Prognostic Impact of High-Risk Pathologic Features in HPV-Related Oropharyngeal Squamous Cell Carcinoma and Tobacco Use

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objectives. To assess the impact of pathologic features and chronic tobacco use on human papillomavirus (HPV)–related oropharyngeal squamous cell carcinoma (OPSCC).

Study Design. Case series with chart review.

Setting. Single tertiary care referral center.

Subject and Methods. A total of 301 patients were treated for OPSCC from 2008 to 2016. Clinical and pathologic T and N stage, American Joint Committee on Cancer (AJCC) stage (seventh and eighth edition staging manuals), cigarette pack years, alcohol use, and presence of extranodal extension (ENE), perineural invasion (PNI), or lymphovascular invasion (LVI) were assessed. Patients were stratified into HPV negative, HPV-positive heavy smokers (>20 pack years), and HPV-positive nonsmokers. Five-year survival by Kaplan-Meier method was assessed.

Results. Of the HPV-positive patients, 97 were nonsmokers and 73 were heavy smokers. HPV-positive heavy smokers had significantly decreased survival compared to their non-smoking counterparts (P = .02). The presence of ENE was associated with a significantly decreased 5-year survival (P = .02) in heavy smokers relative to nonsmokers in HPV-positive patients. Furthermore, for the AJCC eighth edition, clinically stage 1 HPV-positive heavy smokers had significantly decreased survival relative to nonsmokers (P = .01).

Conclusions. This series highlights the potential need for more aggressive therapy for HPV-positive patients with extensive tobacco use under the new staging system.

Keywords

oropharynx, oropharyngeal squamous cell carcinoma, head and neck squamous cell carcinoma, HPV, tobacco use, smoking, survival, AJCC staging

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Approximately 37,000 cases of head and neck squamous cell carcinoma are diagnosed each year in the United States with at least 16,000 of these arising as oropharyngeal squamous cell carcinoma (OPSCC). Since its recognition, the incidence of human papillomavirus (HPV)–related OPSCC continues to increase. While there has been a rise in the incidence of HPV-related (HPV-positive [HPV+]) OPSCC, the incidence of oropharyngeal cancer related to alcohol and tobacco use has seen a downward trend over the past couple decades.

It is accepted by most that HPV-related OPSCC is a different clinical entity compared to non-HPV-related disease. Unlike HPV-negative (HPV−) OPSCC, patients with HPV + OPSCC are often younger, have limited to no smoking history, and are more likely to be white. The prognostic implication of HPV status is well documented in the literature. Patients with HPV+ OPSCC often demonstrate greater response to treatment and improved overall survival compared to those with HPV− disease. With recognition of these prognostic differences, the American Joint Committee on Cancer (AJCC) eighth edition staging manual distinguishes between HPV + and HPV− OPSCC with the generation of 2 separate staging systems. The new staging system places emphasis on the number and laterality of involved cervical lymph nodes but does not incorporate tobacco use

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or any specific pathological features, such as perineural invasion (PNI), extranodal extension (ENE), or lymphovascular invasion (LVI).

While the “new” head and neck cancer patient is often a younger nonsmoker, there are still patients with HPV-related OPSCC who have extensive smoking histories. The clinical impact of smoking on patient outcomes in patients with HPV+ OPSCC is mixed in the literature. Ang et al.8 demonstrated that along with HPV status, patients with a greater than 10 pack-year smoking history had decreased survival outcomes relative to those with no smoking history or less than 10 pack-years. In addition to pack-year history, current smoking status has also been associated with a worse overall 5-year survival in those with HPV-related OPSCC who were treated with primary chemotherapy and radiotherapy (CXRT).8 While data support a direct link between smoking and the risk of death and disease progression in those with HPV-related OPSCC, several studies report that no direct link exists.4,9–11

Improved survival and response to treatment for those with HPV-related OPSCC, coupled with the morbidity of treatment, has led to many ongoing clinical trials investigating de-escalation treatment paradigms. Even though there is some evidence to suggest the contrary, many head and neck oncologists believe that patients with HPV+ OPSCC who are heavy smokers represent a distinct patient population and should be treated as such. The AJCC eighth edition staging manual “down-stages” HPV+ malignancies compared to previous editions, regardless of smoking status or the presence of specific pathological features. Although AJCC staging is not intended to be a treatment guideline, the National Comprehensive Cancer Network develops guidelines based on stage. Therefore, implementation of the AJCC eighth edition raises the concern that a subset of patients may be undertreated since the majority of HPV-related OPSCCs will present with stage I disease. While there is literature demonstrating the negative impact of tobacco history and specific tumor features on survival, to our knowledge, there is no literature regarding the impact of smoking and certain pathological findings in OPSCC that is staged according to the eighth edition staging manual. The authors aim to determine the association between smoking and the presence of certain pathological features in relation to the new cancer staging, as a means to determine if these patients represent a distinct patient population whose disease course is similar to HPV− disease and should be counseled and managed accordingly.

