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HPV status predicts for improved survival following chemotherapy in metastatic squamous cell carcinoma of the oropharynx

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ABSTRACT

Objective: We sought to further define prognostic and predictive value of human papillomavirus (HPV) status in metastatic squamous cell carcinoma of the oropharynx (OPC).

Materials and methods: A Surveillance, Epidemiology, and End Results custom database identified 5940 adult patients, > 18-years-old, with primary SCCHN and known HPV status, diagnosed from 2013 to 2014. Wilcoxon rank-sum and Mantel-Haenszel χ^2 tests compared distributions of continuous and categorical covariates. Fine-Gray competing risks regressions estimated hazard ratios by HPV status, and predictive analyses were performed including the interaction term HPV status × Receipt of Chemotherapy.

Results: 182 of 5940 patients (4.0%) had metastatic OPC at diagnosis (106/3925 [2.7%] HPV+ and 76/1894 [4.0%] HPV−). HPV+ disease was prognostic for improved 20-month cancer-specific mortality (CSM) (47.1% vs 72.5%, HR 0.43, 95% CI 0.26–0.74, p = 0.002) on univariable analysis. HPV status was predictive of response to chemotherapy—adjusted HRs for receipt of chemotherapy were 0.11 (95% CI 0.03–0.37) and 0.34 (95% CI 0.18–0.64) for HPV+ versus HPV− disease, respectively ($P_{HPV\ status*Chemotherapy}$ = 0.036).

Conclusion: HPV status has known prognostic value in locally advanced OPC, but data on metastatic OPC are sparse. In this work, we demonstrate that HPV status is strongly prognostic for CSM in metastatic OPC and show for the first time that HPV status predicts for response to chemotherapy.

Background

Squamous cell carcinomas of the oropharynx (OPC) are a major cause of cancer morbidity and mortality worldwide [1]. Whereas overall cancer incidence and mortality in the United States has declined in recent years, the incidence of human papillomavirus (HPV)-associated oropharyngeal cancer, has been increasing [1,2]. While HPV-negative (HPV−) OPC is generally associated with heavy smoking and alcohol history, HPV-positive (HPV+) cases are associated instead with sexual risk factors [3]. High-risk HPV infection can inactivate p53 and pRB and generate myriad epigenetic and chromosomal alterations leading to tumorigenesis [4]. The benefit of HPV immunization in reducing the incidence of OPC may not be seen for decades.

Numerous secondary analyses of prospective trials have demonstrated that positive HPV testing (or its surrogate p16) is associated with improved local control and overall survival in locally advanced OPC [5–7]. Individuals with HPV+ OPC are less likely to die of their disease than their HPV− counterparts [8]. Since local control is superior in HPV+ OPC, retrospective series and post-hoc analyses of prospective studies have accordingly reported a predominant pattern of distant failure in HPV+ OPC (as opposed to local failures in HPV− OPC) [7,9,10]. In addition, a subset of patients will present with distant metastatic disease at diagnosis (M1).

There are limited therapeutic options for patients with metastatic disease at diagnosis, with treatment typically limited to cytotoxic chemotherapy and palliative radiation therapy or surgery. Most patients will receive platinum- or cetuximab-based systemic therapy, but little is known about the utility of such treatment in HPV+ as compared to HPV− metastatic disease. The prognostic and predictive value of HPV has not been established in the metastatic OPC setting, with most studies limited by small sample sizes [9,11–15]. Furthermore, national databases have not released HPV status in OPC and therefore the nation-wide burden and outcomes associated with HPV-associated OPC in the metastatic setting has not yet been defined.

The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) has recently collected and reviewed information on nearly 6,000 cases of squamous cell carcinoma of the head and neck with known HPV status, diagnosed from 2013 to 2014 [16]. Herein, we present the first large study of clinical outcomes of patients with OPC with M1 disease at diagnosis and report the

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prognostic and predictive value of HPV status in this setting.

Patients and methods

Patient population

The SEER Program collects cancer incidence and survival data from 18 population-based cancer registries encompassing approximately 28 percent of the US population. The SEER registries collect data on patient demographics, primary tumor site, tumor morphology, stage at diagnosis, first course of treatment, and follow-up for vital status. SEER is the only comprehensive source of population-based information in the United States that includes stage of cancer at the time of diagnosis and patient survival data including cause of death as provided by the National Center for Health Statistics.

In this study, we used "SEER * Stat Database: Incidence – SEER 18 Custom Head and Neck (select schemas with HPV recode and additional treatment fields), Nov 2016 Sub (2013–2014)" to identify 5940 patients with primary squamous cell carcinoma of the head and neck, and known HPV status, diagnosed from 2013 to 2014 [16]. We identified 182 of these patients as having primary metastatic OPC. This is a custom linked database which includes HPV status data in OPC linked to the publicly available SEER * Stat Database: Incidence – SEER 18 Regs Research Data. SEER cancer registries code primary cancer site and histology per the International Classification of Diseases for Oncology, third edition (ICD-O-3).

