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Human Papillomavirus-Positive Oropharyngeal Squamous Cell Carcinoma Demographics, Prognosis, and Staging

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Abstract

Human papillomavirus (HPV) is a sexually-transmitted infection that is responsible for increasing rates of oropharyngeal squamous cell carcinoma (OPSCC) in the United States and around the world. Compared to head and heck squamous cell carcinomas (HNSCC) caused by traditional risk factors such as smoking and alcohol, patients with HPV-positive (HPV+) OPSCC are younger, more likely to be male, and enjoy a significantly improved prognosis. As HPV status represents the most important prognostic variable for OPSCC patients, current staging systems which do not take it into account are inadequate for staging HPV+ OPSCC. Herein, we will review the shifting demographics of HPV infection as they relate to OPSCC incidence, outline the data suggesting improved outcomes in HPV+ OPSCC, and highlight current efforts to develop a new staging system for HPV+ OPSCC patients.

Introduction

Human papillomavirus (HPV) has been established as an increasingly important cause of oropharyngeal squamous cell carcinoma (OPSCC) worldwide by the WHO [1]. This understanding, as well as differences in prognosis, treatment response, and failure patterns, has led to a paradigm shift in our management of patients diagnosed with HPV-positive (HPV+) OPSCC. The large increase in HPV+ HNSCC and the associated improved response to treatment and overall survival have brought into question the validity of applying current staging systems to these patients as well as historical results from clinical trials that enrolled individuals with heterogeneous tumor sites in an era when the importance of HPV was not yet understood. Thus, a number of new efforts are under way to stratify patients based on HPV status, using multiple strategies to ameliorate treatment-related toxicities for HPV+ disease.

Demographics and Increasing Incidence of HPV Infection

An increase in OPSCC incidence rates has been observed worldwide over the past few decades, including in the United States [2-6]. In order to examine the potential role for HPV as compared to smoking on incidence trends, Chaturvedi et al analyzed data regarding cancer incidence in the Cancer Incidence in Five Continents database, a worldwide cancer registry. Using data collected from 1983 to 2002, they compared incidence trends across multiple countries for traditionally smoking-associated cancers, including lung and oral cavity squamous cell carcinoma (OCSCC), versus OPSCC. In general, OPSCC incidence rates were noted to increase significantly, primarily in developed countries, despite concomitant decreases in OCSCC and lung cancer incidence in many of the same countries. Men were disproportionately affected as compared to women, and young men (<60 yo) experienced higher rates of OPSCC than older men. Furthermore, incidence rates of all three cancer types were noted to increase in women. Taken together, these suggest a role for HPV infection in the increasing incidence of OPSCC, especially among men, with smoking being the primary driver for increased rates of these cancers among women.

A preponderance of data exists to demonstrate the role of HPV in increasing OPSCC incidence in the United States and abroad [4,7]. Several series have used molecular testing to show increased rates of HPV+ OPSCC while rates of HPV-negative (HPV–) OPSCC continue to decline. Further underscoring this point, a recent meta-analysis of 2,099 OPSCC cases from the US literature showed an increase in the prevalence of HPV+ OPSCC from 20.9% before 1990 to 51.4% between 1990-1999 with further increase to 65.4% for 2000-present [8]. Additional series suggest 72% or more of OPSCC cases occurring in the United States after the year 2000 are attributable to HPV infection [7,9]. Impressively, population level incidence of HPV+ OPSCC was shown to increase by 225% from 1988 to 2004 while incidence of HPV– cancers declined by 50% (Table 1).

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Table 1: Population level incidence of HPV-positive OPSCC was shown to increase by 225% from 1988 to 2004.
From: Chem Res Toxicol. 2014 Apr 21; 27(4): 462–469. Published online 2014 Mar 18. doi: 10.1021/tx500034c.

