Effect of Human Papillomavirus on Patterns of Distant Metastatic Failure in Oropharyngeal Squamous Cell Carcinoma Treated With Chemoradiotherapy

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**IMPORTANCE** Important differences exist in the pattern and timing of distant metastases between human papillomavirus-initiated (HPV+) and HPV− oropharyngeal squamous cell carcinoma (OPSCC). However, our understanding of the natural history of distant metastases in HPV+ OPSCC and its implications for surveillance is limited.

**OBJECTIVE** To investigate the rate, pattern, and timing of distant metastases in advanced-stage OPSCC treated definitively with concomitant chemoradiotherapy.

**DESIGN, SETTING, AND PARTICIPANTS** In a retrospective review, we identified 291 patients with pathologically diagnosed stages III to IVB OPSCC and known HPV status from a tumor registry at the Cleveland Clinic. Patients were treated from January 1, 1996, through December 31, 2013. Details of treatment failure and the natural history of the disease were retrieved from the electronic medical records.

**INTERVENTIONS** All patients were treated with definitive concomitant chemoradiotherapy.

**MAIN OUTCOMES AND MEASURES** The primary outcome was the rate and timing of distant metastases. Secondary outcomes included the pattern of distant failure and survival after distant metastases.

**RESULTS** Thirty-seven patients developed distant metastatic disease after definitive treatment, including 28 of 252 patients with HPV+ disease and 9 of 39 patients with HPV− disease. The 3-year projected distant control rate was higher in the HPV+ group (88% vs 74%; \(P = .01\)). The median time to develop distant metastases was also longer after the completion of treatment for HPV+ disease compared with HPV− disease (16.4 vs 7.2 months; \(P = .008\)). We detected a trend in patients with HPV+ disease for more distant metastatic sites involved than in those with HPV− disease (2.04 vs 1.33 sites; \(P = .09\)). Although the lung was the most common distant site involved in HPV+ and HPV− disease (HPV+ group, 23 of 28 patients [82%]; HPV− group, 7 of 9 patients [78%]), the HPV+ group had metastases to several subsets atypical for head and neck squamous cell carcinoma, including the brain, kidney, skin, skeletal muscle, and axillary lymph nodes in 2 patients each and in the intra-abdominal lymph nodes in 3 patients. The rate of 3-year overall survival was higher in the HPV+ group (89.9% vs 62.0%; \(P < .001\)), as was the median survival after the occurrence of distant metastases regardless of additional treatment (25.6 vs 11.1 months; \(P < .001\)).

**CONCLUSIONS AND RELEVANCE** This retrospective review suggests that distant metastases in patients with HPV+ OPSCC occurs significantly later after completion of chemoradiotherapy than in patients with HPV− disease. Human papillomavirus-initiated OPSCC also appears to involve a greater number of subsites and metastatic sites infrequently seen in head and neck squamous cell carcinoma. Distant metastatic disease in HPV+ OPSCC has unique characteristics and a natural history that may require alternative surveillance strategies.

Published online March 5, 2015. Corrected on March 27, 2015.

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Human papillomavirus-initiated (HPV+) oropharyngeal squamous cell carcinoma (OPSCC) has a unique etiology, histopathology, and clinical behavior compared with tobacco-related head and neck squamous cell carcinoma. Despite a high prevalence of advanced nodal disease at presentation, large randomized clinical trials have shown 3-year locoregional control rates of greater than 85% with multimodality treatment compared with 65% for OPSCC that is negative for HPV (HPV−).1 with an estimated 60% reduction in the risk for death from cancer.2 However, several studies have found similar rates of distant metastases in HPV+ and HPV− disease.3-10 Distant failure may now represent the most common cause of death in these patients.3,11,12 Our understanding of the natural history of distant metastases in HPV+ OPSCC remains limited and in need of further definition. The objective of our study was to investigate the rate, pattern, and timing of distant metastatic failure in advanced-stage OPSCC treated definitively with concomitant chemoradiotherapy (CRT), with an emphasis on the differences between HPV+ and HPV− disease.

Methods

Patient Population

Patients treated from January 1, 1996, through December 31, 2013, at the Cleveland Clinic were identified from a retrospectively maintained institutional review board–approved tumor registry. This study was approved by the Cleveland Clinic Institutional Review Board, and all data were deidentified. All patients with nonmetastatic, locoregionally advanced (American Joint Committee on Cancer stages III-IVB) OPSCC treated with definitive concurrent CRT and who had a known HPV status were included. Human papillomavirus status was determined by genotyping via chromogenic in situ hybridization for HPV DNA and/or by diffuse immunohistochemical nuclear and cytoplasmic staining (>75%) for the presence of the p16 protein, an established surrogate marker for an HPV+ tumor in the oropharynx.13,14 We retrospectively determined HPV status in patients treated before the adoption of routine OPSCC testing at our institution in 2007.

