Prognostic significance of HPV status in postoperative squamous-cell carcinoma of the head and neck

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Background There are limited data on the prognostic significance of human papillomavirus (HPV) status in relation to traditional risk factors for head and neck squamous-cell carcinoma (HNSCC) in the postoperative setting.
Objective To clarify the impact of HPV status on the risk for HNSCC in the postoperative setting.
Methods We retrospectively evaluated an institutional cohort of 128 patients with HNSCC patients who had been treated with definitive surgery with or without adjuvant radiotherapy or chemoradiotherapy. Patient, disease, and treatment factors were analyzed as potential prognostic indicators.
Results Lymph node extracapsular extension (ECE), perineural invasion (PNI), and lymphovascular space invasion (LVSI) positivity predicted poorer locoregional control (LRC), disease-free survival (DFS), and overall survival (OS). Positive margins related to poorer DFS and OS. HPV status alone did not predict LRC, DFS, or OS. Compared with patients who were HPV-positive and ECE-negative, both HPV-positive and HPV-negative patients with ECE experienced significantly poorer OS (78.6%, 60%, and 43.7%, respectively; $P = .010$ and $P = .018$, respectively).
Limitations Retrospective, single-institution study; small patient cohort; short follow-up time
Conclusion The influence of HPV in postoperative HNSCC seems limited compared with traditional risk factors such as ECE, LVSI, and PNI. De-escalation of postoperative treatment based on HPV status alone should be approached with caution.

The criteria for adjuvant treatment with either radiation therapy (RT) or chemoradiotherapy (CRT) after primary surgery for locally advanced head and neck squamous-cell carcinoma (HNSCC) have been well studied. Risk factors such as number of involved lymph nodes and nodal groups, margin status, perineural invasion, subsite, and lymph node extracapsular extension (ECE) represent indications for postoperative adjuvant RT or CRT.[1-4] In the postoperative setting, ECE and margin-positive resection have been shown to be particularly high-risk features with negative prognostic significance on disease-free survival (DSF) and overall survival (OS), meriting escalation of therapy with the use of adjuvant CRT rather than RT alone.[2-4]

Over the last decade, human papillomavirus (HPV) has been established as an etiologic agent in some head and neck tumors, particularly oropharyngeal cancer. The incidence of HPV-associated cancer has been on the rise, with up to 70% of oropharyngeal cancer cases in North America now thought to be viral related.[5] It is now well established that this subset of oropharyngeal tumors carries a more favorable prognosis, with better tumor response to chemotherapy and/or radiotherapy, as well as improved overall survival when compared with their HPV-negative counterparts.[6-10] This has also led to the consideration for de-intensification of therapy in the definitive setting for some patients with HPV-positive HNSCC as examined in the RTOG 1016 protocol and the ongoing NRG HN-002 protocol, among others.[11-14]

Although HPV status has been well established as a prognostic factor in oropharyngeal cancer treated nonoperatively, its prognosis in other head and neck subsites and in the postoperative setting is less clear. Some recent evidence shows a similar, but less dramatic prognostic benefit in nonoropharyngeal HNSCC.[15] Although the evidence of its value as a prognosticator continues to accrue in the definitive treatment setting, there are limited data on the

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TABLE 1 Tumor characteristics (N = 128)

Characteristic	n (%)
Tumor stage	
T0	6 (4.7)
T1	17 (13.3)
T2	28 (21.9)
T3	16 (12.5)
T4	37 (28.9)
Recurrent	24 (18.8)
Nodal stage	
pN0	39 (30.5)
pN1	13 (10.2)
pN2a	5 (3.9)
pN2b	35 (27.3)
pN2c	10 (7.8)
pN3	2 (1.6)
Recurrent	24 (18.8)
Nodal status	
Negative	47 (36.7)
Positive	81 (63.3)

prognostic significance of HPV status in the postoperative setting, particularly in relation to other traditional risk factors. Lohaus and colleagues with the German Cancer Consortium Radiation Oncology Group (DKTK-ROG) found that HPV positivity was a strong prognostic factor to predict locoregional control in postoperative HNSCC patients, but found on multivariate analysis that this finding was driven by a strong effect of the subset of postoperative patients with oropharyngeal primary tumors.[16] This finding has been corroborated by Heiduschka and colleagues who found that HPV status in postoperative oropharyngeal tumors predicted for OS and DFS.[17] These studies focus on the effect of HPV status in postoperative oropharyngeal patients, which at many institutions represent a minority of contemporary postoperative cases. Our study seeks to further clarify the role and relevance of HPV status postoperatively and examine its interplay with other patient, tumor, and treatment factors in a typical postoperative patient population.