Prevalence of HPV in OPSCC in the United States			
time period	**number of studies**	**total number of OPSCCs analyzed**	**mean HPV(+) OPSCC prevalence (95% CI)**
pre-1990	5	82	20.9 (11.8, 37.0)
1990–1999	15	684	51.4 (45.4, 58.2)
2000–present	18	1333	65.4 (60.5, 70.7)

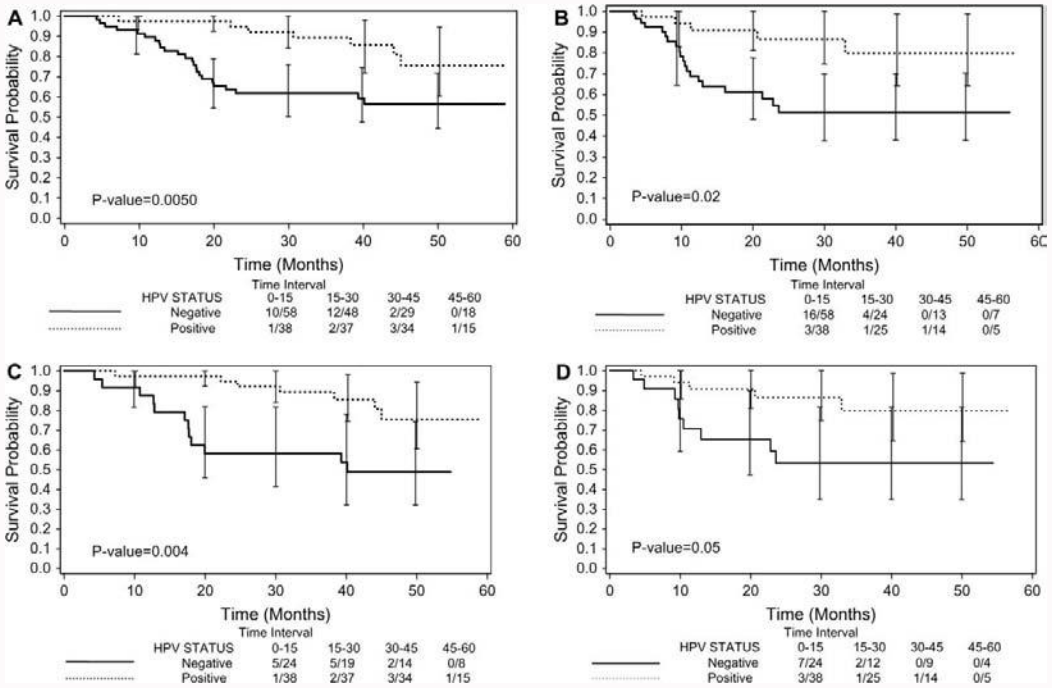

Figure 1: Kaplan–Meier curves for overall and progression-free survival stratified by tumor human papillomavirus (HPV) status.
Kaplan–Meier curves for overall and progression-free survival stratified by tumor human papillomavirus (HPV) status. A) Overall survival (OS) for the entire study population. B) Progression-free survival (PFS) for the entire study population. C) OS for patients with oropharynx cancer only. D) PFS for patients with oropharynx cancer only. From: Carole Fakhry et al. JNCI J Natl Cancer Inst. 2008; 100: 261-269. (Oxford university Press).

The primary risk factor for development of HPV+ OPSCC is oral HPV infection, most frequently by HPV type 16 [10,11]. As the vast majority of oral HPV infections are sexually acquired, sexual behavior has now been established as a risk factor for HNSCC, specifically OPSCC [10,12]. Lifetime number of oral sexual partners is the behavior with the strongest association with OPSCC incidence [13]. The reported rates of engaging in oral sex vary significantly on a geographic basis as well as across birth cohorts, with more recent cohorts reporting significantly higher rates of oral sex [13]. These may help explain the heterogeneous incidence of HPV+ OPSCC worldwide as well as the increasing incidence over time.

In the United States, men have a significantly higher prevalence of overall oral HPV infection (10.1% vs. 3.6%) and oral HPV type 16 infection (1.6% vs. 0.3%) than women, offering an explanation for the gender inequality of OPSCC incidence [12]. The difference in incidence is likely multifactorial as men report a higher number of lifetime sexual partners than women [14], have a higher per-partner increase in risk of high risk oral HPV infection [15], and are less likely to seroconvert after genital HPV infection to provide protection against subsequent oral HPV infection [15]. Prevalence of oral oncogenic HPV infection in the United States has a bimodal distribution with peaks noted between the ages of 25 to 30 years and 55 to 60 years [16], while the median age at diagnosis of HPV+ OPSCC is 58 years [17]. This suggests a latency period of 5-30 years as uncertainty exists regarding which of the two peaks plays the greatest role in HPV-related oncogenesis. Interestingly, long-term partners of HPV+ OPSCC patients do not appear to have elevated oral oncogenic HPV infection rates compared to the general population (1.2% vs. 1.3%) in spite of high prevalence of oncogenic oral HPV in the patients themselves, offering reassurance to partners regarding their risk of developing OPSCC.