Methods

Study Design

This was a retrospective chart review of all patients who received treatment for OPSCC at a single tertiary care institution between January 1, 2008, and December 31, 2016. This study was approved by the Institutional Review Board of the Medical University of South Carolina.

Patients

Patients with OPSCC were identified based on International Classification of Diseases (ICD)/Current Procedural Terminology (CPT) codes. Demographic data, including age at diagnosis, sex, race, ethnicity, tobacco use, and alcohol use, were recorded. Clinical data, including HPV status, defined by p16 status or HPV-DNA of tumor specimens, treatment modality, regional and distant metastasis, and vital status, were recorded. The seventh and eighth edition AJCC staging manuals were used to stage patients both clinically and, if applicable, pathologically. Pathologic data, including nodal status, ENE, PNI, or LVI, for surgically managed patients were recorded as well.

Clinical End Points

The variables assessed were clinical and pathologic T and N stage; cancer stage based on the seventh and eighth edition AJCC staging manuals; cigarette pack-years; alcohol use; the presence of ENE, PNI, or LVI; vital status; and overall, 5-year survival, and disease-free survival. Other clinical variables collected included sex, race, ethnicity, alcohol use, cancer status, grade, anatomic site, treatment, metastasis, and recurrence. Furthermore, the purpose of this study was to evaluate the effect of smoking and HPV status together on survival.

Statistical Analysis

Patients were stratified into 3 groups: HPV− patients, HPV+ nonsmokers, and HPV+ heavy smokers (≥20 pack-year smoking history). Smoking status assessed if extensive tobacco use was distinctly different or behaved more like HPV− disease. Descriptive statistics were used to summarize variables and determine differences between the 3 groups. For categorical variables, a χ² was performed to assess significance. For continuous variables, analysis of variance (ANOVA) was performed for normally distributed data points and Kruskal-Wallis for nonnormal distributions. Kaplan-Meier (KM) survival curves were used to examine unadjusted survival times with significance determined by the log-rank test. Median survival times and their confidence intervals (CIs) were also presented. All statistical analysis was performed on SPSS version 24.0 (SPSS, Inc, an IBM Company, Chicago, Illinois).

Results

Demographics

A total of 314 patients were identified with HPV status and a documented smoking history. In total, 132 (42%) patients were HPV negative, 97 (31%) were HPV+ nonsmokers, and 85 (27%) were HPV+ heavy smokers. Patients were labeled HPV positive based on p16 status in 177 (97%) of cases and by in situ hybridization in 5 (3%) of cases, all of which were diagnosed before 2010. There were significant differences in sex, race, ethanol use, AJCC seventh edition staging, and PNI between treatment groups (Table 1). There were no significant differences between treatment
modality for HPV+ heavy smokers and nonsmokers. No significant difference was noted in HPV+ nonsmokers and heavy smokers either in stage using the seventh or eighth edition of the AJCC staging manual.

**HPV+ Heavy Smokers Have Significantly Decreased Survival**

On Kaplan-Meier analysis, HPV+ heavy smokers had a significantly decreased 5-year survival compared to HPV+ nonsmokers for patients managed surgically ($P < .01$). HPV+ heavy smokers had a 76% survival rate at 5 years compared to 89% for nonsmokers (Figure 1).

**Presence of Adverse Pathologic Features Does Not Affect Survival for HPV+ Heavy Smokers**

The presence of traditional adverse pathologic features in HPV+ heavy smokers did not significantly affect 5-year survival relative to the absence of these features.

