Laryngoscope Investigative Otolaryngology
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published by Wiley Periodicals, Inc. on behalf of The Triological Society

Emerging Insights Into Recurrent and Metastatic Human Papillomavirus-Related Oropharyngeal Squamous Cell Carcinoma

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Objective: To review recent literature on human papillomavirus-related (HPV-positive) oropharyngeal squamous cell carcinoma (OPC) and focus on implications of recurrent and metastatic disease.

Methods: Primary articles from 1990 to 2016 indexed in MEDLINE (1) pertaining to the epidemiology of HPV-positive OPC and (2) providing clinical insight into recurrent and metastatic OPC.

Results: The incidence of HPV-positive OPC is increasing globally. HPV-positive OPC is a subtype with distinct molecular and clinical features including enhanced treatment response and improved overall survival. While disease recurrence is less common in patients with HPV-positive OPC, up to 36% of patients experience treatment failure within eight years. Recurrent and metastatic OPC has historically signified poor prognosis, however recent data are challenging this dogma. Here, we discuss recurrent and metastatic OPC in the context of HPV tumor status.

Conclusion: HPV-positive OPC exhibits distinct genetic, cellular, epidemiological, and clinical features from HPV-negative OPC. HPV tumor status is emerging as a marker indicative of improved prognosis after disease progression in both locoregionally recurrent and distant metastatic OPC.

Key Words: Head and neck, squamous cell carcinoma, HNSCC, human papillomavirus, HPV, oropharyngeal, OPSCC, recurrent, metastatic, prognosis, survival.

Level of Evidence: N/A.

INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPC) constitutes a subset of head and neck cancers (HNC) arising from the squamous epithelium of the oropharynx. Anatomic subsites of the oropharynx include the base of tongue, pharyngeal tonsils, tonsillar pillars, glossotonsillar sulci, soft palate, uvula, and the pharyngeal wall.[1] In 2012, OPC accounted for nearly one quarter of incident cases of HNC and resulted in an estimated 97,000 deaths worldwide.[2]

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States[3] and oral HPV infection is strongly associated with OPC.[4] Indeed, HPV is a well-established cause of OPC.[5] Of the approximately 200 HPV types described,[6] HPV16 is detectable in 87-96% of HPV-positive OPCs in the US.[7–9] Other high-risk HPV types–including 18, 31, 33, 45, 52 and 58–account for the remainder of HPV-positive OPCs.[10–13]

Despite marked geographic heterogeneity, the global incidence and prevalence of HPV-positive OPC have risen significantly over the past three decades.[7–9,14] While the incidence of overall HNC and HPV-negative HNC have declined substantially in industrialized countries, the incidence of HPV-positive OPC has risen significantly and is projected to surpass HPV-related cervical cancer by the year 2020 in the United States.[15]

Accumulating epidemiological, clinical, histopathological, and molecular evidence indicate that HPV status defines a distinct subtype of OPC.[16–19] HPV-positive OPC is associated with increasing number of lifetime sex partners, younger age, male sex, and white race.[4,20] Alcohol or tobacco use, and poor oral hygiene do not appear to be independent risk factors for HPV-positive OPC.[16,21] Conversely, non-oropharyngeal HNC, malignancies arising in the oral cavity, hypopharynx, and larynx, are typically HPV-negative and associated with heavy smoking, alcohol use, and poor oral hygiene but not with sexual behavior.[10,16,22–27] Recent evidence does, however, support complex interactions between the effects of HPV, alcohol, and tobacco exposure in modifying the risk of OPC.[28,29]

HPV-positive tumor status at diagnosis is an independent prognostic indicator of favorable outcome, conferring increased sensitivity to treatment and improved survival.[30–34] Although disease recurrence is less common in patients with HPV-positive OPC, up to 36% of patients experience treatment failure within eight years.[35]

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Editor's Note: This Manuscript was accepted for publication 6 October 2016.

Financial Disclosures: The authors have no financial disclosures.

Conflicts of Interest: The authors have no conflicts of interest to declare.

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DOI: 10.1002/lio2.37

Recurrent and metastatic OPC has historically signified poor prognosis.[36–39] However, the growing proportion of OPCs that are HPV-positive and the improved survival of HPV-positive OPC are challenging this paradigm.[40,41] Here, insights into the epidemiology, clinical features, and molecular biology of recurrent and metastatic oropharyngeal squamous cell carcinoma are reviewed in the context of HPV tumor status.

MATERIALS AND METHODS

Review of primary literature from 1990 to 2016 indexed in MEDLINE. Search terms: 1) "epidemiology" AND "human papillomavirus" AND oropharyn* yielded 501 results; 2) oropharyn* AND (metasta* OR recur*) AND "human papillomavirus" yielded 395 results. Additional articles were selected through the review of references in articles selected by the above search method.