HPV and OPSCC: Prognostic Implications

The most clinically relevant feature of HPV+ OPSCC is the significantly improved prognosis versus HPV– OPSCC. Though observations of multiple retrospective series [19-22] initially suggested this difference in outcomes, it was first confirmed in a prospective manner by Fakhry et al through analysis of the results of ECOG 2399 [23,24]. This Phase II trial included 105 resectable stage III/IVA larynx and OPSCC patients treated with two cycles of induction carboplatin and paclitaxel followed by concurrent paclitaxel and radiation to 70 Gy if no evidence of tumor progression was observed. HPV status was tested prospectively in 96 patients using polymerase chain reaction (PCR) and in situ hybridization (ISH) with 40% of patients harboring oncogenic HPV DNA. Higher response rates to induction chemotherapy (IC) (84% vs. 55%) and chemoradiotherapy (CRT) (84% vs. 57%) were noted among patients

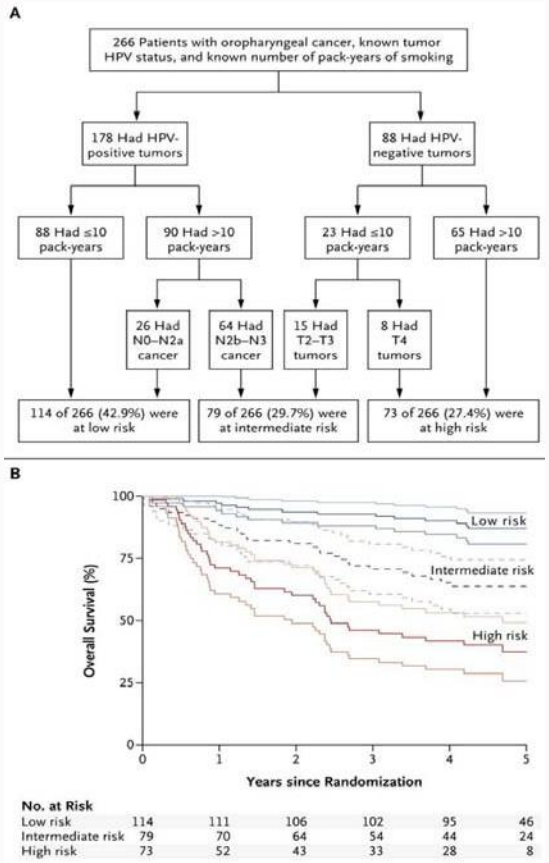

Figure 2: Classification of the study patients into risk-of-death categories and kaplan–meier estimates of overall survival according to those categories.
From: Ang KK et al. N Engl J Med. 2010; 363: 24-35.

with HPV+ versus HPV– tumors, respectively, as well as improved 2-year overall survival (OS) (95% vs. 62%) (Figure 1).

Bonner et al performed a phase III randomized study of 424 patients with locally-advanced HNSCC comparing radiotherapy alone with radiotherapy plus cetuximab with updated 5-year results confirming improved locoregional control (LRC), progression-free survival (PFS), and OS in the combined modality group [25,26]. A retrospective analysis of 182 patients from the trial with OPSCC and evaluable HPV status via IHC confirmed these improved outcomes in both the HPV+ and HPV– OPSCC patient subsets suggesting no predictive ability of HPV-status for response to cetuximab [27]. Additionally, improvements in LRC, PFS, and OS were noted in the HPV+ versus HPV– OPSCC patient populations, again confirming the prognostic role of HPV.