Treatment

All patients were treated with definitive concurrent CRT with salvage neck dissection if needed for residual bulky neck disease. Details of the chemotherapy administration and the radiotherapy dose and fractionation were recorded. Radiotherapy generally consisted of 70 Gy in 35 fractions with once-daily fractionation for 7 weeks. Patients receiving split-course radiotherapy with palliative intent, and those not treated definitively were excluded from this analysis. Before 2008, our institutional approach was to administer concurrent chemotherapy with 2 cycles of cisplatin and fluorouracil. More recently, high-dose bolus cisplatin or weekly cetuximab has been used increasingly.15

Follow-up

Details regarding patterns of distant metastatic failure and natural history were retrieved from the electronic medical record. At our institution, patients are routinely followed up by our multidisciplinary team every 3 months for the first 2 years after completing therapy, every 4 months for the third year, every 6 months during years 4 and 5, and annually thereafter, with repeated imaging studies obtained approximately 12 weeks after completion of treatment and then subsequently as clinically indicated. The length of follow-up was calculated from the start date of radiotherapy to the last date of follow-up or death. We identified patients who experienced distant failure and recorded the details regarding their outcome and any additional therapies. All sites of distant metastases, including those that were discovered after the initial distant failure, were noted. Patients with polymetastatic disease (≥2 discrete foci within an organ) on imaging were documented as having distant failure when biopsy specimens were unavailable. Those with a single focus of pulmonary parenchymal disease were differentiated from patients with a second primary tumor of the lung by results of HPV DNA testing and/or p16 staining (n = 3) or by a strong morphologic similarity to the primary carcinoma (n = 1).

Results

Patient Population

We identified a total of 291 patients with known HPV status who met the inclusion criteria for the study; 252 patients (86.6%) had HPV+ disease and 39 patients (13.4%) had HPV− disease. A comparison of the clinical characteristics between the HPV+ and HPV− patient groups is shown in Table 1. The HPV+ group was less likely to have a significant history of smoking or alcohol use (P < .001) and more likely to have smaller primary tumors (P < .001) and a greater nodal burden (P = .02). We found no significant difference in the definitive chemotherapeutic regimen or radiotherapy treatment between groups.
At a median follow-up of 3.1 years, 37 patients (12.7%) developed distant metastatic disease after definitive treatment, including 28 (11.1%) in the HPV+ group and 9 (23.1%) in the HPV− group (P = .04). The Kaplan-Meier 3-year projected distant control rate was higher in the HPV+ patients (88% vs 74%, P = .01) (Figure 1). Although all HPV− patients with distant metastases experienced treatment failure within 16 months, those with HPV+ disease continued to develop distant metastases as late as 6 years after the diagnosis. As such, the median time to distant failure was longer in patients with HPV+ disease than those with HPV− disease (16.4 vs 7.2 months; P = .008).

### Sites of Distant Metastases
Overall, a trend existed in the HPV+ group for a greater mean number of distant metastatic sites involved than in the HPV− patients (2.04 vs 1.33; P = .09). The most common site of distant metastases in the HPV+ and HPV− patients groups was the lung, which was involved in 23 of 28 patients (83%) with HPV+ disease and 7 of 9 patients (78%) with HPV− disease. Osseous
metastases were present in 12 of 28 patients (43%) with HPV+ disease and 2 of 9 patients (22%) with HPV− disease. Patients with HPV+ disease also had distant metastases to several atypical sites, including the intra-abdominal lymph nodes, axillary lymph nodes, skeletal muscle, brain, kidney, skin, pericardium, and peritoneum (Table 2). Furthermore, 9 of 28 patients (32%) with HPV+ disease had dissemination to more than 2 subsites compared with 1 of 9 patients (11%) with HPV− disease, although this difference was not statistically significant (P = .21).

Survival
The Kaplan-Meier 3-year projected overall survival for all patients was higher in the HPV+ group than the HPV− group (89.9% vs 62.0%; P < .001). Even after the occurrence of distant metastases, patients with HPV+ disease had a longer median overall survival (25.6 vs 11.1 months; P < .001) regardless of treatment (Figure 2).

Table 2. Metastatic Sites

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Patients With Metastatic Disease at Each Site</th>
<th>Metastatic Sites, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPV− Status</td>
<td>HPV+ Status</td>
</tr>
<tr>
<td>Overall No.</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>Lung</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>Bone</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Intra-abdominal lymph nodes</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Axillary lymph nodes</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Brain</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Kidney</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Muscle</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Skin</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pericardium</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: HPV, human papillomavirus; HPV−, not HPV initiated; HPV+, HPV initiated.