Materials and methods

Patients and treatments

We performed a retrospective review of the medical records of all patients treated for squamous-cell carcinoma of the head and neck at the University of Louisville James Graham Brown Cancer Center in Kentucky during 2009-2014. From an initial cohort of 927 patients, 128 were nonmetastatic and treated with definitive surgery with or without adjuvant RT or CRT. Oral cavity, laryngeal, oropharyngeal, and unknown primary subsite cases were included. Cancers of the hypopharynx, nasopharynx, salivary glands, and paranasal sinuses were excluded. Both newly diagnosed and recurrent patients were included. Patients were excluded if their initial treatment modality was not surgical resection or if they were not treated with curative intent.

Patients were considered to have HPV-related tumors if surgical pathologic specimens were positive by in situ hybridization (ISH) for high-risk HPV 16 and/or p16 positive by immunohistochemistry (IHC). HPV 16 ISH was performed on formalin fixed and paraffin embedded tumor samples, and p16 IHC required strong staining at >70% to be considered positive. Tumors were staged using the AJCC seventh edition TNM classification system (2010).

Statistical methods

Descriptive analyses determined patient demographic and clinical characteristics. Patient, disease, and treatment factors were analyzed as potential prognostic indicators in Cox proportional hazard regression models. Predictive factors of interest were entered using a backward stepwise approach. These factors included patient's age, sex, disease site, T and N stage, presence of ECE, lymphovascular space invasion (LVSI), perineural invasion (PNI), smoking status, HPV and p16 status, and treatment modality. The endpoint measure was effect on locoregional control (LRC), DFS, and OS either as an independent prognostic factor or how they interplayed with other factors to affect outcomes. Chi-square and independent samples *t* tests confirmed no significant differences between primary versus recurrent cases on the outcomes of interest. Thus, all patients were included in tests of hypotheses. Post hoc analyses confirmed significant results by adjusting models for characteristics that may impact on outcomes, including patient age and site of disease. Kaplan-Meier plots were generated to illustrate survival results. All statistical tests were completed using SPSS (version 22), 2-sided with a $P < .05$ to identify statistical significance.

Results

Patient demographics and clinical characteristics

A total of 128 patients met inclusion criteria for the study and were included in the cohort. Median age of patients was 60 years (range, 24-85). The median follow-up period for survivors was 18.4 months (range, 0.6-66.9). The patient population represented a typical squamous-cell carcinoma of the head and neck cancer cohort. There was a larger percentage of men (68.8%), and more than 70% of patients had a >10 pack-year history of smoking. Most patients (n = 104; 81.2%) were treated for newly diagnosed primary disease, and 24 (18.8%) were treated for locoregionally recurrent HNSCC. Tumor characteristics are listed in Table 1.

TABLE 2 Tumor high-risk features

Risk factor	n (%)
HPV status	
Negative	86 (78.2)
Positive	24 (21.8)
ECE status	
Negative	31 (38.3)
Positive	50 (61.7)
Margin status	
Negative	95 (74.2)
Positive	33 (25.8)
LVSI status	
Negative	67 (52.3)
Positive	42 (32.8)
Unknown	19 (14.8)
PNI status	
Negative	59 (46.1)
Positive	50 (39.1)
Unknown	19 (14.8)

ECE, extracapsular extension; HPV, human papillomavirus; LVSI, lymphovascular space invasion, PNI, perineural invasion

TABLE 3 HPV status by primary site

Primary tumor site	HPV+, n (%)	HPV-, n (%)
Oral cavity	9 (13.8)	56 (86.2)
Oropharynx	8 (61.5)	5 (38.5)
Larynx	4 (16.0)	21 (84.0)
Unknown primary	3 (50.0)	3 (50.0)
Overall	*24 (21.8)*	*86 (78.2)*

HPV, human papillovirus

The primary site of disease was oral cavity (n = 81; 63.3%), larynx (27; 21.1%), oropharynx (13; 10.1%), and unknown primary or other subsite (7; 5.5%). The modality of treatment was surgery alone in 19 patients (14.8%), surgery plus adjuvant radiotherapy in 49 (38.3%), and surgery plus adjuvant chemoradiotherapy in 60 (46.9%). For the 109 patients receiving radiation, the median prescribed radiation dose was 6100 cGy (interquartile range, 6000-6600 cGy), with 107 patients treated with external beam radiation therapy (EBRT), and 2 treated with postoperative brachytherapy. External beam radiation was delivered with postoperative intensity-modulated radiation therapy (IMRT) in 67 patients (62.6%) and 3-dimensional conformal radiation therapy (3DCRT) in 40 patients (37.4%).