RESULTS AND DISCUSSION

Mechanisms of HPV-mediated oncogenesis and implications for the accurate detection of HPV-positive OPC

HPV is a DNA virus with a circular genome that exists in the nucleus separate from the host genome.[42] Integration of HPV DNA into the host genome is associated with stabilization of viral oncogenes[43] and is observed in the majority of HPV-positive OPCs.[44] The role of HPV in carcinogenesis relies primarily on the expression of two oncogenic proteins, E6 and E7. Oncoprotein E6 binds the gene product of *TP53* (p53), the most mutated tumor suppressor gene in cancer and "guardian of the genome",[45] targeting it for degradation.[46] Similarly, oncoprotein E7 binds and targets the Retinoblastoma tumor suppressor protein (Rb) for degradation.[47] Rb protein degradation triggers a regulatory cascade resulting in the compensatory upregulation of another tumor suppressor, $p16^{INK4A}$ (p16).[48]

The mechanisms of HPV-mediated oncogenesis guide the strategies contemporary diagnostic laboratories employ to detect HPV in tumor samples. A critical feature of a diagnostic test for HPV-related cancer is its ability to determine if a detected virus is an oncogenic driver of that tumor.[8,49] Highly sensitive assays such as polymerase chain reaction (PCR) based methods can detect well below one viral copy per cell. This level of sensitivity increases the possibility of detecting cross-contaminants in clinical samples, which is an unfortunately common occurrence in the conventional diagnostic laboratory. For this reason, if a sensitive assay such as PCR is employed, it is typically performed in combination with a more specific test such as in-situ hybridization (ISH) or immunohistochemistry (IHC).

Despite the necessity of a reliable method to detect HPV-driven OPC, variability in HPV tumor detection remains both in research and clinical practice. Available assays detect HPV DNA, HPV RNA, HPV oncoproteins, host cellular proteins dysregulated by viral infection (such as p16), and HPV-specific serum antibodies. These strategies were comprehensively detailed in two recent reviews.[50,51]. It is worth emphasizing that differences in methodology of HPV detection may contribute to the observed heterogeneity in reported epidemiological data[52] and that potential misclassification of HPV-related tumors limits understanding of the impact of HPV-positive OPC in clinical studies.[53]

Epidemiology of Oropharyngeal Carcinoma

Trends in incidence. Over the past three decades the relative proportion that each anatomic subsite contributed to the overall incidence of HNC has changed. Analysis of the Surveillance, Epidemiology, and End Results (SEER) data from 1973-1999 across 9 state registries found that while the incidence of some non-oropharyngeal HNC declined in the United States (U.S.), the contribution of OPC to total incidence of HNC increased from 17.6% in 1974 to 22.6% in 1999.[37]

Indeed, a SEER analysis segregated oral tumors into HPV-related (base of tongue, lingual tonsil, oropharynx, and Waldeyer's ring) and HPV-unrelated (tongue, gum, floor of mouth, palate, and unspecified parts of the mouth) based on prior associations between anatomic subsite and tumor HPV-status.[54] Consistent with the possibility that HPV was driving trends in HNC, from 1973 to 2004 an increase in the proportion of tumors arising from HPV-related subsites and a reduction in the proportion of tumors arising from HPV-unrelated subsites[20] was shown. This was confirmed with contemporary gold standard tumor HPV detection in 271 OPCs, demonstrating that from 1984 to 2004 the incidence of HPV-positive OPC increased by 225%, while the incidence of HPV-negative OPC declined by 50%.[15]

A more recent SEER analysis suggested that increases in the incidence of OPC are accelerating. The overall incidence of OPC has increased by 63% from 1975-2012. However, the most dramatic rise in OPC incidence occurred from 1998-2012. Specific subsets of the U.S. population have experienced the greatest increases in incidence. Incidence for men and white individuals were observed to increase at annual percent changes (APC) of 0.94%/year (yr) and 0.66%/yr, respectively, from 1975-1998. From 1998-2012, the APC rose more than three-fold to 3%/yr for men and 3.29%/yr for whites.[55]

Other studies have made similar observations, demonstrating rises in the incidence of OPC in the U.S. and abroad.[56–61] Analysis of the Cancer Incidence in Five Continents (CI5) database performed in 23 countries across 4 continents from 1983-2002 found that 8 of 9 "more developed" countries (Denmark, Estonia, France, the Netherlands, Poland, Slovakia, Switzerland, and the United Kingdom) experienced median annual increases in the incidence of OPC of 2.5%/yr in men and 3.4%/yr in women.[14]

