95%CI=0.74-0.98, p=0.025), lip (HR=0.85, 95%CI=0.51-0.97, p=0.031), and nasopharynx (HR=0.70, 95%CI=0.57-0.85, p<0.001) in the multivariate analysis. Other pharynx primary was associated with worse OS (HR=9.43, 95%CI=1.31-67.91, p=0.026), however, this type represented a relatively small sample of patients. A higher Charlson-Deyo score, age greater than 70, and higher AJCC stage were significantly associated with worse OS.

Discussion

The results of this large retrospective cohort study demonstrate that HPV positivity is an independent and positive prognostic factor in non-OPSCC. These findings are supported by the results of another recent study (17), but are contradictory to the results of several other studies (5, 10, 11, 13). The reason for these discrepant results may be the smaller sample size of many of these previous studies. Those studies may not have had enough statistical power to show significant differences in OS. Though our sample size was large, HPV status was not recorded for the majority of patients diagnosed prior to 2010 and is only routinely tested in OPSCC (12), so many patients were excluded from the analysis due to unknown HPV status. The population included in this study was homogeneous (mostly white, non-Hispanic males), but is fairly reflective of the population with HNSCC (8).

Table II. *Predictors of overall survival on multivariate analysis*.

		Hazard ratio	95% Hazard ratio confidence limits		*p*-Value
			Lower CL	Upper CL	
HPV	Negative	1.00		Referent	
	Positive	0.83	0.74	0.93	0.002
Gender	Male	1.00		Referent	
	Female	0.87	0.79	0.95	0.002
Age	≤40	1.00		Referent	
	41-50	1.85	0.82	4.15	0.138
	51-60	1.84	0.82	4.11	0.139
	61-70	2.21	0.98	4.95	0.055
	71-80	3.04	1.35	6.85	0.007
	81-90	4.36	1.93	9.86	<0.001
Race	White	1.00		Referent	
	Black	1.11	0.97	1.26	0.124
	Other	0.85	0.69	1.04	0.116
Charlson-Deyo comorbidity score	0	1.00		Referent	
	1	1.15	1.04	1.27	0.009
	2+	1.55	1.32	1.81	<0.001
Treatment	No treatment	1.00		Referent	
	SCRT	0.27	0.22	0.32	<0.001
	Chemo	0.66	0.52	0.83	<0.001
	CRT	0.26	0.23	0.31	<0.001
	RT	0.51	0.41	0.62	<0.001
	SCT	0.52	0.37	0.72	<0.001
	SRT	0.21	0.17	0.25	<0.001
	Surgery	0.25	0.21	0.30	<0.001
	Unknown treatment	0.26	0.17	0.41	<0.001
Primary site	Floor of mouth	1.00		Referent	
	Gum & other mouth	0.85	0.74	0.98	0.025
	Hypopharynx	0.93	0.80	1.09	0.389
	Lip	0.70	0.51	0.97	0.031
	Nasopharynx	0.70	0.57	0.85	<0.001
	Other pharynx	9.43	1.31	67.91	0.026
	Tongue (excluding base)	0.99	0.86	1.14	0.896
AJCC clinical stage	1	1.00		Referent	
	2	1.85	1.58	2.17	<0.001
	3	2.89	2.46	3.41	<0.001
	4	3.86	2.95	5.06	<0.001
	4A	3.70	3.18	4.31	<0.001
	4B	4.43	3.57	5.51	<0.001
	4C	6.71	5.32	8.46	<0.001
Insurance	Not insured	1.00		Referent	
	Medicaid	0.98	0.80	1.20	0.831
	Medicare	0.89	0.73	1.08	0.223
	Other	0.93	0.71	1.22	0.595
	Private insurance	0.63	0.53	0.76	<0.001

All variables listed in the table were included in the multivariable model. chemo: Chemotherapy; RT: radiation therapy; SCT: surgery and chemo; CRT: chemo and RT; SRT: surgery and RT; SCRT: surgery, chemo and RT; AJCC: American Joint Committee on Cancer.

Females had an increased OS over males in non-OPSCC, independent of HPV status, and this is similar to what has been described in OPSCC (5). Though the reason for improved OS in females is unclear, it has been postulated that it may be due to less tobacco exposure and fewer comorbidities among females (5). The clinical significance of this association is uncertain as the HR is similar to one, though statistically significant.

HPV can be detected by various mechanisms, and increased p16 protein expression by IHC is a commonly used and well established surrogate marker for detection of HPV in OPSCC (9), but not yet in non-OPSCC (18). Overexpression of p16

can occur in HPV-negative tumors; hence this is thought to be a less specific surrogate marker for HPV in non-OPSCC when compared to the detection of HPV by *in situ* hybridization (ISH), in part, because of the lower prevalence of HPV positivity (14). Overexpression of p16, independent of HPV status, has been demonstrated to predict increased OS in laryngeal SCC (14). However, another study has shown no prognostic significance of p16 overexpression in hypopharyngeal or laryngeal SCC (13). The method of HPV detection was not included dataset and represents one of the largest limitations of this study.

The main strengths of this study include a large sample size gathered from a national database that provides information on treatment modalities. Unfortunately, the NCDB does not include information on alcohol or tobacco use, traditional risk factors for the development of HNSCC (2). Tobacco smoking has also been associated with worse treatment outcomes independent of HPV status (9), and the lack of tobacco data could represent a potential confounder. Local extension from other primary sites in the head and neck and misclassification of oropharyngeal tumors as other primary sites are possible and represent other potential confounders. Potential errors in the classification could lead to a higher proportion of primary sites with favorable prognosis being represented in the HPV positive group. The NCDB also does not provide data on disease-free survival, locoregional control or cancer specific mortality, which do not affect OS, but are still clinically significant outcomes.

Another limitation of this study is the exclusion of a large number of patients due to unknown HPV status. As routine testing of HPV status in non-OPSCC is not performed, the reasons for testing HPV status in our cases are unknown and could represent a selection bias. While this study showed a significant association of HPV positivity and improved OS, the method of HPV testing was not defined, and further studies should be performed with routine testing of HPV status, using a consistent method, in non-OPSCC to confirm these results. The positive association of HPV positivity with improved survival may have less clinical significance in non-OPSCC compared to OPSCC (9, 19), though is likely still clinically meaningful.

Due to the improved prognosis of HPV-positive OPSCC (5, 8-11), clinical trials evaluating the de-escalation of treatment in these patients are ongoing, and new staging guidelines specific for HPV-positive OPSCC have been proposed (20). The results of this study are provocative in that they show the prognostic ability of HPV positivity and female gender in non-OPSCC. These results at the very least provide an impetus to further evaluate the role of HPV in non-OPSCC and provide support for routine testing of HPV status in non-OPSCC of the head and neck. If further studies confirm this data, future clinical trials evaluating de-escalation of treatment in HPV positive non-OPSCC of the head and neck should be considered.

Conflicts of Interest

The Authors have no conflicts of interest to disclose.

Authors' Contributions

Vanessa Wookey was responsible for conceptualization, investigation, visualization of the project, writing the original draft, and review and editing of the manuscript. Adams Appiah was responsible for data curation, formal analysis, visualization, writing, review and editing of the manuscript. Avyakta Kallam and Vinicius Ernani were responsible for conceptualization, writing, reviewing and editing of the manuscript. Lynette Smith was responsible for data curation, formal analysis, writing, reviewing and editing of the manuscript, and project supervision. Apar Ganti was responsible for conceptualization, finding resources, supervision, writing, reviewing and editing of the manuscript.

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