



Human papilloma virus positive cancers of the oral cavity: the UCLA experience

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Abstract

Human papilloma virus (HPV) is associated with increased incidence and improved prognosis in oropharyngeal cancers.¹ Patients are typically younger and never smokers. A disproportionate number of oral tongue cancers has also been reported to arise in young non-smokers; however, the association between oral cavity squamous cell carcinoma (OCSCC) and HPV has not been established, with HPV positivity rates reported to range from 2-91%.²⁻⁴ Given a paucity of data, we sought to review cases of OCSCC from a single tertiary referral center to evaluate the rate of HPV positivity within this oral cavity.

Our findings suggest that the rate of HPV-positive OCSCC may be higher than commonly reported. Similar to OP cancers, patients tend to be younger. These patients tend to have similar profiles to patients with non-HPV related cancers with regard to smoking/alcohol status. Oral cancers should be tested for p16, and further investigation should be directed at the impact of HPV-positivity on further outcomes.

Introduction

Oral cavity malignancies are widely prevalent, estimated to represent 3% of all new cancers diagnosed in 2016.⁶ Tobacco and alcohol use are well demonstrated to be associated with development of these cancers, but as use of these substances has decreased, the rate of malignancy has not decreased as would be expected.^{4,7} HPV (particularly high-risk subtypes HPV-16 and 18) has been well documented to be associated with the development and improved prognosis of squamous cell carcinoma in the oropharynx, but a similar relationship has not been demonstrated in malignancies of the oral cavity.^{1, 2, 5} The range of HPV positivity in oral cavity malignancy ranges widely, and its impact on prognosis is unknown.^{2-4,8} Given the lack of consensus, we sought to review the UCLA experience of prevalence, tumor characteristics, and patient demographics with respect to HPV positivity in oral cancers.

Methods and Materials

Patients selected for inclusion were identified by reviewing all pathology specimen evaluated by the Head and Neck Pathology department between 2008 and 2012. Patients who met inclusion criteria were those who had a biopsy and/or surgical specimen diagnostic of squamous cell carcinoma of the oral cavity collected within the specified time frame. A pathology specimen was excluded if no HPV or p16 testing was performed. A retrospective chart review was then performed. Collected data included age at diagnosis, alcohol/tobacco history, ethnicity, tumor characteristics (T, N, and M stage, tumor grade, perineural invasion (PNI), lymphovascular invasion, and depth of invasion for oral tongue lesions), and treatment modality pursued. Survival and quality of life data were also collected, but was limited due to lack of long-term follow-up in this tertiary care center.

Fischer-exact tests were used to assess significance of variation between HPV-positive and HPV-negative tumors with respect to regional lymphatic spread, perineural invasion, extracapsular spread, and lymphovascular invasion. A one-tailed t-test assuming non-equal variance was used to assess for significance of variation between age, t-stage, overall tumor size, and tumor grade in the two groups.