The available data suggests that countries defined by the United Nations[55] as "less developed" may not have similarly rising trends in HPV-positive OPC.[23,24,62] This was explored in a recent analysis of HNC incidence rates in four independent databases: GLOBOCAN 2012, CI5, World Health Organization Mortality Database, and SEER. In this study, Gupta et al found that Western Europe, South-Central Asia, Central and Eastern Europe, and North America represented regions with the highest incidence rates of HPV-related HNC

subsites: the tonsils and oropharynx. Regions with the highest incidence rates of HPV-unrelated HNC subsites, the lip and oral cavity, included the Caribbean, Central and Eastern Europe, Southern Europe, and Western Asia.[63] The analysis did not, however, directly account for regional differences in the percentage of HNC resulting from HPV-infection (termed the HPV-attributable fraction: HPV-AF) which are known to vary significantly by region.[52] Approximately 40-70% of OPCs are HPV-positive in more developed countries,[9,15,62,64] while fewer than 26% of OPCs are HPV-positive in less developed regions.[23,24,62,65] Combining the analysis by Gupta et al with recent regional estimates of the HPV-AF of OPC[52] is likely to show more profound regional differences in incidence of HPV-positive OPC.

Collectively, the observations made over the past two decades support the conclusion that increases in HPV-positive OPC incidence are disproportionately affecting men and individuals in countries designated as "more developed". These findings suggest an underlying divergence in risk factor exposure among populations that are experiencing rises in OPC relative to those that are not.

Risk factors. Trends in the incidence of oropharyngeal and non-oropharyngeal HNC can be at least partially attributed to changing exposures to HNC risk factors. Historically, the primary risk factors for HNC have been smoking[22] and alcohol consumption.[27]

Since the mid-1970s smoking and alcohol consumption have declined by 42%[39] and 20%,[66] respectively, in the U.S. Although the global prevalence of smoking has also declined significantly between 1980 and 2012, significant variability existed with regard to sex and region. Smoking prevalence was significantly higher in men, with more men smoking in less developed countries.[67] Consistent with the notion that smoking played a role in HPV-unrelated HNC, partial overlap existed between countries (e.g. Eastern and Southern Europe and East and Central Asia) with higher incidence of HPV-unrelated HNC[63] and high smoking prevalence and consumption of cigarettes.[67] Declining rates of smoking were observed in parallel with declining rates of HPV-unrelated HNC in Western Europe[14] and Southeastern Asia, regions with rising rates of HPV-positive OPC.[63]

In populations with declining alcohol and tobacco consumption yet increasing incidence of OPC, HPV has emerged as a dominant risk factor.[16] In an international study, incidence trends for oral cavity cancer (OCC, an HPV-unrelated HNC) and OPC (an HPV-related HNC) were evaluated to determine the relative effects of HPV and smoking on the incidence trends of these tumor types.[52,68] Two patterns were suggestive of HPV as a primary cause of OPC: an increasing incidence of OPC accompanied by an unchanging or declining incidence of OCC and statistically stronger increases in the incidence of OPC relative to OCC. Interestingly, all countries exhibiting either of these patterns also displayed significant declines in squamous cell carcinoma of the lung, a strongly tobacco-related tumor, further supporting a divergent etiology between oropharyngeal and non-oropharyngeal HNC.[14] Consistent with these findings, other studies have reported decreasing incidence of tumors in patients with a history of heavy smoking (>20 pack-years) and an increasing incidence of OPC arising in never smokers and those smoking fewer than 20 pack-years.[69]

In the United States, the prevalence of oral HPV infection among men and women age 14-69 in 2009-2010 was approximately 7%.[70] One percent of Americans in this age group had a detectable oral HPV16 infection, the most prevalent high-risk HPV infection detected in oral samples, and the predominant type responsible for HPV-positive OPCs in the US.[70] As would be expected in sexually transmitted infection, the prevalence of oral HPV infection increases with increasing exposure, whether measured by number of sexual partners, oral sex partners, or younger age of sexual debut. For example, prevalence of oral HPV is 21% among individuals who reported 21 or more sexual partners.[70] Interestingly, oral infection with high-risk HPV types showed strong bimodal age distribution with peak prevalence at ages 25-30 and 55-64.[70] In addition, male sex and current smoking intensity are independently associated with an increasing prevalence of oral HPV infection.[70–72]

