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The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas

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SUMMARY

Human papillomavirus (HPV) is etiologically responsible for a distinct subset of head and neck squamous cell cancers (HNSCCs). HPV-positive HNSCCs (HPV-HNSCCs) most commonly arise from the oropharynx and are responsible for the increasing incidence of oropharyngeal SCC (OSCC) in the United States (US) and abroad. HPV-positive OSCC (HPV-OSCC) has a unique demographic and risk factor profile and tumor biology. HPV-OSCC patients tend to be white, younger, and have a higher cumulative exposure to sexual behaviors as compared with HPV-negative OSCC patients. HPV-positive tumor status also significantly improves survival, and is indeed the single strongest prognostic factor for OSCC. The mechanisms that underlie the improved prognosis conferred by HPV-positive disease are unknown. The purpose of this review is to describe the clinical impact of HPV status in HNSCC, particularly in OSCC, both in terms of the unique clinic-demographic profile and prognostic implications.

Keywords

Head and neck cancer; Oropharyngeal neoplasms; HPV; Risk factors; Prognosis

Introduction

Human papillomavirus (HPV) is etiologically responsible for a distinct subset of head and neck squamous cell cancers (HNSCCs). While the incidence of HNSCC overall has declined in the United States (US) [1], the incidence of oropharyngeal SCC (OSCC) – specifically HPV-positive OSCC (HPV-OSCC) – has increased in the US as well as abroad [2–5]. In the

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Conflict of interest statement

None declared.

US, HPV was estimated to account for 16% of OSCCs in the early 1980s, yet prevalence in the most recent studies exceeds 60% [2,3,6–9]. It is estimated that by 2020, the incidence of HPV-OSCCs in the US will be greater than HPV-related cervical cancers [3]. HPV-positive HNSCC has unique risk factors, tumor biology and clinical characteristics when compared to HPV-negative HNSCC [6–14]. HPV has been shown to confer a survival advantage, and is indeed the single strongest prognostic factor for OSCC [6,7,9,13,14]. The purpose of this review is to describe the clinical impact of HPV tumor status in HNSCC and in particular OSCC, both in terms of the unique clinic-demographic profile and prognostic implications.

Clinic-demographic profile of HPV-HNSCC

Site

HPV-HNSCC most commonly arises from the oropharynx, primarily the lingual and palatine tonsils [8,15,16]. One-quarter to one-half of unknown primaries are HPV-OSCC [17,18] and the presence of HPV in cervical metastases is a strong predictor of oropharyngeal site for squamous cell cancers with unknown primary site [17,19,20]. Whereas the prevalence of HPV in OSCC is at least 60–70% in recent studies and projected to be on the rise [2,3,6,7,9,21], prevalence in other head and neck sites appears to be substantially lower. Estimated prevalence in squamous cell cancers of the oral cavity is 6–20%, 24% in the larynx, 21% in the sinonasal tract and 31% in the nasopharynx [22,23]. Whereas HPV tumor status in OSCC is a strong independent prognostic indicator [6,7,9,13,14], the implications are unknown for non-oropharyngeal sites [22].

Staging and histology

HPV-positive disease tends to present with smaller primary tumors (T stage) but more advanced nodal stage [7,8,14,24–28]. This confers an overall later American Joint Committee on Cancer (AJCC) stage [14,29–31], which historically was a reasonable surrogate for prognosis and was used to guide treatment decisions [32]. Cystic metastatic neck nodes have been strongly associated with HPV-HNSCC and are a frequent radiographic finding at presentation, which may lead to an erroneous diagnosis of branchial cleft cyst [28,33–36]. HPV-positive tumors are also more likely to present as metastatic nodal disease with an unknown primary site when compared with HPV-negative tumors [8,18]. Histologically, HPV-HNSCCs are non-keratinizing with basaloid features [11,25,26]. Although initially described as poorly differentiated, on further analysis they are similar in morphology to the reticulated epithelium of the tonsillar crypts from which they are thought to arise and therefore are more appropriately now described as well-differentiated [37]. HPV-HNSCCs sometimes exhibit central necrosis in expanding lobules of tumor [37].

Demographics

Individuals diagnosed with HPV-HNSCC are significantly younger than HPV-negative patients with an average age difference of 4–10 years [6,24,26,38–41]. This age difference may account for an increasing incidence of OSCC in younger patients in developed countries [3,4]. Although HNSCC overall is more commonly diagnosed in men than women, a significantly larger proportion of HPV-OSCC than HPV-negative OSCC is found in men [3,40,42,43]. This is consistent with findings that oral HPV16 infection, which is responsible

for the overwhelming majority of HPV-OSCC, is five times more likely to be found in men than in women in the US (prevalence ratio (PR) 5.4, 95% confidence interval (CI) 2.1–13.8) [44]. Recent cancer statistics in the US demonstrate that the largest burden of HPV-related malignancy across anatomic sites in men is OSCC [45].