Tumor high-risk features are described in Table 2. The majority of patients (63%) had pathologically positive nodal disease. Of the 81 patients undergoing a neck dissection with involved lymph nodes, 50 (62%) had evidence of ECE. Of the 110 patients with known HPV-p16 status, 24 (21.8%) were HPV positive. The results of HPV analysis by primary tumor subsite is shown in Table 3. Notably, of the 24 patients who were HPV positive, 8 (33%) were oropharynx primary subsite. LVSI was found in 42 patients (33%), and PNI was present in 50 (39%). Surgical margins were free of malignancy in 74% of patients.

Clinical outcomes

At 2 years follow-up, 18 patients (14.1%) experienced locoregional treatment failure. Of those, 3 (2.3%) also experienced a distant failure. An additional 12 patients (9.4%) experienced a distant failure without locoregional failure. In the 15 patients with distant failure, the lung was most commonly involved (n = 9; 56%), with other failures occurring in brain and bone. Overall, 38 patients (29.7%) died during the follow-up period of the study. The impact of various patient and disease factors was analyzed for this set of postoperative patients in terms of 2-year LRC, DFS, and OS, and results are summarized in Table 4.

Impact of HPV status. We found no significant impact of HPV status in this patient subset on the outcomes of OS, DFS, or LRC, even after adjusting for primary tumor location in the oral cavity compared with other subsites. Locoregional control was not significantly influenced by HPV status, with 2-year LRC rates of 88.5% and 83.7% for HPV-positive and HPV-negative patients, respectively (P = .912). DFS in HPV-negative patients was 75.6%, compared with 83.3% in HPV-positive patients (P = .750). Similarly, there was no difference in 2-year OS in HPV-negative patients (66.3%), compared with HPV-positive patients (75.0%; P = .415).

Impact of ECE. There was a statistically significant detriment in OS, DFS, and LRC among patients who were found to be ECE positive on pathology. LRC was 78.0% in ECE-positive patients and 91.1% in ECE-negative patients (P = .026). DFS decreased from 85.9% in patients without ECE to 64.0% when ECE was present (P = .001). In ECE-positive patients, 2-year OS was 54.0%, compared with 80.8% in ECE-negative patients (P < .001).

Impact of LVSI, PNI, and margin status. LVSI also significantly predicted poorer LRC, DFS, and OS. Locoregional control decreased from 94.2% to 76.2% in the presence of LVSI (P = .028). LVSI conferred worse 2-year DFS (89.6% vs 64.3%, P = .005), and OS (88.1% vs 52.4%, P < .001). There was a significant reduction in LRC (94.9% vs 76.0%, P = .013), DFS (89.8% vs 64.0%, P = .006), and OS (81.4% vs 62.0%, P = .022) when PNI was present. Positive pathologic margins after surgical

TABLE 4 Multivariate analyses of prognostic factors[a]

Factor	LRC		DFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
HPV negativity	1.08 (0.29-3.97)	.912	0.84 (0.28-2.53)	.750	0.69 (0.28 – 1.70)	.415
ECE positivity	3.03 (1.14-8.05)	.026	3.64 (1.69-7.85)	.001	3.35 (1.70-6.59)	<.001
PNI positivity	5.52 (1.44-21.1)	.013	3.69 (1.45-9.38)	.006	2.52 (1.15-5.54)	.022
LVSI positivity	3.73 (1.15-12.1)	.028	3.67 (1.49-9.03)	.005	4.47 (1.94-10.3)	<.001
Margin positive	2.28 (0.88-5.88)	.088	2.40 (1.15-5.02)	.020	2.38 (1.23-4.62)	.010

CI, confidence index; ECE, extracapsular extension; DFS, disease-free survival; HPV, human papillomavirus; HR, hazard ratio; LRC, locoregional control; LVSI, lymphovascular space invasion, OS, overall survival; PNI, perineural invasion

[a]Cox proportional hazard regression models were adjusted for age at diagnosis and primary site.

resection trended toward, but did not significantly predict, worse LRC (75.8% vs 89.5%, *P* = .088). Patients with positive margins experienced poorer DFS when compared with patients with negative margins (60.6% vs 82.1%, respectively; *P* = .020) and poorer OS (54.4% vs 75.8%, *P* = .010).