Prognosis of human papillomavirus-related oropharyngeal carcinoma. Initial evidence that HPV-positivity in HNC was associated with improved prognosis came from an early study which foreshadowed that HPV-positive OPC was a distinct disease entity. In this retrospective study, Gillison and colleagues found that patients with HPV-positive HNC had a 59% reduction in risk of death from cancer after adjustment for age, alcohol consumption, and lymph node status.[5] Consistent with this finding, a meta-analysis investigating the role of HPV status on prognosis of HNC found HPV-positive OPC showed a 28% reduced risk of death relative to HPV-negative OPC. No HPV-related survival benefit was observed in non-oropharyngeal HNC.[73]

The first prospective trial demonstrating the impact of HPV-status on prognosis in HNC was nested in an Eastern Cooperative Oncology Group (ECOG) chemoradiation trial which investigated the role of tumor HPV-status on therapeutic response and survival in patients with stage III/IV disease.[31] Compared to HPV-negative tumors, HPV-positive OPCs were found to have improved response rates to induction chemotherapy (82% vs. 55%) and chemoradiation (84% vs. 57%). At 2 years, patients with HPV-positive tumors showed significantly improved progression-free (86% vs. 53%) and overall survival (95% vs. 62%).

These findings have been corroborated by numerous studies in a variety of settings.[5,15,30,34,35,74–79] A meta-analysis of 42 studies investigating the impact of HPV on HNC survival reported improvements of 53% and 72% in overall and disease-specific survival, respectively, in HPV-positive OPC compared to HPV-negative HNC.[76] The preponderance of data thus indicates that HPV tumor status in OPC is a favorable prognostic indicator associated with longer overall and disease-specific survival.

Similarly, a recent population-based study of 529 oropharyngeal tumors from 1994-2005 across 6 cancer

registries in the United States found that patients with HPV16-positive OPC showed improved 5-year overall survival (OS) relative to HPV-negative tumors (65% vs. 28%). The authors found that OPC unstratified for HPV-status exhibited subsite specific differences in prognosis. OPC arising from the palatine tonsils was associated with the most favorable 5-year OS followed by the base of tongue, then by other sites of the oropharynx (62% vs. 50% vs. 31%, respectively). Interestingly, this study suggested the benefits in survival observed in HPV16 tumors may be attenuated by non-HPV16 oncogenic types (5-yr OS – HPV16-positive: 65%, non-HPV16-positive: 46%, HPV: 28%).[80]

Additionally, recent The Cancer Genome Atlas (TCGA) data support the possibility that the improved survival observed in HPV-positive OPC might be confined to HPV16-driven tumors. Bratman et al interrogated TCGA transcriptome data for viral gene expression in 515 HNCs. Seventy-three (14%) of these tumors expressed viral transcripts, of which 61 were HPV16-positive and 12 were positive for other oncogenic subtypes: HPV 33, 35, and 56. Overall survival of patients with HPV16-positive HNC was significantly better than non-HPV16 oncogenic type tumors (3-yr: 88% vs. 49%).[81] These studies suggest the possibility that the underlying tumor biology of HPV16 may differ from that of non-HPV16 types. Arguing against their findings, a single institution analysis of survival associated with HPV16-positive OPC versus non-HPV16 oncogenic HPV-positive OPC found no difference in survival.[82] Given that non-HPV16 types comprise a small proportion (<8%) of HPV-positive OPC,[12] the surprising observation that HPV16-positive OPC may display a distinct prognosis from other high-risk HPV-positive OPC warrants further investigation.

Trends in prevalence. Epidemiologic phenomena associated with HPV-positive OPC—including rising incidence rates, significantly prolonged survival, and significant increases in tumors attributable to HPV—are driving an increase in the prevalence of individuals with HPV-positive OPC (Figure 1).

The survival advantage associated with HPV-positive OPC has resulted in significant improvements in OPC survival rates.[55,69] From 1975 to 2007, the average annual percent change in cause-specific survival for OPC rose by 1%/yr in the United States. Additionally, during 1985-2012, the average rate of increase in the prevalence of 5- to 10-year survivors reached 18 individuals per 100,000 per year. As a result, the total prevalence of OPC survivors has increased by 115 individuals per 100,000 per year.[55] In comparison, the prevalence of survivors of oral cavity cancer—a primarily HPV-negative HNC[68] – decreased by 16 individuals per 100,000 per year during the same period.[55]