HPV-HNSCC has been found to overwhelmingly afflict white vs. black patients. Among all tumors examined for HPV status, 29–34% of whites' tumors were HPV-positive compared with only 0–4% of blacks' tumors [46,47] and 92–97% of HPV-positive tumors vs. 75–78% of HPV-negative tumors occur in whites [6,9,46]. Indeed, in the US the incidence of OSCC has increased in whites but has decreased in blacks, which is likely due to higher rates of HPV-OSCC in whites than blacks [45].

HPV-positive patients also differ from HPV-negative patients in terms of socioeconomic status. HPV-positive patients report higher income and more years of education. They are also are more likely to be married [8,26].

As would be expected given that HPV-positive patients are younger at diagnosis, they have been shown to have improved performance status on several scales including Eastern Cooperative Oncology Group (ECOG) [6,7,9] and World Health Organization (WHO) [13], with fewer comorbid illnesses [6,7,26].

Risk factor profile

HPV-OSCC has a unique risk factor profile. Sexual behaviors have a pivotal role when comparing patients with and without HPV-OSCC. Case-control studies have linked HPV-HNSCC with ever having had oral sex, increased lifetime number of oral and genital sexual partners, history of casual sex, younger age at both oral and vaginal sexual debut, lack of barrier use during oral sex, and a history of previous sexually transmitted infection [8,16,48]. Oral HPV infection is also strongly associated with these collinear sexual behaviors [44].

HPV-HNSCC patients are more likely to report a history of marijuana use as compared with HPV-negative HNSCC patients. Among HPV-positive patients, increasing intensity and duration of exposure to marijuana was associated with increasing odds of HPV-HNSCC, but not HPV-negative HNSCC [8].

Historically, the most important risk factors for HPV-negative HNSCC have been heavy use of tobacco and alcohol, which are believed to have a synergistic effect and are implicated in 75% of all HNSCC cases [49,50]. In fact, the decline of HNSCC in the US appears to correlate with falling tobacco use [51,52]. While a proportion of patients with HPV-HNSCC do have a history of tobacco use, smoking is significantly less common among patients with HPV-OSCC than HPV-negative OSCC. Indeed, the odds of HPV-HNSCC decrease in a dose–response fashion with increasing lifetime tobacco exposure, while a significant inverse relationship is observed for HPV-negative HNSCC [8]. Rates of past and current tobacco use in HPV-OSCC are reported to be 65% as opposed to 74% in HPV-negative OSCC [6]. By contrast, the presence of oral HPV infection is independently associated with current cigarette smoking, not lifetime history of smoking [44]. Although tobacco use is less

prevalent in HPV-HNSCC, whether it is a synergistic risk factor with HPV is presently unknown.

Heavy alcohol use is less prevalent amongst patients with HPV-HNSCC than HPV-negative HNSCC [8,53,54], and the odds of developing an HPV-negative HNSCC increase with increasing intensity of alcohol use [8]. Similar to tobacco, heavy alcohol use (>21 drinks per week) has been associated with increased odds of HPV-HNSCC and HPV-negative HNSCC [55]. However, alcohol use is not associated with oral HPV infection after adjustment for sexual behavior [44]. The impact of alcohol use both independently and in association with either HPV or tobacco smoking remains to be fully described.

Prognosis

Staging of HNSCC

HNSCC tumor site and AJCC staging based on tumor, nodal status and distant metastasis have traditionally been used to predict prognosis and to guide treatment decisions. Other established risk factors known to modify prognosis include patient comorbidities and tobacco and/or alcohol use [32]. Despite presenting with late stage AJCC tumors [14,29–31], HPV-positive patients have improved responses to therapy, overall survival and progression-free survival when compared to their HPV-negative counterparts [6,11,24,29,56]. OSCC historically carried a poor prognosis due to the larger proportion of HPV-negative tumors in the past, with 44% overall survival at 5 years [57]. However, as the burden of OSCC has shifted from HPV-negative to HPV-positive, prognosis for OSCCs overall has improved. A recent meta-analysis demonstrated 53% improved overall survival for HPV-OSCC compared with HPV-negative OSCC (hazard ratio (HR) 0.47, 95% CI 0.35–0.62) [58]. HPV status has been identified as the strongest independent prognostic factor for OSCC [59,60].

Table 1 summarizes selected published data comparing outcomes between HPV-HNSCC and HPV-negative HNSCCs, with a more complete summary presented in Supplemental Table 1. Given that HPV-HNSCCs tend to arise from the oropharynx and the unknown significance of HPV in non-oropharyngeal HNSCC [11,22], the remainder of this discussion will focus largely on HPV-OSCC.