Discussion
In our series, patients with HPV− disease had a higher rate of distant metastases after treatment with CRT than those with HPV+ disease. Other reports have suggested that the incidence of distant disease is similar in the HPV+ and HPV− populations,1,3–7 and the difference seen in our series may reflect only our relatively small sample size of patients with HPV− disease and/or the inclusion of a few patients with unusually aggressive tumors.
The timing of distant failure also differed between patients with HPV+ and HPV− disease. Although all patients with HPV− disease and distant metastases experienced treatment failure within 2 years of completion of CRT, 10 of 28 patients with HPV+ disease (36%) developed distant metastases more than 2 years after definitive treatment. This finding is consistent with those of studies from the University of Toronto5,16 and a recent report from Washington University.7 Those results and ours appear to differ from those of Fakhry et al10 in a recent review of the patients enrolled in Radiation Therapy Oncology Group trials 0129 and 0255. However, Fakhry et al reported only the timing of any known recurrence, which was locoregional in most of the patients. No information is known about the difference in timing between locoregional progression and distant metastases.

Distant metastases in HPV+ disease appear to involve a greater number of subsites than in HPV− disease. In addition, dissemination to distant sites that are unusual for OPSCC was common in our HPV+ group, including the intra-abdominal lymph nodes, kidney, muscle, and skin. Late-onset brain metastases were also observed in our cohort, as have been described in several case reports.17-19 Among our patients with HPV+ disease, 32% displayed what Huang et al5,16 termed the disseminating phenotype, with dissemination to more than 2 organ systems compared with 1 of 9 patients with HPV− disease. Our study also corroborates their observation of unusual metastatic sites for HPV+ OPSCC.5,16 Although Sinha et al7 did not note a difference in the number of metastatic subsites, they found an increased rate of nonregional lymphatic metastases seen in patients with HPV+ disease and twice the rate of disseminating phenotypes. However, Fakhry et al10 observed similar rates of lung, bone, and liver metastases between patients with HPV+ and HPV− disease but did not report information regarding the number of subsites involved or the involvement of more unusual metastatic sites. These data may be difficult to retrieve from multi-institutional trials that were not focused on this outcome measure. In addition, these trials may not have recorded in full data regarding subsequent sites of distant metastases after initial distant failure; such information may be more readily available in a retrospective single-institution review.

Despite the improved survival and locoregional control seen in HPV+ OPSCC treated with CRT, unique biological characteristics in certain HPV+ tumors appear to predispose patients to an unusual pattern of distant metastases. Alternative surveillance strategies after completion of definitive CRT may be necessary in HPV+ OPSCC, including more intensive follow-up for a longer period than what is usually practiced in head and neck squamous cell carcinoma. Ultimately, further study of the genomics and proteomics of HPV+ distant metastatic tumor cells may help to determine which patients might be at higher risk for delayed recurrence.

We confirm previously reported observations7,10 that patients with HPV+ disease have a significantly improved overall survival after the detection of distant metastases compared with patients with HPV− disease. This finding was true regardless of any treatments attempted. These findings illustrate another biological difference between HPV+ and HPV− disease (especially if the metastases are amenable to additional treatment modalities) and underscore the importance of continued posttreatment surveillance for distant failure. Information regarding the differences in disease-free survival after treatment of distant metastases would also be important in future studies to determine whether the cure rate with salvage is greater in patients with HPV+ disease.

Our study has several limitations. The accuracy of p16 testing as a surrogate marker for HPV infection has been questioned by some investigators.20-22 Although other assays in isolation may have a higher specificity than p16 immunohistochemistry, p16 expression has been shown to have very good agreement with the presence of HPV DNA in oropharyngeal tumors specifically1 and is an accepted marker in nearly all clinical trials for treatment of OPSCC. Furthermore, when combined with an HPV-specific assay, the sensitivity and specificity of testing are very high.23 In addition, our study was limited by its retrospective nature, which precluded complete uniformity of the radiotherapy doses, chemotherapeutic regimens, and follow-up schedules. Also, the relatively low number of patients with HPV− OPSCC may affect the comparisons between groups because we believe that an unusually large number of patients within the HPV+ cohort had distant metastases compared with previous reports. However, the large number and close follow-up of our patients with HPV+ disease and treatment with CRT provides some validity to our observations about the pattern and rate of distant metastases.

Conclusions

This retrospective cohort review demonstrates a pattern of distant metastatic failure in advanced-stage HPV+ OPSCC that differs from HPV− OPSCC after definitive treatment with CRT. Patients with HPV+ disease have a longer interval to distant metastases than those with HPV− disease, with a significant number of patients experiencing distant failure more than 2 years after completion of treatment. Distant metastases in HPV+ disease also appear to involve a greater number of subsites as well as metastatic sites infrequently seen in malignant neoplasms of the aerodigestive tract. These findings emphasize the importance of more extended multidisciplinary surveillance after completion of CRT in patients with HPV+ disease.
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Drafting of the manuscript: Trosman, Ward, Scharpf, Lorenz, Adelstein.

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Study supervision: Koyfman, Al-Khudari, Greskovich, Lamarre, Khan, Lorenz, Adelstein, Burkey.

Conflict of Interest Disclosures: None reported.

Previous Presentation: Preliminary data from this study were presented as a poster and as a press release for the Multidisciplinary Head and Neck Symposium, February 20, 2014; Scottsdale, Arizona.

Correction: This article was corrected on March 27, 2015, to fix the Author Affiliations.

REFERENCES