Increases in the proportion of OPC attributable to HPV also help explain the rising prevalence of HPV-positive OPC. A systematic review of 5,046 HNC from 60 studies reported through the year 2004 calculated the worldwide HPV-attributable fraction (HPV-AF) of OPC and non-OPC to be 35.6% and 24%, respectively.[7] Tumor site misclassification in advanced tumors, inclusion of a large portion of small case series, heterogeneity in specimen quality in individual studies, and HPV detection methods limit this analysis and may have resulted in underestimation of HPV-AF of OPC and overestimation of HPV-AF of non-OPC.[7] A more recent meta-analysis found that, while the reported HPV-AF was 40.5% before 2000, it rose to 64.3% between 2000-2004, and further increased to 72.2% between 2005-2009.[9] Meanwhile, the prevalence of HPV in non-oropharyngeal HNC declined from 22.2% to 17.2% to 6.1%,[9] respectively, partially addressing the possibility that these findings may be a result of improvements in HPV detection. Consistent with this conclusion, a series of 520 consecutive OPC patients presenting to 10 Australian hospitals from 1985-2010 also showed an increase in the HPV-positive rate of OPC from 20.2% in 1987-1995 to 63.5% in 2006-2010. Uniform testing for HPV-status in this study supports the notion that observed increases in HPV-AF are not a result of improvements in viral detection.[64]

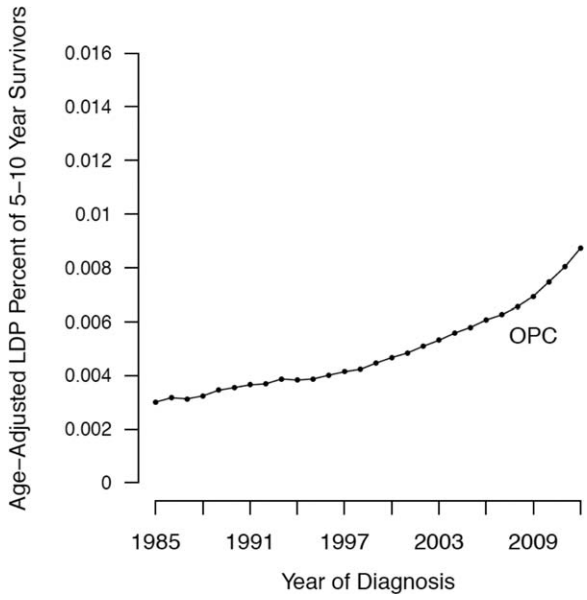


Fig. 1. Rising prevalence of long-term oropharyngeal squamous cell carcinoma survivors. Age-adjusted limited-duration prevalence (LDP) in 5-year to 10-year survivors of oropharyngeal squamous cell carcinoma (OPC). Adapted figure from Patel et al modified with the removal of curves representing overall oral squamous cell carcinoma and oral cavity cancer[55].

The collective effects of epidemiologic trends and improved survival rates has led to an accelerating prevalence of HPV-positive OPC survivors in the United States[55] and Europe.[83] This increase in OPC survivors represents a growing population of patients susceptible to disease recurrence and highlights the importance of better understanding the influence of HPV-status in recurrent and metastatic OPC.

The Impact of Human Papillomavirus on Recurrent and Metastatic Oropharyngeal Carcinoma

HPV-positive tumor status is well established as a significant determinant of favorable outcome.[31,34,74,76,84]

Yet 13-25% of HPV-positive OPC recur within 2 years[31,34,74,79,84,85] and up to 36% within 8 years.[35] Although less evidence is available to evaluate the role of HPV in the survival of recurrent and metastatic OPC, emerging data suggest that tumor HPV-status also influences prognosis after disease recurrence.

A secondary analysis of Radiation Therapy Oncology Group (RTOG) trials 0129 and 0522 provided evidence that p16-status, a reliable surrogate for tumor HPV-status in OPC,[86,87] showed prognostic relevance after disease progression.[40] Patients with OPC who experienced local, regional, or distant progression were eligible for analysis (n=181, p16-positive=105, p16-negative=76).[88] Consistent with demographic differences observed between HPV-positive and HPV-negative OPC patients at primary diagnosis, a greater proportion of p16-positive patients were younger, white, and had lower tobacco exposure at the time of disease progression. Median time to progression was similar for p16-positive and p16-negative OPC (8.2 vs. 7.3 months), with the majority experiencing disease progression in the first year after completion of therapy. Fifty-five percent of study patients displayed isolated locoregional progression. Despite similar rates of local, regional, and distant progression, patients with p16-positive OPC survived significantly longer than their p16-negative counterparts (2.6 vs. 0.8 years). After adjustment for other factors independently associated with overall survival, p16-positive status was associated with a 52% reduction in risk of death.[40]

Another analysis of prospective clinical trials evaluating the influence of HPV-status on HNC (rather than OPC) provided further support for the influence of HPV-status in recurrent and metastatic (R/M) OPC.[30] Analysis of ECOG trials 1395 and 3301 found improved PFS (5.9 vs. 3.2 months) and OS (12.9 vs. 6.7 months) in R/M HPV-positive relative to HPV-negative HNC.[30]