Studies confirming the prognostic role of HPV tumor status

The favorable prognosis of HPV-HNSCC particularly originating in the oropharynx was elucidated early on in single-institution retrospective studies involving multiple subsites, heterogeneous treatment strategies, and variable tumor HPV detection methods [11,24–26,42,61]. The evaluation of tumor HPV status has evolved over the past two decades and at present clinical testing incorporates in situ hybridization (ISH) for HPV DNA and immunohistochemistry (IHC) for p16, a cell cycle protein that is upregulated in HPV-induced oncogenesis [62]. These are applied as either stand-alone tests or in combination, depending on clinical centers [63,64]. A more in-depth discussion of HPV detection algorithms is beyond the scope of this review (refer to manuscript by Westra et al. in this special edition). Henceforth tumor HPV status will be referred to as defined by individual studies.

Gillison et al. in 2000 retrospectively examined 252 patients with HNSCC from all sites, including 60 oropharyngeal primary cancers [11]. Oropharynx as a site was strongly associated with the presence of HPV in tumor. Patients with HPV-HNSCC from all sites had a 40% reduction in risk of death from all causes and a 59% reduction in risk of death from their disease when adjusted for age, nodal disease, and alcohol consumption (95% CI 0.35–1.0, $p = 0.07$ and 95% CI 0.20–0.88, $p = 0.02$, respectively). Among OSCCs, disease-specific survival was significantly improved in HPV-positive vs. HPV-negative patients [11]. Other retrospective studies have shown similar findings [24,26,61].

In the first multi-institutional cooperative group (ECOG 2399) prospective study to evaluate the impact of HPV tumor status on survival, patients with HPV-positive tumors had a significantly improved response to induction chemotherapy (82% vs. 55%, $p = 0.01$) and concomitant chemoradiotherapy (84% vs. 57%, $p = 0.007$) as compared to those with HPV-negative tumors [9]. At 2 years, after adjusting for age, tumor stage and ECOG performance status, HPV-positive patients had a significant reduction in the risk of death (HR 0.36, 95% CI 0.15–0.85) and progression (HR 0.27, 95% CI 0.10–0.75) [9].

Building upon these findings, 323 OSCCs from Radiation Therapy Oncology Group (RTOG) 0129, a phase III trial designed to evaluate concurrent cisplatin and standard or accelerated-fractionation radiotherapy, were retrospectively evaluated for tumor HPV status. HPV-OSCC had improved 3-year overall survival (82.4% vs. 57.1%, $p < 0.001$) as compared with HPV-negative OSCC. HPV-positive tumor status was independently associated with a 58% reduction in risk of death overall (HR 0.42, 95% CI 0.27–0.66) [6]. This study delineated the relationship between tobacco exposure and HPV tumor status and its effect on survival estimates (discussed below) and provides the longest median survival time for a cooperative study investigating the prognostic significance of HPV tumor status. The results of other Phase III clinical trials have confirmed HPV tumor status as a robust predictor of prognosis regardless of treatment regimen [7,13,14].

There is a suggestion that HPV copy number in pre-treatment tumor may affect survival. In a study population of 42 patients with stage ≥3 OSCC, increased tumor HPV copy number was associated with improved response to both induction chemotherapy ($p = 0.001$) and to chemoradiotherapy (odds ratio (OR) 1.4, 95% CI 1.08–1.83, $p = 0.005$) [40]. After adjustment for age, gender, past or current tobacco exposure, T-stage, N-stage, and primary site, greater intratumoral HPV DNA copy number was associated with improved disease-specific and overall survival ($p = 0.004$ and $p = 0.008$, respectively) [40]. Higher viral load was also associated with improved recurrence-free ($p = 0.0037$) and overall ($p = 0.028$) survival in patients with tonsil squamous cell carcinoma (SCC) [65]. Another study demonstrated that the presence of HPV16 by PCR and concomitant p16 expression conferred significant improvement in prognosis, as compared with either p16 or HPV16 alone, which potentially illustrates distinct molecular groups of HPV-OSCC [25].

Survival modifiers

Tobacco

Tobacco exposure, in addition to being the most significant risk factor for HNSCC overall, is also recognized to negatively impact treatment response and survival [66,67]. It is not unexpected, then, that tobacco use is now emerging as an important independent prognostic factor for HPV-OSCC, predicting cancer progression and risk of death in a dose-dependent fashion [6,68]. After adjustment for HPV tumor status and other significant factors, the risk of progression and death for patients with OSCC increases by 1% for each pack-year of tobacco use. The risk of second primary tumors increases by 1.5% for each pack-year of smoking, and there is a doubling in the risk of death if patients smoke during radiation treatment [68].

There is strong evidence to support risk stratification of patients with OSCC by tumor HPV status, history of tobacco use (>10 pack-years) and disease stage [6,54]. Three distinct clinical risk categories have been determined in which low-risk patients have HPV-positive tumors, and are either nonsmokers with any stage disease or smokers with N0–N2a disease [6]. Intermediate-risk patients are either smokers with HPV-positive tumors and N2b-N3 disease or nonsmokers with HPV-negative tumors and T2–T3 disease. High-risk patients all have HPV-negative tumors, and are either nonsmokers with T4 disease or smokers with any T or N classification. Three-year overall survival is 93% (95% CI 88.3–97.7) for low risk, 70.8% (95% CI 60.7–80.8) for intermediate risk, and 46.2% (95% CI 34.7–57.5) for high risk patients. Of note in this schema, HPV-OSCC is low risk with the exception of a history of smoking and at least N2b nodal disease, and HPV-negative disease is high risk except for ≤10 pack-years smoking history [6].

