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HPV Associated Head and Neck Cancer

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Abstract

Human papillomavirus (HPV) - associated head and neck squamous cell carcinoma (HNSCC) is an entity with unique clinical and molecular characteristics, which mainly arises from the palatine tonsils and base of the tongue. Nowadays, oropharyngeal cancers are increasing in incidence despite declining prevalence of smoking and in direct opposition to a decreasing incidence of all other HNSCC. An epidemic of HPV-associated oropharyngeal cancers seems to account for these incidence trends. HPV-positive malignancies represent 5-20% of all HNSCC and 40-90% of those arising from the oropharynx. HPV-16 is by far the most common high-risk HPV genotype detected in oropharyngeal squamous cell carcinoma (SCC). HPV-associated HNSCC have a strikingly better prognosis with improved responsiveness to the treatment options including radiotherapy and chemo-radiotherapy and favorable survival rates. Therefore the treatment selection for HPV-associated oropharyngeal carcinoma is becoming a critical issue. Novel studies about HPV-associated oropharyngeal carcinoma have contributed to our increased understanding of this new entity. Multiple clinical trials are currently underway to determine whether some of these patients can be satisfactorily managed with a de-escalated treatment approach. However, data are currently insufficient to change treatment strategies for HPV-associated oropharyngeal carcinoma.

Keywords

Human papillomavirus, Head and neck cancer, Oropharyngeal cancer, Oral cancer, Squamous cell carcinoma

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the fifth most common non-skin cancer worldwide, with an annual incidence of 600,000 cases and about 60,000 cases in the United States and Europe [1]. Despite histological homogeneity, HNSCC are an extremely heterogeneous group of tumors both from molecular [2-4] and clinical points of view [5]. The main clinical heterogeneity factor is the site of origin, which also correlates with the specific risk factors [2,5,6]. The best-established risk factors for HNSCC are tobacco and alcohol abuse [6]. Overall incidence of HNSCC has fallen in the last three decades; however the incidence of oropharyngeal carcinoma, mainly tonsil and base of tongue, has been increasing both in United States and Europe [7-12]. High-risk human papillomavirus (HPV) infection, whose role in the carcinogenesis of cervical cancer has been well established and extensively studied [6], is now a well-recognized [13,14] and emerging risk factor for HNSCC [2]. An epidemic of HPV-associated oropharyngeal cancers seems to account for these incidence trends of HNSCC. This rise in incidence is mostly occurring in individuals aged between 40-55 years, without history of tobacco and alcohol consumption, and is associated with persistent HPV infection [2,7]. Approximately 90% of HPV-positive oropharyngeal squamous cell carcinomas (SCCs) are attributable to HPV type-16 (HPV-16), compared with only 60% of cervical cancers [15,16].

HPV are small deoxyribonucleic acid (DNA) viruses that are widely distributed in vertebrates. The papillomavirus genome comprises early and late genes that encode early proteins E1-E7 and late proteins L1-L2. The early proteins are nonstructural proteins involved in replication and transcription of the genome (E1-E5) or in host cell tumoral transformation (E6 and E7), whereas L1 and L2 are the structural capsid proteins of the virion. The HPV E6 and E7 oncogenes encode proteins consisting of approximately 151 and 98 amino acids, respectively. These genes are largely responsible for the onset and persistence of the malignant process in both head and neck and anogenital cancers [17]. At the molecular level, the ability of E6 and E7 proteins to transform cells relates in part to their interaction with two intracellular proteins, p53 and retinoblastoma (Rb), respectively. Integration of HPV into the host genome disrupts or deletes the E2 viral gene, leading to increased expression of the E6 and E7 genes. The increased expression of E6 and E7, in turn, inactivates tumor suppressor protein p53 and the Rb pathway, resulting in increased proliferation and genomic instability [15,18].

In the normal cell, the p53 protein is a negative regulator of cell growth, controlling cell cycle transit from G0/G1 to S phase, and also functions as a tumor suppressor protein by halting cell growth after chromosomal damage and allowing DNA repair enzymes to function [17,19,20]. E7 protein sensitizes wild-type p53-containing cells to apoptosis, but exerts an anti-apoptotic effect in cells with mutated p53 [17,21,22]. High-risk HPV oncoprotein E7 promotes oncogenesis by blocking the activity of the Rb protein and increasing the transcriptional activity of E2F transcription factors, leading to aberrant p16 protein over expression.

The Rb protein inhibits the effect of positive growth regulation and halts cell growth or induces cell apoptosis in response to DNA damage [17,23]. One of the functions of Rb is to bind and render inactive the E2F transcription factor. E2F controls DNA synthesis and cyclin function and promotes the S phase of cell cycling. E7 interacts with Rb protein via an E2F/Rb protein complex. When E7 binds to Rb protein, E2F is released and allows cyclin A to promote cell cycling [17]. The interaction of E7 with Rb may permit cells with damaged DNA to bypass the G1 growth arrest normally induced by wild-type p53 [24]. These processes allow unchecked cell growth in the presence of genomic instability that may lead to malignant change.