Two reports which evaluated the effect of HPV-status in R/M HNC suggested little to no effect of HPV-status on survival.[32,89] However the absence of a difference, may be due to study design.[53] Reanalysis of the EXTREME trial was limited by a low proportion (5%) of HPV-positive tumors and the categorization of OPC with non-OPC patients.[32,90] The SPECTRUM trial relied on a p16-positivity threshold (10% of cells) to define HPV-status, which is substantially lower than the commonly used standards (≥70% of cells).[89,91,92] These studies underline the importance of applying established principles for HNC subsite stratification and criteria for HPV-positivity in studies investigating the role of HPV-status in R/M HNC survival.[37,91–93]

Distant metastatic disease. The influence of HPV-status on metastatic disease has been a point of recent controversy. A series of retrospective analyses suggested that HPV-positive OPC displays an atypical pattern of distant metastatic recurrence.[94–97]

A single institution retrospective series in which patients were heterogeneously treated generally without systemic therapy, suggested that HPV tumor status influenced the time course, distribution, and propensity of distant recurrence.[85] This analysis evaluated any

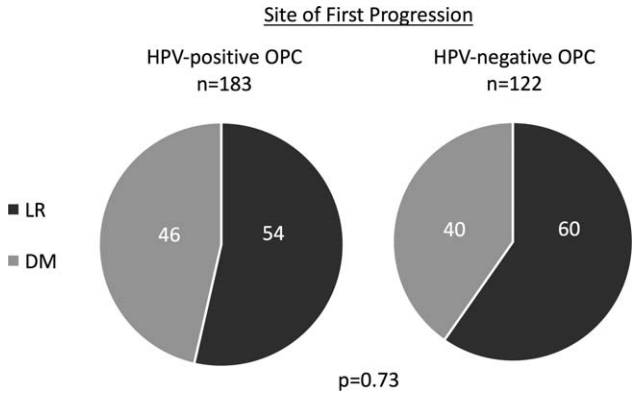


Fig. 2. Site of first progression in HPV-positive and HPV-negative oropharyngeal squamous cell carcinoma. Published studies[35,98,99] describing the first event of recurrence were evaluated to determine the proportion of first recurrence events in OPC representing locoregional recurrence or distant metastatic disease. Patients who experienced local or regional recurrence without distant metastases were categorized as locoregional recurrence (LR). Patients who experienced distant metastasis as the first event of recurrence, with or without concurrent local or regional recurrence, were categorized as distant metastasis (DM). Data was pooled across studies and proportion with LR and DM as first event were calculated and compared by HPV tumor status using chi-square test (GraphPad Prism 7, La Jolla, CA). Pie charts represent the proportional contribution of locoregional recurrence (LR) and distant metastasis (DM) as the site of first progression in HPV-positive and HPV-negative oropharyngeal squamous cell carcinoma (OPC). Based on pooled data from Nguyen-Tan et al, Guo et al, and Sinha et al[35,98,99]. Patients with synchronous DM and LR were included in the DM subgroup.

event of disease progression rather than restricting analysis to the initial event of recurrence. Given prolonged PFS associated with HPV-positive OPC, it is not surprising that Huang et al concluded that HPV-negative OPC exhibited early distant metastatic (DM) disease. All HPV-negative OPC showed DM within 2.1 years of therapy, while one third of HPV-positive OPC DM occurred beyond two years. HPV-negative OPC was reported to most commonly metastasize to the lung (88% of patients with DM), liver (16%), and bone (12%). Similarly, HPV-positive OPC also most often metastasized to the lung (78%), with 'atypical' metastases found at appreciable frequencies in the skin (22%), brain (14%), and intra-abdominal lymph nodes (14%). Finally, Huang et al concluded that HPV-positive OPC more frequently recurred at distant sites, citing that 72% of patients with distant metastasis did not have locoregional recurrence.[85] Studies investigating the first event of progression, however, have found no significant difference in HPV-status on the propensity to recur at locoregional versus distant sites (Figure 2).[35,97–99]

The retrospective observations by Huang et al[85,97] and others[95,96,98,100] seem to imply that the features of HPV-positive OPC which render it histopathologically, epidemiologically, and clinically distinct from HPV-negative OPC extend to its metastatic behavior. Suggestive of a potential role for HPV-related expression profiles in driving a unique metastatic phenotype, distant metastases of HPV-positive OPC do retain HPV and p16 positivity.[96,97,101] Nonetheless, tumors arising from the