Clearly, the favorable prognosis associated with HPV positivity is tempered in a dose-dependent fashion by tobacco history. It is becoming increasingly evident that quantification of tobacco use must be incorporated into studies of prognosis and response to treatment going forward.

Gender considerations

There is no consensus with regard to the effect of gender on prognosis in HPV-OSCC. In the University of Michigan Cancer Center organ sparing trial for OSCC, female gender was associated with poor prognosis independent of HPV tumor status and smoking, albeit only 12 women were enrolled in this study [39]. Tumor HPV status has been shown to confer improved prognosis in males, but for females HPV tumor status does not appear to impact survival estimates [42,69]. These studies are limited by the small numbers of females. With the increasing incidence of HPV-OSCC [3], future studies should stratify by gender and be powered to detect gender-specific differences in prognosis.

Race considerations

There is a dramatic difference in survival between black and white patients with HNSCC overall, with black patients experiencing twice the mortality of whites [46,70,71]. Recent evidence points to the higher prevalence of HPV-HNSCC in whites as a major contributor to

this disparity; when HPV-HNSCCs and/or HPV-OSCCs are excluded, the survival difference is drastically reduced [46,71].

There is limited data for the survival of HPV-OSCC in white vs. black patients, largely due to a scarcity of black patients with HPV-positive disease. More studies are required to compare the survival of HPV-OSCC in black vs. white patients, and to explore the underlying epidemiological and/or biological phenomena accounting such disparate rates of HPV-positive disease by race.

Mechanisms of improved response to treatment

The prognostic advantage of HPV-OSCC can partially be attributed to the unique patient population affected, with fewer comorbidities, younger age, decreased tobacco exposure and a higher performance status. However, the improved prognosis of HPV-positive disease persists in multivariate analyses with adjustment for these confounders [6,7,9,11,13,14,24–26,61]. In fact, age, tobacco use, performance status, etc. only account for approximately 9% of the difference in overall and progression-free survival between patients with HPV-positive and HPV-negative tumors, so that the difference in survival appears to be largely driven by HPV tumor status [6,58]. It is evident that the enhanced response of HPV-HNSCC to therapy of all modalities underlies a fundamental biological difference in HPV-positive vs. HPV-negative HNSCC, although the specific mechanisms by which HPV-positive disease achieves favorable outcomes remain to be elucidated.

HPV-induced oncogenesis

HPV has been demonstrated in epidemiological and molecular studies to satisfy causal criteria as an etiological agent in malignant transformation of OSCC [72]. Oncogenic HPV types 16, 18, 31, 33 and 35 are associated with HPV-HNSCC, and HPV16 is responsible for at least 90% of HPV-HNSCCs [72]. The natural history of HPV infection, clearance, persistence and ensuing carcinogenesis is still under investigation. It is apparent that oral HPV infection is frequently cleared and does not inevitably lead to malignancy [73], and detection of HPV DNA in tumor tissue does not qualify the tumor as being caused by the virus [72]. However, the transformative pathways in HPV-induced oncogenesis that lead from infection to cancer have been well described and involve the expression of viral oncoproteins E6 and E7, leading to the degradation of tumor suppressor proteins p53 and retinoblastoma (Rb) respectively. This results in cell cycle dysregulation and proliferation [74]. E7-induced downregulation of Rb also leads to increased p16 expression, which allows for the use of p16-based assays to detect oncogenic HPV activity [25]. There is evidence that HPV exerts its oncogenic effect through various other mechanisms [75,76]; however, it has been consistently shown that HPV-induced carcinogenesis involves significantly fewer genomic alterations than HNSCC carcinogenesis independent of HPV. Specifically, HPV-HNSCC is less likely to have mutated p53, high expression of EGFR, and chromosomal aberrations of 3p, 9p and 17p [11,39,77,78].

Recent whole-exome sequencing of HNSCCs confirmed that HPV-HNSCC has a genetic landscape that is distinct from that of HPV-negative HNSCC. Independent of smoking status, more mutations were found in HPV-negative tumors than in HPV-positive tumors

[12,79]. Tumor suppressor gene TP53 mutation was inversely associated with HPV tumor status [12,79]. None of the HPV-positive samples had TP53 mutations, but TP53 was mutated in 78% of the remaining samples [12]. The accumulated evidence points to an overall lesser degree of cellular dysregulation associated with HPV-induced oncogenesis. This is suspected to underlie its superior response to treatment given a simpler path to the restoration of normal cell cycle regulation.