The study inclusion period of 2013–2014 represents the years in which HPV status has been collected and reviewed for quality assurance. Patients with multiple primaries or where diagnosis was made at autopsy or death certificate were not queried. The study cohort was limited to patients ages 18 and older.

TNM staging was determined using the American Joint Committee on Cancer (AJCC) 7th edition. Race was classified by SEER as white versus non-white (black, Asian/Pacific Islander, American Indian/Alaskan Native, or unknown). Small area estimates for percent ever smoker was linked to SEER via estimates developed from the Behavioral Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS).

The study was deemed Institutional Review Board exempt.

Statistical analyses

Comparison of baseline patient characteristics by HPV status

The Wilcoxon rank-sum and Mantel-Haenszel χ^2 tests compared distributions of continuous and categorical covariates, stratified by HPV status (N = 240). Multivariable logistic regression was used to identify associations between patient characteristics and HPV status.

Prognostic analyses: CSM estimates by HPV status

Stata/SE 14.2 (StataCorp, College Station, TX, USA) was used for cause-specific survival analyses of patients with metastatic disease and at least 1 month of follow-up (N = 207), where the primary independent variable of interest was HPV status and the primary endpoint was cancer-specific mortality (CSM).

Univariable and multivariable Fine-Gray competing-risks proportional hazards regression was used to estimate hazard ratios by HPV status (HPV− [referent] versus HPV+). Additional variables included in the model were, receipt of treatment (none [referent], surgery, radiotherapy, and/or chemotherapy), age (continuous), race (non-white [referent] versus white), sex (female [referent] versus male), and smoking propensity (determined as a continuous variable from SEER provided % ever smoker small area estimates).

Predictive analyses: CSM estimates by receipt of chemotherapy, stratified by HPV status

To ascertain whether there is a differential response to chemotherapy by HPV status, a second Fine-Gray competing-risks regression model for CSM included an HPV status (positive versus negative) × Receipt of Chemotherapy (Yes versus No/Unknown) interaction term.

Using the aforementioned models, cumulative incidence plots for CSM were generated for the purposes of illustration. Adjusted hazard ratios with associated 95% confidence intervals and P-values were calculated for all covariates in the Fine-Gray competing-risks regression analyses. Statistical testing was two-sided with level of significance set at P = 0.025 after Bonferroni correction for examination of CSM outcomes stratified by HPV status (N = 2 groups).

Table 1
Distribution of baseline patient characteristics by HPV status with associated multivariable odds ratios for odds of HPV-positive disease among U.S. patients age 18 and older with M1 disease (N = 182). P < 0.05 when comparing across HPV status for all baseline characteristics.

Characteristic[a]	HPV-positive disease (N = 106)	HPV-negative disease (N = 76)	Odds of HPV-positive disease	
			AOR (95% CI)	P
Treatment received, N (Percent)[a]				
None	7 (6.6)	14 (18.4)	N/A (not patient level characteristic)	
Surgery	16 (15.1)	3 (3.95)		
Radiation therapy	69 (65.1)	46 (60.5)		
Chemotherapy	86 (81.1)	53 (69.7)		
Age at diagnosis, median (IQR)	62 (54–70)	64 (57–72)	0.97 (0.97–0.98)	< 0.001
Race, N (Percent)				
Non-white	14 (13.2)	20 (26.3)	1.0 (Referent)	
White	92 (86.8)	56 (73.7)	2.00 (1.67–2.39)	< 0.001
Sex, N (Percent)				
Female	23 (21.7)	17 (22.4)	1.0 (Referent)	
Male	83 (78.3)	59 (77.6)	1.78 (1.51–2.09)	< 0.001
Smoking Propensity[b], Median (IQR)	40.9 (34.9–45.7)	37.5 (31.6–45.5)	0.997 (0.988–1.005)	0.52

Abbreviations: AOR, Adjusted Odds Ratio; CI, confidence interval; HPV, Human Papillomavirus.
N/A, not applicable.
[a] Percent may not add up to 100 due to rounding (Percent for Initial Definitive Treatment does not add up to 100 due to receipt of multiple treatments).
[b] Percent ever smoker determined by small area estimates, linked to SEER via estimates developed from the Behavioral Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS).

Results

Patient characteristics

We identified 182 out of 5940 patients (3.1%) with metastatic OPC (M1) at diagnosis (106/3925 [2.7%] HPV+ and 76/1894 [4.0%] HPV− (Table 1). Median age at diagnosis was 62-years-old (IQR 54–70) and 64-years-old (IQR 57–72) for HPV+ and HPV− groups, respectively (AOR 0.97, p < 0.001). More men than women were affected in both HPV+ and HPV− cohorts—78.3% men for HPV+ and 77.6% men for HPV− (AOR 1.78, p < 0.001); likewise, the majority of patients in both groups were white—86.8% white for HPV+ and 73.7% white for HPV− (AOR 2.00, p < 0.001). Amongst HPV-positive patients who did not receive chemotherapy, 67.1% (53/79) received radiation therapy, and 15.2% (12/17) received surgery. For those with HPV-negative OPC, 71.7% (33/46) received radiation therapy, and