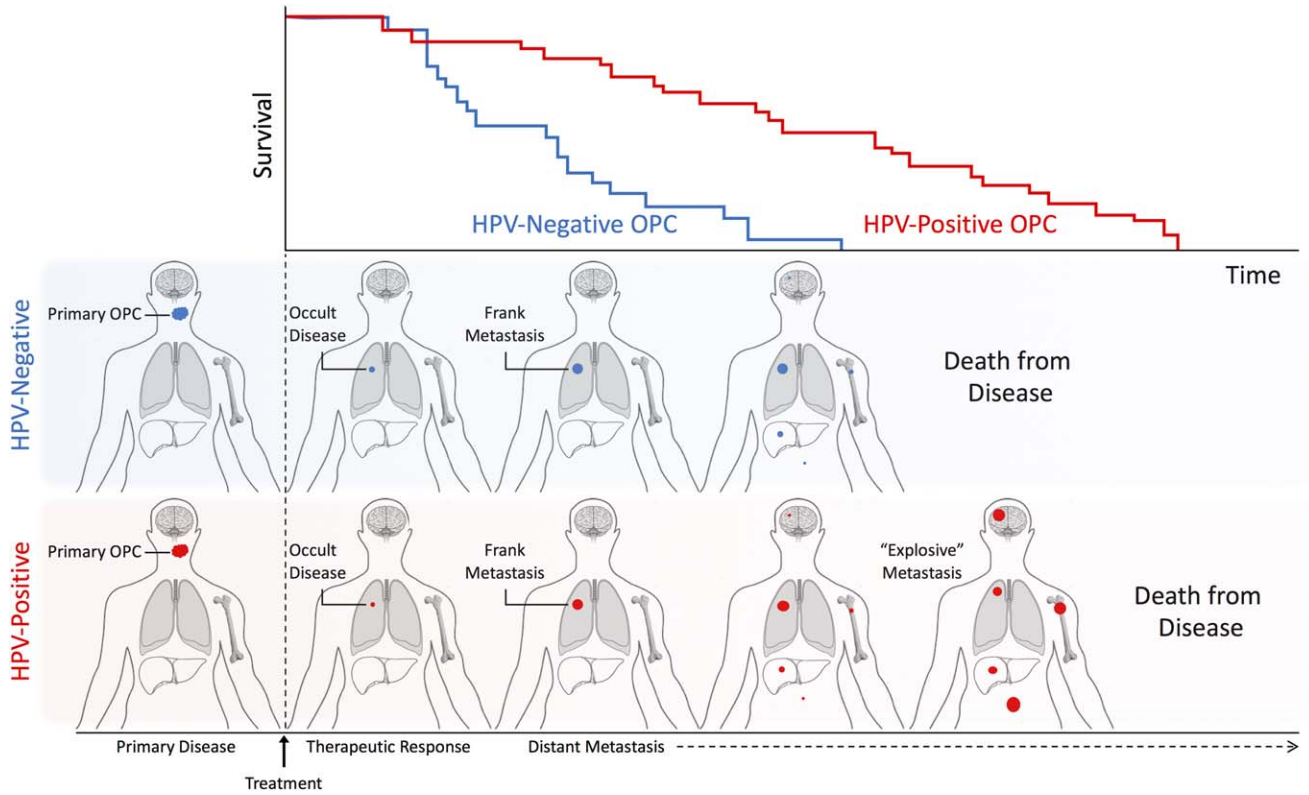


Fig. 3. Schematic representation of time- and survival- dependent differences observed in distant metastatic recurrence of HPV-positive and HPV-negative oropharyngeal squamous cell carcinoma. Top panel depicts representative survival curves for HPV-positive and HPV-negative squamous cell carcinoma (OPC). The two rows below correspond in time course to the survival curve and represent the typical disease course of HPV-positive and HPV-negative OPC. Patients with HPV-positive and HPV-negative OPC display approximately cotemporaneous distant recurrence[40] at common sites (e.g. lung, bone, liver) with the potential presence of additional occult or subclinical distant disease at rare sites (e.g. brain, abdominal lymph nodes, skin). While patients with HPV-positive OPC show survival durations adequate to display clinically detectable metastasis at rare distant sites, those with HPV-negative OPC do not.

oral cavity and hypopharynx—predominantly HPV-negative subsites—have also been reported to metastasize to uncommon distant sites including the brain,[102] skin,[103] muscle,[104] and abdominal organs.[105] In addition, prospective and retrospective studies alike have consistently demonstrated that the great majority of distant metastases occur within 3 years of primary presentation in both HPV-positive and HPV-negative OPC.[34,35,40,97,98]