Interplay of ECE and HPV. Of the historical risk factors that guide treatment intensity (ECE and margin status), ECE was the strongest predictor in our population. Because of this, we analyzed the interaction of HPV status with the presence vs absence of ECE on overall survival (Figure). The HPV-positive and ECE-negative patient population was set as the reference group. Compared with this group, there were no significant differences in outcomes of patients with HPV-negative and ECE-negative disease in terms of 2-year DFS (85.7% vs 88.9%, *P* = .841) or OS (78.6% vs 74.1%, *P* = .48). Again using the HPV-positive, ECE-negative patients as the reference group, there was a significant decrease in OS seen in patients who were ECE positive regardless of their HPV status. Compared with the 78.6% 2-year OS in HPV-positive, ECE-negative patients, OS in ECE-positive, HPV-negative patients was 43.7% (*P* = .018) and in ECE-positive, HPV-positive patients OS was 60.0% (*P* = .010).

Discussion

Despite progressive improvements in the current treatment of head and neck cancers, 15%-50% of patients will experience treatment failure and develop recurrent disease.[18-20] Patients with HNSCC, especially in the postoperative setting, are often classified into risk categories based on patient and disease factors to determine which patients will benefit from escalation of therapy.[2,21,22] Although PNI, LVSI, and especially ECE and positive surgical margins are well established as poor prognostic factors that require consideration before treatment,[4,23] the seminal studies that established the prognostic significance of these factors were performed prior to the era of understanding the importance of HPV status.

Over the past decade, advances have been made in under-

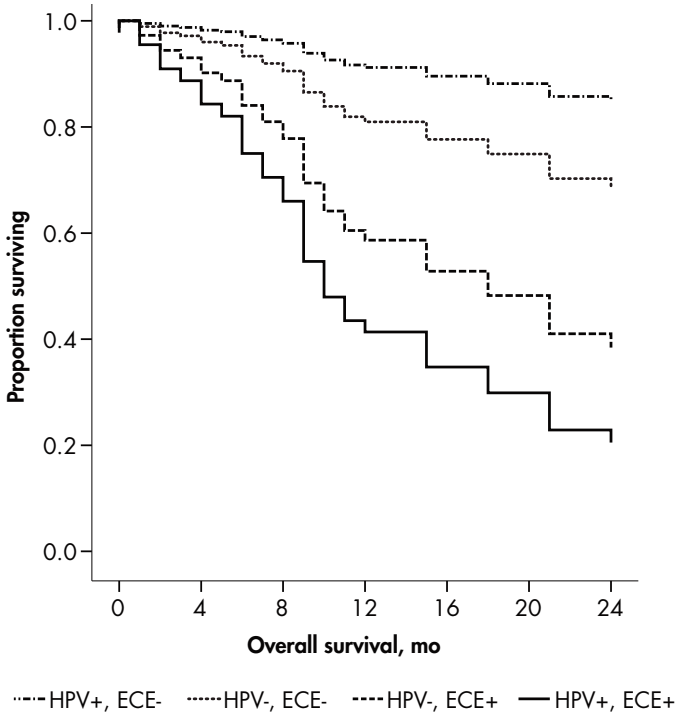

FIGURE Overall survival curves for groups stratified by HPV and ECE status. Analyses demonstrate a significant decrease in overall survival among ECE-positive patients with either HPV-positive or HPV-negative disease.

ECE, extracapsular extension; HPV, human papillomavirus

standing the significance of HPV status,[6,9] but the impact of HPV in the postoperative setting remains unclear. The recent reports from Lohaus and Heiduschka and their respective colleagues suggest that HPV positivity is likely an important prognostic factor in postoperative oropharyngeal HNSCC patients,[16,17] but the role of HPV status in nonoropharyngeal patients and in relation to more traditional risk factors is less well understood.