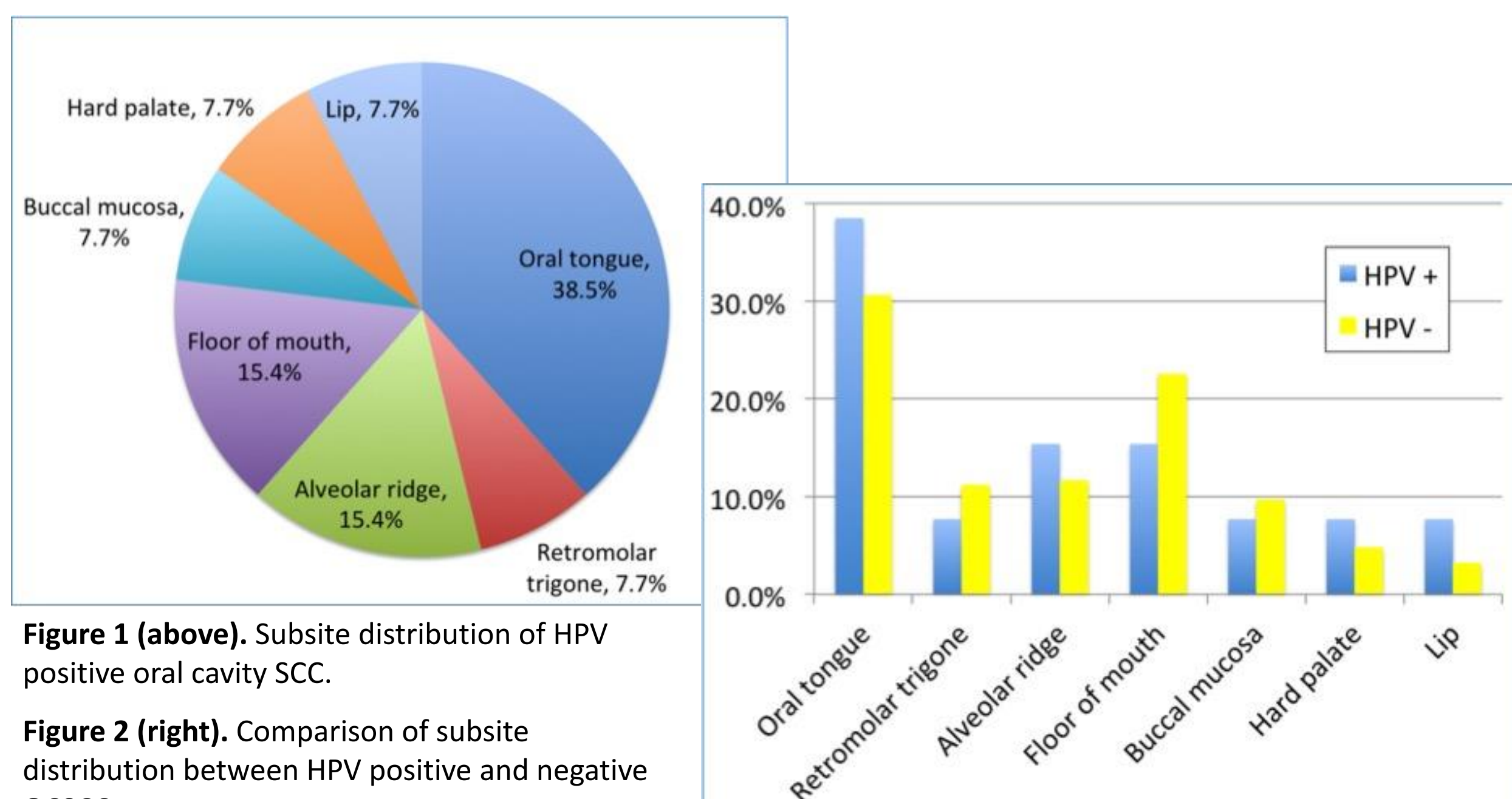


Figure 1 (above). Subsite distribution of HPV positive oral cavity SCC.

Figure 2 (right). Comparison of subsite distribution between HPV positive and negative OCSCC.

Results

75 patients diagnosed with OCSCC between 2008 and 2012 met inclusion criteria, 62 (82.7%) were HPV-negative, and 13 (17.3%) were HPV-positive. The average age of HPV-positive subjects was 60.5 +/- 10.1 years, while the average age of HPV-negative participants was 66.6 +/- 15.0. This is a statistically significant difference in age (p=0.041). 27 (43.5%) of the HPV-negative patients were smokers, with an average of 10.0 cumulative pack-year smoking history, as compared to 7 (53.8%)/13.4 pack-years in HPV-positive patients, which was a non-significant difference (p=0.353). Alcohol use was reported by 25 (40.3%) of HPV-negative patients and 9 (69.2%) of HPV-positive subjects.

Distribution of subsites within the oral cavity is represented in figures 1 and 2. The average T-stage of HPV-negative patients was 2.76, versus 2.46 in HPV-positive patients. There was no statistical difference observed in the T-stage at the time of diagnosis (p=0.415). The average tumor size (largest dimension) was 2.58 +/- 1.78cm for HPV-positive patients and 3.34 +/- 1.81cm for HPV-negative subjects. This difference trended toward significance (p=0.087). Nodal disease was present in 23 (37.1%) of HPV-positive patients and 3 (23.1%) of HPV-negative patients (p=0.717). No difference in rate of lymphovascular invasion or extracapsular spread was observed (p=0.719 and p=0.759, respectively). There was, however, a difference in observed PNI (p=0.649), with PNI found in 30% of HPV-positive tumors and 50% of HPV-negative.

Patient/Tumor Demographics	HPV +	HPV -
	n (%)	n (%)
Total patients (n = 75)	13 (17.3)	62 (82.7)
Age	60.5 (+/- 10.1)	66.6 (+/- 15.0)
Gender		
Male	10 (76.9)	34 (54.8)
Female	3 (23.1)	28 (45.2)
History of tobacco use	7 (53.8)	27 (43.5)
Average pack years	10 years	13.4 years
History of alcohol use	9 (69.2)	25 (40.3)
Subsite		
Oral tongue	5 (38.5)	19 (30.6)
Retromolar trigone	1 (7.7)	7 (11.2)
Alveolar ridge	2 (15.4)	11 (17.7)
Floor of mouth	2 (15.4)	14 (22.6)
Buccal mucosa	1 (7.7)	6 (9.7)
Hard palate	1 (7.7)	3 (4.8)
Lip (upper or lower)	1 (7.7)	2 (3.2)
Tumor Characteristics		
Mean T-stage	2.46	2.76
Mean tumor size (largest dimension)	2.58 +/- 1.78cm	3.34 +/- 1.81cm
Presence of regional nodes	3 (23.1)	23 (37.1)
Perineural invasion	4 (30.8)	38 (50.6)

Table 1. Patient and tumor characteristics.

Discussion

Our results demonstrate a high rate of HPV positivity in OCSCC (17.3%). Although limited by small sample size, the results did demonstrate significant differences between HPV-positive and HPV-negative tumors/patient populations. HPV-positive patients were significantly younger, and were more likely to have less aggressive tumor characteristics including perineural invasion. This observed prevalence as well as significantly increased rate of high-risk tumor features warrant focused evaluation in future studies, which should focus on patient survival.

The study is limited by absence of long-term patient follow-up, likely due to the fact that the population was recruited from a cohort of patients identified in a tertiary care center, where patients were often referred for a surgery requiring greater resources than a community-based institution can provide. Following surgery, patients often return to the community for surveillance, thereby limiting survival/outcomes data.

Conclusions

The rate of HPV-positive OCSCC may be higher than previously reported. These tumors tend to arise in younger patients, and may have distinct tumor characteristics. Oral cancers should be tested for HPV/p16, and further investigation should be directed at the impact of HPV-positivity on patient outcomes including survival and patient quality of life.

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