Secondary analysis of RTOG0129 and RTOG0522[40] found that 41% of HPV-positive and 38% of HPV-negative OPC displayed isolated distant metastatic disease at first progression. Median time to distant metastasis did not differ based on p16-status (11.9 vs. 12.4 months).[106] Further contrasting with the study by Huang et al,[85] p16-positive and p16-negative OPC were found to have similar anatomic distribution of distant metastasis (lung: 73% vs. 70%; bone: 14.6% vs. 15.2%; liver: 8.3% vs. 15.2%; other 16.7% vs. 12.1%). Despite these similarities, patients with HPV-positive disease showed significantly improved OS relative to those with HPV-negative disease (2.6 vs. 0.8 years, respectively).[40]

The discrepancies in findings reported by Huang[85] and the RTOG reanalysis[40] may be a result of differences in study design. Huang et al derive observations from retrospective review of patients who received curative intent radiotherapy or chemoradiation from 2000-2010.[85] Although also retrospective in nature, the RTOG reanalysis comprised of two randomized, controlled, prospectively collected, and uniformly treated cohorts with a median of 4 years follow-up after disease progression.[40] Whereas the RTOG reanalysis reported survival after the first event of tumor progression, Huang reported survival after distant metastasis.[40,85,106–108] Since PFS and OS are significantly diminished in HPV-negative OPC, it is likely that some HPV-negative OPC patients with occult distant metastases succumb to other sequelae of disease. As such, the prolonged survival associated with HPV-positive OPC may allow patients to survive long enough to develop metastases at sites infrequently reported for HPV-negative OPC (Figure 3). Although median follow-up of 4 years in the combined secondary analysis of RTOG 0129 and 0522[40] may have been insufficient to monitor for late metastatic events, reanalysis of RTOG 0129 at 8 years also failed to observe a distinct metastatic pattern or significant differences in distant metastatic disease for HPV-positive OPC.[35]

Reports suggesting an atypical natural history of metastatic HPV-positive OPC[85,100] contrast with findings of the RTOG reanalysis[40] on two inter-related points:

that HPV-positive OPC has a distinct anatomic distribution of distant metastasis and a delayed time to distant metastasis. Patients who survive beyond three years, including the minority of HPV-negative HNC, continue to be susceptible to distant metastatic disease. Observations of the basic biology of metastatic colonization suggest that although specific tumor types display distinct patterns of organotropism,[109] single tumor cells disperse widely and may remain dormant for many years.[110] In this setting, long-term survival may serve as the rate-limiting step to metastasis of atypical or rare organs by providing time for disseminated tumor cells to convert from dormant to actively proliferating[111,112] (Figure 3). As such, retrospective analyses of patients with long follow up periods may inadvertently select for long-surviving patients who have acquired apparently unique disease features. Consequently, a rise in the prevalence of HPV-positive OPC-associated distant metastases is likely to follow the increase in long-term survival associated with HPV-positive OPC, and this may be mistaken as a difference in the metastatic behavior of HPV-positive OPC.

A recent reanalysis of a retrospective OPC cohort demonstrated how such survival bias might occur. Guo et al stratified patients into "early" and "late" survivor groups based on survival less than or greater than 24 months, respectively.[33] While late survivors were significantly more likely to be HPV-positive, 20% of late survivors were HPV-negative. Additionally, late recurrences were significantly more common among late survivors for both HPV-positive and HPV-negative patients. Indeed, recurrence occurred significantly later in late survivors regardless of HPV-status. With this survival-based stratification strategy Guo et al explained the notion that late recurrence is dependent on late survivorship.[33]

CONCLUSION

Epidemiologic trends indicate a global upsurge in the incidence of HPV-positive oropharyngeal cancer, with the strongest effects observed in white men residing in North America and Western Europe. The rise of HPV-positive OPC combined with its improved outcomes have resulted in an increased prevalence of OPC survivors. Long-term follow up of patients with HPV-positive OPC indicates that greater than one third of survivors will experience locoregional or distant recurrence in the first decade after treatment. Current data suggests HPV-positive tumor status also confers a survival advantage in recurrent and distant metastatic disease. However, further long-term prospective studies are required to understand the mechanism of HPV in OPC survival after progression. The success of such studies relies on the standardization of HPV detection strategies and consistent reporting of clinical data, especially patterns of distant metastatic disease and measurements of survival metrics after the first event of tumor progression. Longer-term observation of HPV-positive OPC survivor cohorts will clarify the role of HPV-status in late recurrence and distant metastatic disease and better inform current efforts focused on tailoring therapeutic strategies to HPV-status.

Acknowledgments

Oral Cancer Foundation

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