The Radiation Therapy Oncology Group (RTOG) 0129 trial included a total of 743 patients with stage III/ IV HNSCC randomized to concurrent cisplatin plus accelerated fractionation radiation with a concomitant boost versus standard fractionation radiation [28]. With 8 years of follow-up, no OS difference was seen between the two radiation fractionation regimens. However, the study did confirm a survival difference between HPV+ and HPV– OPSCC regardless of treatment modality at 8 years (71% vs. 30%, respectively). A retrospective analysis performed by Ang et al identified the dominant prognostic factors predictive of overall survival in the 323 OPSCC patients on trial tested for HPV which included HPV status, pack-years of tobacco smoking, tumor stage, and nodal stage [29]. Importantly, smoking history was shown to abrogate the beneficial effects of HPV status as the risks of cancer death or relapse were increased by 1% for each additional year of tobacco smoking in both HPV– and HPV+ cohorts. A cut-off point of 10 pack-years was found to be the best predictor of survival related to smoking status. Using a recursive partitioning analysis (RPA), patients were classified as having a low, intermediate, or high risk of death based on these four factors with 3-year survival rates of 93%, 71%, and 46%, respectively (Figure 2).

A retrospective analysis of 505 patients with OPSCC and evaluable HPV status treated with definitive radiation (RT) or CRT between 2001 to 2009 was performed by O'Sullivan et al in order to identify subgroups of patients suitable for treatment deintensification based on low risk of distant metastasis [30]. HPV+ patients were noted to have improved local (94% vs. 80%) and regional (95% vs. 82%) control versus HPV– patients, though similar distant control (90% vs. 86%) was found. Smoking pack-years >10 was confirmed

Table 2: Proposed ICON-S stage tabulation grid for 8th edition TNM Note that distant metastatic disease (M1) is considered stage IV.
From: O'Sullivan B, et.al. Lancet Oncol. 2016 Feb 26. pii: S1470-2045(15)00560-4. doi: 10.1016/S1470-2045(15)00560-4.

RPA stage Classification	T1	T2	T3	T4
NO	I	I	I	III
N1	I	I	I	III
N2a	I	I	I	III
N2b	I	I	I	III
N2c	II	II	II	III
N3	III	III	III	III
AHR-Orig stage classification	T1	T2	T3	T4
NO	I	I	II	III
N1	I	I	II	III
N2A	I	I	II	III
N2B	I	II	II	IVA
N2C	II	II	III	IVA
N3	III	III	IVA	IVA
AHR- New stage Classification				
NO	I	I	II	III
N1	I	I	II	III
N2A	I	I	II	III
N2b	I	I	II	III
N2c	II	I	II	III
N3	III	III	III	III
ICON – S stage classification	T1	T2	T3	T4
NO	I	I	II	III
N1	I	I	II	III
N2	II	II	II	III
N3	III	III	III	III

to be associated with reduced overall survival. RPA was performed to segregate patients into low-risk (T1-3, N0-2c) and high-risk (T4 or N3) groups for distant metastasis with distant control of 93% and 76%, respectively. Notably, distant control rates were similar for HPV+, low-risk N0-2a patients or less than 10 pack-year N2b patients regardless of treatment with RT or CRT but were worse for HPV+ N2c patients managed with RT alone versus CRT (73% vs. 92%, respectively), indicating that this patient subset is not ideally-suited for chemotherapy de-intensification.

HPV and OPSCC Staging Systems

As HPV status has become the most important prognostic variable for OPSCC patients, efforts are underway to refine the current traditional TNM staging system defined by the American Joint Committee on Cancer (AJCC) which does not account for HPV [31]. Significant stage migration has occurred over time with the increasing incidence of HPV+ OPSCC as these patients typically present with a lower T stage and higher N stage than their HPV− counterparts [32,33]. Unsurprisingly, the AJCC TNM stage is no longer prognostic for HPV+ patients, though it does retain prognostic capacity for HPV− patients [32-35]. Underscoring the point, improved survival has been observed in OPSCC patients in the United States with N2a versus N0 nodal stage, ostensibly due to the frequency of lymph node (LN) metastasis with HPV+ patients [36,37].

Several groups have sought to refine the current AJCC staging system for non-metastatic HPV+ OPSCC. Huang et al performed an analysis of 573 HPV+ OPSCC patients treated at Princess Margaret from 2000 to 2010 using RPA to derive prognostic groups [35]. Their initial RPA defined risk groups based solely on AJCC T and N stage classifications and divided patients into RPA-I (T1-3N0-2b), RPA-II (T1-3N2c), and RPA-III (T4 or N3) groups with 5-year OS of 82% vs. 76% vs. 54%, respectively. An additional RPA which included age and smoking pack-years in addition to RPA stage further segregated the cohort into four prognostic groups: group I (T1-3N0-N2c, <20 pack-years), group II (T1-3N0-2c, > 20 pack-years), group III (T4 or N3, age < 70), and group IV (T4 or N3, age >70) with 5-year OS 89%, 64%, 57%, and 40%, respectively. The model was validated internally, but external validation was not performed as part of the analysis.