Response to therapy

The relative degree to which the improved prognosis of HPV-OSCC is attributable to an increased responsiveness to chemotherapy, radiotherapy, and/or surgery is unclear. HPV tumor status has been shown to confer a significant prognostic advantage independent of therapeutic approach [80]. Although there is very limited evidence for patients undergoing surgery alone, small series show that even without chemotherapy or radiation, HPV tumor status is significantly associated with prognosis [77].

HPV-OSCC has been shown to respond better than HPV-negative OSCC to platinum-based induction chemotherapy regimens [9,40]. HPV-OSCC has also been uniformly shown to respond better to radiation therapy independent of the radiation regimen, the addition of radiation sensitizers [7,81], or the addition of chemotherapy [6,14,61]. Population-based data in the US from Surveillance, Epidemiology and End Results (SEER) demonstrated that the survival difference between HPV-OSCC and HPV-negative OSCC was greater for patients treated with radiation therapy (HR 0.23, 95% CI 0.09–0.59 and HR 0.80, 95% CI 0.40–1.60 respectively; p interaction = 0.002) [3].

In vitro cell-line experiments are conflicting in their support of an inherently increased radiation sensitivity in HPV-positive disease. HPV-positive cell lines have been shown to undergo increased apoptosis and decreased survival with radiation exposure [82,83]. A recent study demonstrated increased radiation sensitivity in HPV-positive compared to HPV-negative cell lines, and concluded that this was secondary to compromised DNA repair capabilities rather than increased apoptosis [84]. Other studies, however, report increased survival of HPV-positive compared with HPV-negative HNSCC cell lines after exposure to radiation [85]. There is scant data available for in vitro response to chemotherapy by HPV-positive vs. HPV-negative HNSCC cell lines, but studies performed thus far have failed to elicit any improvement in response to platinum-based and other chemotherapeutic agents [85–87].

Immune surveillance

The immune system is known to play an integral part in viral oncogenesis and there is an increased rate of virus-associated malignancies in immune compromised patients [88], so the implication of immune surveillance in the clearance of HPV-positive disease is not unexpected.

Interestingly, a 2009 study by Spanos et al. showed HPV-positive tonsillar SCC cell line resistance to both radiation and cisplatin in vitro, but when transferred to in vivo mouse models, corresponding HPV-positive tumors demonstrated significantly improved responses

to both radiation and cisplatin relative to HPV-negative tumors. The favorable responses were abrogated in immune-compromised mice, but enhanced when mice were immunologically primed with an adenovirus vector vaccine targeting E6 and E7 [85].

Another study of tonsillar SCC mouse models demonstrated increased survival and a higher likelihood of tumor clearance for wild-type mice with HPV-positive compared to HPV-negative tumors, but immune compromised mice showed no difference in survival and lost the ability to clear their tumors. The improved outcomes associated with HPV-positive disease were only found in mice with both CD8+ and CD4+ lymphocytes [89]. These animal studies suggest a role for immune surveillance in the clearance of HPV-positive tumor cells, which is enhanced after treatment with chemoradiation but worsened by immune compromise.

Studies have also corroborated a role for immune surveillance in human subjects. HPV16-specific T-cell immunity has been identified in tumors of patients with HPV-positive but not with HPV-negative cancer [90], and E7-specific circulating T lymphocytes are found with higher frequency in patients with HPV-HNSCC [91]. There is also some evidence that viral load may correlate with prognosis [40,65,92], which may suggest that failed immune regulation of viral replication is a risk factor for poor outcome.

Efforts are underway to exploit the immune response to treatment-sensitized tumors bearing HPV antigens E6 and E7 using vaccine administration in conjunction with radiation and chemotherapy [93]. The responsiveness of HPV-OSCC to immune surveillance may undergird its superior outcome with treatment, and the development of immune-modulating therapies holds promise to further improve an already favorable prognosis.

Current evidence indicates that the improved prognosis of HPVOSCC is attributable to nearly intact cell cycle machinery that is altered by HPV oncoproteins E6 and E7, but that may be restored to normal functioning by exposure to chemoradiotherapy. Increased susceptibility to immune surveillance likely plays a role in the eradication of post-treatment tumor cells. Further epidemiological and molecular-level studies are needed to define the precise mechanisms by which HPV-OSCC carries a better prognosis than its HPV-negative counterpart. Ultimately, this information will lend itself to targeted, effective and patient-centered treatment with reduced toxicity.

Therapeutic considerations

Deintensification of therapy

Radiotherapy and chemotherapy carry significant morbidity with effects on quality of life, including high rates of dysphagia after radiotherapy [94,95], and systemic sequelae such as renal, otologic, hematologic, neurologic, and gastrointestinal toxicities of platinum-based agents [96]. Given the better response to treatment, longer survival and younger patient population with generally improved performance status characteristic of HPV-OSCC, attempts are underway to deliver attenuated doses of chemotherapy or radiation in order to reduce treatment-related morbidity while still achieving oncologic cure [97]. Several single- and multi-institutional Phase II and III trials of deintensification therapy for advanced HPV-

OSCC are ongoing. In the Phase III RTOG 1016 trial either cisplatin or cetuximab are administered with concurrent standard-dose radiotherapy to assess non-inferiority of the less-toxic cetuximab compared to cisplatin. The Phase II ECOG 1308 trial evaluates induction chemotherapy followed by a response-based dose of radiotherapy, in order to examine outcomes with reduced radiation doses.