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**Table 1. Patient Demographics for HPV-Negative Patients, HPV+ Nonsmokers, and HPV+ Heavy Smokers.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HPV Negative (n = 132)</th>
<th>HPV+ Nonsmoker (n = 97)</th>
<th>HPV+ Heavy Smoker (n = 85)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>61 (54-68)</td>
<td>58 (52-63)</td>
<td>60 (55-66)</td>
<td>.293</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>.003</td>
</tr>
<tr>
<td>Male</td>
<td>97 (73)</td>
<td>85 (87)</td>
<td>80 (94)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35 (27)</td>
<td>12 (12)</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White</td>
<td>92 (70)</td>
<td>92 (95)</td>
<td>79 (93)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>40 (30)</td>
<td>5 (5)</td>
<td>6 (7)</td>
<td></td>
</tr>
<tr>
<td>Alcohol useab</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>None</td>
<td>43 (33)</td>
<td>52 (54)</td>
<td>24 (29)</td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>68 (52)</td>
<td>42 (43)</td>
<td>44 (52)</td>
<td></td>
</tr>
<tr>
<td>Past use</td>
<td>19 (15)</td>
<td>3 (3)</td>
<td>16 (19)</td>
<td></td>
</tr>
<tr>
<td>AJCC clinical stage 7</td>
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<td></td>
<td></td>
<td>.027</td>
</tr>
<tr>
<td>I</td>
<td>10 (8)</td>
<td>2 (1)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>12 (9)</td>
<td>7 (8)</td>
<td>6 (7)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>30 (23)</td>
<td>16 (18)</td>
<td>13 (15)</td>
<td></td>
</tr>
<tr>
<td>IVa</td>
<td>64 (50)</td>
<td>59 (69)</td>
<td>57 (67)</td>
<td></td>
</tr>
<tr>
<td>IVb</td>
<td>7 (6)</td>
<td>2 (2)</td>
<td>6 (7)</td>
<td></td>
</tr>
<tr>
<td>IVc</td>
<td>5 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>AJCC clinical stage 8c</td>
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<td>55 (59)</td>
<td>47 (55)</td>
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<tr>
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<td>III</td>
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<tr>
<td>IVc</td>
<td>5 (4)</td>
<td></td>
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<td>Treatment modality</td>
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<tr>
<td>Surgery</td>
<td>27 (22)</td>
<td>12 (13)</td>
<td>5 (7)</td>
<td></td>
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<tr>
<td>Radiation</td>
<td>5 (4)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
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<tr>
<td>Chemoradiation</td>
<td>55 (44)</td>
<td>41 (43)</td>
<td>30 (44)</td>
<td></td>
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<tr>
<td>Surgery + RT</td>
<td>11 (9)</td>
<td>15 (16)</td>
<td>12 (17)</td>
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<tr>
<td>Surgery + CRT</td>
<td>21 (17)</td>
<td>22 (23)</td>
<td>21 (30)</td>
<td></td>
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<tr>
<td>RT + surgery</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>CRT + surgery</td>
<td>5 (4)</td>
<td>5 (5)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Perineural invasion</td>
<td>27 (49)e</td>
<td>7 (14)e</td>
<td>18 (45)e</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>16 (21)e</td>
<td>12 (19)e</td>
<td>19 (37.0)e</td>
<td>.065</td>
</tr>
<tr>
<td>Extramodal extension</td>
<td>12 (37)e</td>
<td>17 (37)e</td>
<td>22 (56)e</td>
<td>.148</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; HPV, human papillomavirus; RT, radiotherapy.

aValues are presented as number (%) unless otherwise indicated.

bDenotes discrepancy in number of patients due to information being unavailable.

cDenotes discrepancy in numbers of patients between AJCC 7 and AJCC 8. The authors only restaged patients with detailed information about node numbers.

dDenotes P value between HPV+ short-term vs long-term smokers.

eDenotes percentage of patients with pathology reports available.

*Values are presented as number (%) unless otherwise indicated.*
Kaplan-Meier survival curves for patients with ENE or LVI appeared to be divergent from patients without those adverse features, but this finding was not statistically significant (Figure 2).

**Adverse Pathologic Features Decreased Survival in HPV-Negative Patients and HPV+ Heavy Smokers Relative to Nonsmokers**

Compared to HPV+ nonsmokers with ENE, HPV+ heavy smokers had a 10-month decrease in mean survival over 5 years compared in the presence of ENE ($P = .03$) (Figure 3). Furthermore, HPV+ heavy smokers with pathologically proven ENE had similar survival outcomes compared to HPV– patients. HPV– patients with PNI had significantly worse survival than both HPV+ heavy and nonsmokers ($P = .01$). There was no significant difference in 5-year survival for patients with LVI in HPV+ nonsmokers or heavy smokers.

**Early Stage HPV+ Heavy Smokers Have Decreased Overall Survival Compared to Nonsmokers**

When staged according to the eighth edition of the AJCC staging manual, HPV+ heavy smokers with early stage disease had a significantly decreased 5-year survival compared to nonsmokers ($P = .01$). Mean survival for heavy smokers was decreased by 20.5 months (Figure 4). When restaging from the seventh to eighth edition, most patients had stage I disease (66%, $n = 74$). The majority of these patients (55%, $n = 41$) would have previously been considered stage IV (Table 1).

**Discussion**

Demonstrating the prognostic implications of HPV status and tobacco use is not novel, but with the introduction of the AJCC eighth edition, the clinical implications of tobacco use need to be heavily considered in treatment planning.