Although HPV status plays a major role in the affecting outcomes of nonoperative HNSCC, especially oropharyngeal cancer, its influence on a typical population of postoperative patients, which often includes a higher percentage of nonoropharynx tumors seems to be limited based on the results in this series. This is true even when controlling for primary site in the oral cavity compared with other subsites on multivariate analysis. This is likely in part because, depending on institutional preference, patients undergoing primary surgical intervention less commonly have an oropharyngeal primary, which is the primary group of patients known to have improved outcomes with HPV-associated tumors. Despite recent reports of the possible prognostic significance of in nonoropharyngeal head and neck cancer,[15,24] the role of HPV status as a predictor of disease response and survival in this subset is still in question.

The lack of a significant prognostic effect in regard to HPV status may be due to several factors. First, although the majority of oropharyngeal tumors in this study were HPV positive (61.5%), only one-third of HPV-positive patients in this study had a primary tumor of the oropharynx. This may demonstrate that HPV loses prognostic significance in nonoropharynx primary HPV-positive patients. Alternatively, it may be that HPV status, which has been shown to be significant in patients undergoing treatment of oropharyngeal cancer with definitive chemoradiation, is a relatively less significant factor in the setting of treatment of HNSCC with primary surgery. Because of the limited number of oropharyngeal tumors in our patient population, it is difficult to make any definitive conclusions in this small subset. Similarly, increasing the length of follow-up may allow for a greater number of events to be analyzed.

Despite its lack of significance in our findings, it is possible that HPV status still plays a role in determining outcomes in the postoperative setting, which may manifest with higher patient numbers allowing further stratification of the data. In this particular patient population, it appears HPV status is overshadowed by other traditional disease factors such as ECE, which have been consistently shown to have a strong impact on control and survival. It may also be that HPV status is simply less predictive of patient outcomes in the postoperative setting as it has been shown to be in patients with oropharyngeal tumors who are predominantly treated with definitive chemoradiation. This may in part be related to the inherent chemoradiosensitivity seen in HPV-driven tumors, making them particularly responsive to nonoperative therapy.

Our findings conflict somewhat with the contemporary report from the DKTK-ROG.[16] That group found that HPV and p16 status had a significant impact on locoregional tumor control and OS, but not on distant metastases. They went on to describe that their results were driven by the effect of HPV in the subset of patients with oropharyngeal primary tumors, which made up the majority of their cohort. Our patient set contained only 10.2% oropharyngeal primary tumors, which more closely mirrors a typical population of patients treated initially with surgical resection in the United States. As such, a comparison of our results with the DKTK-ROG data is difficult. It is likely that the discrepancy in our outcomes is driven by the disparity in primary tumor types. In addition, the fact that our institutional HPV-positive population has a high incidence of patients with a >10 pack-years of smoking may also mitigate the protective effect of HPV, as has been shown elsewhere.[25] It is also interesting that despite the inclusion of oropharynx patients in our data set, HPV took a back seat to traditional risk factors such as ECE, LVSI, and PNI.

Our findings demonstrate that HPV does not fundamentally change the paradigm of adjuvant therapy in postoperative HNSCC. Particularly in a population driven by oral cavity tumors, classic risk factors continue to dictate decisions on adjuvant treatment. At this point, HPV does not merit consideration of de-escalation of therapy. Granted, these conclusions are constrained by the inherent limitations of a single institution retrospective series, including selection bias, regional patient population, and limited follow-up. We believe this warrants further prospective investigation to determine the appropriate treatment approach in this subset of patients.

The ongoing phase 3 trial of surgery and postoperative radiation in high-risk HNSCC, RTOG 1216,[26] may provide additional prospective insight into the effect of HPV in the postoperative setting, although HPV analysis is not mandatory for nonoropharyngeal patients, which may limit the ability to compare prospective data with our findings. Another ongoing prospective trial being undertaken by the DKTK-ROG is attempting to more firmly define the prognostic value of HPV status in terms of local control in the postoperative setting after adjuvant CRT.[16] In addition, another trial (ADEPT, NCT01687413) is exploring the feasibility of treatment de-escalation with omission of chemotherapy in a patient cohort that our data suggest is higher risk based on ECE positivity. These and other future prospective data should more clearly establish the importance of HPV status in HNSCC patients after upfront surgical resection. In the interim, postoperative treatment de-escalation based on HPV status alone should be approached with caution.

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