Conversely, optimal treatment of HPV-negative OSCC as a separate entity with distinctly poor outcomes is also under study. RTOG 1221 is a randomized Phase II trial examining treatment of HPV-negative OSCC patients with radiotherapy and cisplatin with or without transoral surgical resection.

It is important to note that at present, OSCC patients are treated independent of HPV tumor status. HPV tumor status is only a consideration for patients enrolled in clinical trials. Despite the worse prognosis of HPV-negative OSCC, there are no additional treatment recommendations at this time for these patients [98].

Primary transoral surgery

Primary transoral surgery techniques including transoral robotic surgery (TORS) and transoral laser microsurgery have emerged as alternatives to traditional external, invasive surgical approaches to tonsil and base of tongue tumors that historically have been difficult to access transorally. This is being considered in the context of therapeutic de-intensification [97].

TORS is hypothesized to have several advantages to chemotherapy and radiation alone, although prospective multi-institutional long term data are presently unavailable. Surgical exploration of the primary tumor and of the neck lymph node basins may provide objective criteria by which to determine the indication for and/or intensity of adjuvant treatment. In the primary ablative approach to treatment of OSCC, the need for adjuvant chemotherapy and radiation therapy is dictated by tumor stage, margin status of the resection specimen, and the presence of high-risk nodes with extracapsular extension [97,99]. In one case series, 38% of patients were spared chemotherapy and 11% of patients avoided adjuvant radiotherapy with concurrent chemotherapy [100]. Tumor resection may also reduce the volume and dose of radiation delivered to the pharyngeal constrictors and normal aerodigestive tissue [99], important elements in the reduction of postradiation swallowing dysfunction and xerostomia [95]. The role of TORS in the treatment of OSCC is an area of active investigation and the first cooperative group trials with this treatment schema are soon to start.

Distant control

Notably, while loco-regional control is significantly better in HPV-HNSCC, one outcome that has not been consistently improved in HPV positive tumors is distant recurrence [6,7,13,27,101]. Distant metastases may arise after longer intervals and in unusual sites [27,102]. Although long-term distant control is similar by HPV tumor status, the rate of distant control decreases sharply and then stabilizes at 2 years among HPV-negative OSCCs, while distant control for HPV-OSCCs continues to decline up to 5 years after therapy before stabilizing [27]. In a study of 318 OSCCs treated with radical radiotherapy, there was no

difference in rates of distant metastasis in HPV-OSCC vs. HPV-negative OSCC, however HPV positive metastases were more likely to involve multiple organs, including the skin, intra-abdominal lymph nodes, and brain. Distant metastases also occurred significantly later in HPV-OSCC than in HPV-negative OSCC [102]. HPV-positive status does not exclusively relegate a patient to a low-risk, high survival prognostic subgroup. This warns against cavalier use of attenuated therapeutic regimens. It is strongly recommend that de-intensification only take place in the setting of controlled clinical trials with vigilant cognizance of the accompanying oncologic risks [98].

Conclusion

The epidemiology of HPV-OSCC and the etiology of its superior prognosis are under active investigation. More research is necessary to define the therapeutic implications of HPV-OSCC's improved response to current treatment, the extent to which toxic treatment regimens can be de-intensified without compromising survival, and the role of advances in surgical technique. There is hope that the development of new therapies specifically targeting the pathophysiology of HPV-OSCC will further enhance prognosis. HPV-OSCC is a distinct clinical entity with a unique clinic-pathologic profile, compelling prognostic advantage and rising incidence that warrants widespread efforts to increase our understanding of this disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.oraloncology.2013.09.008.

Abbreviations

HPV	human papillomavirus
HNSCC	head and neck squamous cell carcinoma
US	United States
OSCC	oropharyngeal squamous cell carcinoma
HPV-OSCC	HPV-positive oropharyngeal squamous cell carcinoma
AJCC	American Joint Committee on Cancer
ECOG	Eastern Cooperative Oncology Group
WHO	World Health Organization
IHC	immunohistochemistry
ISH	in situ hybridization

RTOG	Radiation Therapy Oncology Group
SCC	squamous cell carcinoma
Rb	retinoblastoma
SEER	Surveillance, Epidemiology and End Results
TORS	transoral robotic surgery

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Table 1

Selected references that demonstrate an association of tumor HPV status with prognosis.