Previous work demonstrated that p16-positive patients with more than 10 pack-year smoking histories had decreased
survival outcomes than patients with less than 10 pack-year smoking histories and a progressive increase in hazard for every year beyond 10 years. A more rigorous definition of heavy smokers was chosen to highlight the progressively increasing hazard associated with heavy tobacco use. Furthermore, this study demonstrates that HPV+ heavy smokers with early stage disease under the new staging manual have a poorer prognosis. Our findings corroborate with prior studies and demonstrate that HPV+ heavy smokers have significantly poorer survival compared to nonsmokers. Although tobacco use has been implicated as a negative prognostic feature in OPSCC, a large, prospective study of all head and neck sites found that smoking had a marginally significant impact on survival on univariate analysis but was not significant on multivariate analysis. However, there is evidence that current tobacco use is associated with poorer prognosis regardless of HPV status.

In an effort to identify etiology for the poorer overall survival, we investigated the impact of traditional adverse pathologic features on survival in HPV+ patients stratified into short-term/nonsmokers vs heavy smokers. The presence of LVI and PNI was not correlated with worse survival outcomes in HPV+ heavy smokers (Figure 2). This finding is consistent with a large retrospective study, which found no increase in hazard for HPV+ patients. However, the presence of ENE was associated with a significantly decreased survival in HPV+ heavy smokers compared to HPV+ nonsmokers (Figure 3).

The current study demonstrates that the eighth edition of the AJCC staging manual results in the 55% of HPV+ disease being reclassified as earlier stage disease. However, in heavy smokers, this may be inappropriate since these data demonstrate that the patients who are heavy smokers and down-staged have a significant decrease in their overall survival relative to nonsmokers. While most HPV+ patients should be considered for de-escalated treatment, it is possible that patients with extensive smoking history may require

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**Figure 3.** (A) Human papillomavirus (HPV)–positive smokers with extranodal extension (ENE) had significantly decreased survival. HPV+ smokers with (B) LVI (lymphovascular invasion) and (C) PNI (perineural invasion) did not have a significant decrease in survival.

*Denotes difference between HPV+ groups. †Denotes difference between HPV– patients and HPV+ smokers.

**Figure 4.** Heavy smokers have significantly decreased survival compared to nonsmokers with early stage disease under the American Joint Committee on Cancer eighth edition staging manual. Median survival was significantly decreased: 61.2 months vs 81.7 months (P < .05). HPV, human papillomavirus.
a different treatment protocol. Although AJCC staging is not a treatment guideline, current National Comprehensive Cancer Network (NCCN) guidelines recommend treatment based on stage of disease and do not delineate between HPV+ and HPV− disease. The discordance between staging and treatment guidelines potentially could lead to the undertreatment and decreased survival of patients with early stage HPV+ OPSCC.

The epidemic of HPV+–related OPSCC is a reality that affects patients beyond the archetype: young, nonsmokers, and nondrinkers. While it is important to acknowledge that p16-positive disease is less common among heavy smokers, a large percentage of patients with HPV+ disease are heavy smokers. Furthermore, heavy smokers have a poorer prognosis compared to their nonsmoking counterparts. The eighth edition AJCC staging manual results in the downstaging of most of these patients. Our work demonstrates that these patients have significantly poorer outcomes and raises concerns that down-staging these patients could result in their undertreatment and ultimately decreased survival outcomes.

There are several limitations noteworthy of this study. Primarily, the lack of detailed tobacco history and HPV status in many patients limited a full analysis of patients seen at this cancer center. While we report survival outcomes for heavy smokers, we must recognize that detailed smoking histories are often difficult to obtain retrospectively, and we cannot exclude recall bias. Furthermore, a multivariate analysis could not be performed on this cohort due to the small sample size. This does not diminish from the fact that this is the first study to demonstrate that HPV+ heavy smokers with early stage disease under the new staging manual have poorer prognosis and may resultantly be undertreated.

Conclusions

The presence of ENE has a significant impact on survival for HPV+ heavy smokers relative to nonsmokers, which is similar to patients with HPV− disease in this single-institution study. Furthermore, heavy smokers with early stage disease (AJCC eighth edition) have decreased survival than their nonsmoking counterparts. Further work investigating the role of tobacco use and the new staging system should be encouraged. This series highlights the potential need for more aggressive therapy for HPV+ patients with extensive tobacco use in the presence of ENE.

Author Contributions

Anvesh R. Kompelli, design, data acquisition, drafting, final approval; Patrick Morgan, design, data acquisition, drafting, final approval; Hong Li, design, data acquisition, drafting, final approval; William Harris, data collection, revising, final draft approval; Terry A. Day, data collection, revising, final draft approval; David M. Neskey, design, data acquisition, drafting, final approval.

Disclosures

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trials, critical issues and perspectives. 