Using a separate cohort of 662 HPV+ OPSCC patients treated at MD Anderson between 2003 and 2012, Dhalstrom et al were unable to validate the stage and prognostic groups proposed by Huang et al [38]. They proposed their own staging system using nasopharyngeal (NPC) N categories rather than the traditional OPSCC regional LN categories citing the similarity between NPC and HPV-related OPSCC in regards to their viral causation and different natural history versus other HNSCC subsites. RPA stratified patients into the following stages: stage IA (T1, N0-2), stage IB (T2, N0-2), stage III (T1-3, N3), stage IV (T4, Any N). 5-year OS for the risk groups were 94%, 87%, 76%, and 69%, respectively. Though smoking history (< 10 vs. >10 pack-years) was predictive for OS for the whole cohort of patients, it was not able to stratify patient outcomes within each stage group. Though the two models differ significantly, they do share tumor volume as measured by T stage as an important prognostic variable. This finding confirms observations made by others regarding the prognostic importance of T stage versus N stage in HPV+ OPSCC [33,34,39].

The International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) sought to further refine and validate the work undertaken by Princess Margaret to develop a TNM classification system specific to HPV+ OPSCC in a multi-institutional cohort study involving 7 centers across Europe and North America [40]. The original training cohort from Princess Margaret was expanded to 661 patients with further follow-up time, and 1246 patients were enrolled in a validation cohort at 6 additional centers for a total of 1907 patients. Definitive treatment for the vast majority of patients (98%) was non-surgical. RPA and adjusted hazard ratio (AHR) modeling were used to create new staging classifications for HPV+ OPSCC in the training cohort. These were subsequently verified in the validation cohort. As noted previously, similar 5-year OS was seen for AJCC 7th edition stage I, II, III, and IVa patients, though stage IVb did prove to have a worse survival. Patients in the AJCC N0, N1-N2a, and N2b subsets did not have a difference in 5-year OS, though survival was significantly lower for those with N3 disease. AHR modeling produced the TNM stage classification that was most predictive of survival. As patients classified with T4a and T4b disease experienced similar 5-year OS, T4 was no longer subdivided in the new ICON-S T stage classification. Given the similar prognosis for N1, N2a, and N2b patients, the following ICON-S N stage classifications were proposed which closely parallel those for NPC: ICON-S N0 (no LN); ICON-S N1 (ipsilateral LN); ICON-S N2 (bilateral or contralateral LN); ICON-S N3 (LN > 6 cm). The proposed ICON-S TNM staging classifications were as follows: stage I (T1-2, N0-1); stage II (T1-2 N2, or T3N0-N2); stage III (T4 or N3); stage IV (M1). These closely parallel the initial findings from Huang et al except in the case of T3N0-N2b which is considered ICON-S stage II rather than stage I. Heterogeneity tests showed that HRs between the proposed stage groups were consistent across all institutions, suggesting wide applicability of the staging system across varied patient populations. In an exploratory training cohort of 702 patients, the additional risk factors of lower neck LN involvement and > 5 positive LNs were investigated. Lower neck involvement did appear to be associated with worse survival, but his was not an independent effect and was left out of the final staging model. As with lower neck involvement, > 5 LNs did not predict for survival across all cohorts and was omitted from the staging system. Notably, though smoking status was used as a variable to derive the prognostic groupings, it was not included as a staging variable as the authors wished to derive an anatomical stage classification (Table 2).

Conclusion

HPV+ OPSCC is a separate disease entity from HPV− HNSCC that increasingly impacts younger, healthier patients and portends a markedly improved prognosis. Further work is needed to establish staging systems that accurately stratify OPSCC based on outcomes. This will aid current efforts at treatment modification based on HPV status which aim to de-intensify therapy in HPV+ patients in order to reduce the long-term toxicities of treatment while escalating therapy in HPV− patients.

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