Reference (author, year)	Country	N	Anatomic site (or subsite)	HPV detection method (PCR, p16, ISH)[a]	Prevalence of HPV-positive disease[b]	Follow-up time[c] (*median, **mean)	Prognosis for HPV-positive vs. HPV-negative disease[d]	Factors adjusted for
Andl (1998) [103]	Germany	31	Tonsil	PCR, p16	48%	28 months**	OS: improved (p = 0.0071) DFS: median 61.1 months vs. 25.8 months (p = 0.028)	Overall stage
Gillison (2000) [11]	US	259	HNSCC	PCR, ISH	25% overall; 57% OP	31 months*	OS: 91 months vs. 76 months. HR 0.6 (0.35–1.0, p = 0.07); DSS: HR 0.41 (0.20–0.88, p = .02)	Age, LN disease, alcohol
Mellin (2000) [24]	Sweden	60	Tonsil	PCR	43%	59 months*	OS: 5-yr 53.5% vs. 31.5%; RFS: OR 19.6 (p = .014); DSS: improved (p = 0.047)	RFS: Overall stage DSS: Overall stage, LN Metastases, age, gender
Lindel (2001) [61]	Switzerland	99	OP	PCR	14%		LFFS: RR 0.31 (0.09–0.99, p = .048)	T, alcohol, intratumoral Microvessel density
Schwartz (2001) [26]	US	254	OC, OP	PCR	15%	54 months**	OS: HR 0.34 (0.14–0.83, p=.008) DSS: HR 0.17 (0.04–0.76)	Age, overall stage, surgery Tobacco, alcohol, education Comorbidity
Li (2003) [104]	Australia	67	Tonsil	PCR, p16	48%	4 years*	OS: 5-yr 89% vs. 65% (p < 0.01). Improved on multivariate analysis (p < 0.05) RFS: Risk of recurrence decreased on Multivariate analysis (p < 0.05)	Cell cycle proteins (p53, p21, p27), overall stage, pathologic N, tumor grade, age, gender treatment
Ritchie (2003) [42]	US	139	OC, OP	PCR	21%	4.8 years*	OS: 5-yr 71% vs. 49%, RR 0.3 (0.1–0.8)	Age, gender, tumor grade. Overall stage, treatment. Tobacco, alcohol, tumor Histology
Weinberger (2006) [25]	US	79	OP	PCR, p16	61%	22 months**	OS: 5-yr 79% vs. 18–20%, HR0.19 (0.1–0.7, p = 0.13) DFS: 5-yr 75% vs. 13–15%, HR0.20 (0.1–0.6), p = 0.005)	Primary vs. recurrence. Treatment, overall stage, grade
Licitra (2006) [77]	Italy	90	OP	PCR, p16	19%	5.8 years*	OS: 5-yr 79% vs. 46% (p = 0.0018). Improved when adjusted for stage	Overall stage
Reimers (2007) [105]	Germany	106	OP	PCR, p16	30%		DFS: 85% vs. 49% (p = 0.009). HR for HPV-negative tumors 7.5 (1.22–46.19), p = 0.030	EGFR expression status, overall stage
Lindquist (2007) [106]	Sweden	153	Tonsil	PCR	49%	59.4 months**	DSS: 81% vs. 36% (p, 0.001), HR0.17 (0.09–0.32)	Age, gender, overall stage
Klozar (2008) [107]	Czech Republic	81	OC, OP	PCR	64%	3.3 years*	OS: 73% vs. 35% (p = 0.0112). HR 0.27 (0.12–0.61)	Extracapsular spread, T, alcohol. Tobacco, age, gender, site.

Reference (author, year)	Country	N	Anatomic site (or subsite)	HPV detection method (PCR, p16, ISH)[a]	Prevalence of HPV-positive disease[b]	Follow-up time[c] (*median, **mean)	Prognosis for HPV-positive vs. HPV-negative disease[d]	Factors adjusted for
								Grade, N
Smith (2008) [108]	US	301	HNSCC	PCR, p16	35%	1.8 years*	OS: HR for HPV-negative tumors 3.6 (1.6–8.1) DSS: 5-yr 53% vs. 0–20% (p = 0.004–0.2). HR for HPV-negative tumors 3.6 (1.2–10.3)	Age, overall stage, treatment. Alcohol, tobacco, site
Chien (2008) [109]	Taiwan	111	Tonsil	PCR, ISH	13%	41.1 months**	DSS: 5-yr 92.9% vs. 46.3%, RR 0.126 (0.017–0.914), p = 0.04	Age, gender, T, LN status. Overall stage, differentiation
Fakhry (2008) [9]	US	96	OP, larynx	PCR, ISH	63% OP, 0% Larynx	39.1 months*	OS: 2-yr 95% vs. 62% (p = 0.005). HR 0.36, (0.15–0.85) PFS:HR 0.27 (0.10–0.75)	Age, overall stage, ECOG Performance status
Worden (2008) [40]	US	66	OP	PCR	64%	64 months*	OS: improved (p = 0.008) DSS: improved (p = 0.004)	Gender, smoking, T, N, age, site
Fischer (2010) [110]	Switzerland	365	HNSCC	P16	57.5% OP	>5 years	OS (OP): 5-yr 57.1% vs. 26.8% (p = 0.007), HR 0.47 (0.3–0.9)	T, N, treatment
Jung (2010) [111]	France	231	HNSCC	PCR, ISH	13%	41 months*	OS: HR 0.40 (0.163–0.978) p = 0.048	Gender, age, T, N, site. Differentiation
Hong (2010) [112]	Australia	270	OP	PCR, p16	37%	2.5 years*	OS: HR 0.35 (0.19–0.62), p = 0.0002 EFS: HR 0.32 (0.19–0.52), p < 0.0001 LRR: HR 0.31 (0.15–0.61), p = 0.0005	Age, year of diagnosis, gender, grade, T, N, site, treatment, EGFR status
Ang (2010) [6]	US	323	OP	ISH, p16	63.8%	4.8 years*	OS: 3-yr 82.4% vs. 57.1% (p < 0.001). HR0.42 (0.27–0.66) PFS: 3-yr 73.7% vs. 43.4% (p < 0.001).	Age, race, T, N, tobacco Exposure, treatment Assignment
Rischin (2010) [7]	US, Canada, Australia, New Zealand, W. Europe	184	OP	PCR, ISH, P16	57%	29 months**	OS: 2-yr 91% vs. 74% (p = 0.004). HR0.43 (0.20–0.93), p = 0.031	ECOG performance status. Hemoglobin, T, N
Hannisdal (2009) [69]	Norway	137	Tonsil	PCR	52%		OS: 5-yr 54% vs. 33% (p < 0.05)	Age, gender, overall stage
Chaturvedi (2011) [3]	US	271	OP	PCR, ISH	44%	112 months*	OS: median 131 vs. 20 months (p < 0.001). HR 0.31 (0.21–0.46)	Age, calendar period of Diagnosis, overall stage. Treatment
Lassen (2011) [14]	Denmark	794	HNSCC	P16	23% overall, 42% OP, 17% larynx. 16% other Pharynx, 14% OC	>5 years	OS: 5-yr 62% vs. 47% (p < 0.0001). HR 0.54 (0.42–0.68) DSS: 5-yr 78% vs. 64% (p = 0.001). HR0.47 (0.33–0.67)	T, N, performance status. Treatment

Reference (author, year)	Country	N	Anatomic site (or subsite)	HPV detection method (PCR, p16, ISH)[a]	Prevalence of HPV-positive disease[b]	Follow-up time[c] (*median, **mean)	Prognosis for HPV-positive vs. HPV-negative disease[d]	Factors adjusted for
							LRC:HR 0.58 (0.43–0.78)	
Hong (2011) [113]	Australia	226	OP	PCR, p16	37%	2.1 years*	OS: HR 0.33 (0.19–0.56), $p < 0.0001$ LRR: HR 0.29 (0.15–0.53), $p = 0.0001$ EFS: HR 0.30 (0.18–0.48), $p < 0.0001$	Age, gender, T, N, site. Treatment
Sethi (2012) [114]	US	385	HNSCC	PCR	29.5% overall. 50.6% OP	3.98 years**	OS (OP): HR 0.45 (0.21–0.96)	Race, stage (in situ, local. Regional, distant), smoking
Deng (2012) [115]	Japan	121	HNSCC	PCR	28.1% overall. 47.4% OP	22 months*	RFS: 3-yr 91.2% vs. 66.6% ($p = 0.022$). HR for HPV-negative tumors 5.95 (1.71–20.73), $p = 0.005$	Age, sex, T, N, alcohol, site. SCCA2/SCCA1 ratio
Park (2013) [116]	Korea	79	Tonsil	ISH, p16	80%	62.9 months*	OS: 5-yr 78% vs. 63% ($p = 0.025$). HR for HPV-negative tumors 3.23 (1.25–8.31), $p = 0.015$	Age, T

Abbreviations: PCR – polymerase chain reaction to assess for HPV-related DNA; ISH – in situ hybridization; P16 – immunohistochemical assay for p16 expression; OS – overall survival; DSS – disease-specific survival; RFS – recurrence-free survival; EFS – event-free survival; LR – local recurrence; LFFS – local failure free survival; FFS – failure-free survival; LRC – locoregional control; LRR – locoregional recurrence; HR – hazard ratio; OR – odds ratio; RR – relative risk; yr – year; LN – lymph node; OC – oral cavity; OP – oropharynx; BOT – base of tongue; DSS – disease-specific survival; FOM – floor of mouth; T – tumor stage; N – nodal stage.

[a] PCR is polymerase chain reaction to assess for HPV-related DNA; p16 refers to immunohistochemistry for HPV oncoprotein p16, a surrogate of HPV tumor status; ISH is in situ hybridization for HPV.

[b] HPV tumor status as defined by individual study.

[c] Follow-up time included when reported (*median, **mean).

[d] Includes prognostic data when available and as reported. HRs are adjusted and for HPV-positive tumors unless indicated otherwise. 95% confidence intervals are included in parentheses.