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The molecular profiles of HPV positive tumors are distinct from those of HPV negative cancers. The absence of genetic or epigenetic alterations in the p53 and pRb pathways in HPV positive head and neck cancers is in sharp contrast to what is observed in HPV negative head and neck cancer. In the typical HPV negative squamous cell carcinomas, p53 mutations are very frequent, along with decreased levels of p16 and increased levels of pRb. By contrast, HPV positive carcinomas are associated with wild-type p53, down regulation of pRb, and upregulation of p16. These differences in gene expression suggest that HPV positive and HPV negative head and neck cancers [17]. Recent studies reported that genetic features are different between HPV-positive and HPV-negative SCC. For example, EGFR gene copy number gains present only in HPV-negative SCC, and such tumors show worse prognosis than HPV-positive /EGFR gain-negative tumors. As EGFR is a therapeutic target, such molecular characteristics might influence the therapeutic strategy for SCC in the future.It is well-established that HPV confers a survival advantage in oropharyngeal SCC [25-29]; however Lim et al. found no significant difference in survival dependent on if HPV was integrated or not [15].

A growing number of research papers about HPV-associated HNSCC have been published in recent years. These novel studies have contributed to our increased understanding of this new entity. Multiple clinical trials are currently underway to determine whether some of these patients can be satisfactorily managed with a de-escalated treatment approach. However, data are currently insufficient to change treatment strategies for HPV-associated oropharyngeal carcinoma. The present review highlights the HPV-associated HNSCC by the light of the novel publications.

Determination of HPV Status and Diagnosis

Although the management of oropharyngeal SCC has not required the evaluation of HPV status yet, HPV-testing is the standard care in many institutions. The HPV-induced oropharyngeal cancer constitutes a new tumor entity with improved prognosis; however heterogeneous results are obtained from the clinical studies with respect to the clinical and biological behavior among-HPV positive patients [30-32]. This may be due to differences between viral load and or viral gene expression [32], and highlights the need for assessing the presence of HPV in the tumor [2].

Histologically HPV-positive HNSCCs are poorly differentiated with a basaloid morphology and lack of keratinization [16]. However, histologic criteria are insufficient and unreliable in making an HPV diagnosis. Immune-histochemical testing and/or HPV DNA/RNA testing are required and standard of care. A useful proxy for HPV-associated HNSCC is p16 immunohistochemistry (IHC) when used for oropharynx primary tumors. However, p16 IHC is not useful as an HPV surrogate for other anatomic sites, where HPV-associated tumors are rare, resulting in a high false-positive rate for calling HPV-associated tumors.

Numerous HPV biomarkers exist, including detection of HPV DNA in tumors and serologic markers indicative of cumulative viral exposure (antibodies to HPV16 L1, the virus' capsid protein) or expressed oncoproteins (antibodies to HPV16 E6 and E7 proteins [33,34]. In addition, p16 overexpression in the tumor has been used as an indirect biomarker of HPV, as expression of the E7 oncoprotein suppresses pRb and increases the level of p16 protein via a negative feedback mechanism [33]. Currently, there is no consensus on the most appropriate method to detect HPV in HNSCC. The HPV testing methods are mostly based on detecting HPV-DNA in cancer tissues either with in situ hybridization (ISH) or polymerase chain reaction (PCR) or both [35].

Clinical Features of HPV-Associated Head and Neck Cancer

Patients with HPV-positive HNSCC tend to bemiddle-aged white man, non-smokers, non-drinkers or mild to moderate drinkers, and have a higher socioeconomic status and better performance status than patients with HPV-unrelated HNSCC [2,35-37]. Usually, the patients with HPV-induced HNSCC have a higher number of sexual partners and more oral sex partners [38]. Open-mouthed kissing was found to be associated with the development of oral HPV infection [39]. Nevertheless, HPV-induced oropharyngeal carcinoma occurs both among exposed and non-exposed to tobacco/alcohol, with cigarette smoking being a consistently associated risk factor for oral HPV infection and a suspected modifier of the natural history of HPV-induced HNSCC [2]. Distinct molecular profiles separate them from HPV-negative cancers and show many similarities with HPV-positive cervical squamous cell cancer. There is evidence that HPV-positive HNSCC is a sexually transmitted disease. Current literature has shown that, the risk factors of HNSCC are surprisingly similar to those of cervical cancer and cervical intraepithelial neoplasia (CIN), including the number of sexual partners, younger age at first sexual intercourse, practice of oral sex, history of genital warts and younger age [33,40,41].

As mentioned earlier HPV-associated HNSCC mainly develops from oropharynx. The palatine tonsils and base of the tongue are more frequently involved than other oropharyngeal subsites [2,42].

Prognosis of HPV-Associated Carcinomas

Fakhry and colleagues established in 2008 that HPV-positive tumors have a strikingly better prognosis with improved responsiveness to both chemotherapy and chemo-radiotherapy and favorable survival rates [25]. In this study, ninety-six patients with oropharyngeal or laryngeal cancer were prospectively treated with two cycles of paclitaxel and carboplatin induction chemotherapy, followed by concomitant chemo-radiotherapy using weekly paclitaxel. Oncogenic HPV was detected in 40% of patients. The patients with HPV-positive tumors had higher response rates and an improved two-year overall survival of 95% compared with 62% of patients with HPV-negative tumors. After the study by Fakhry and colleagues, many studies evaluated the impact of HPV in prognosis, and their results suggested that the patients with HPV-positive HNSCC, particularly those with oropharyngeal primary, treated by radiotherapy, chemo-radiotherapy, and surgery or combined modality therapy, have better outcome than those with HPV-uninduced cancer [28,43]. In these studies suggested that the HPV-positive SCC patients were estimated to have up to an 80% reduction in risk of disease failure compared to HPV-negative patients. Additionally, retrospective analyses of archival tumor specimens from patients enrolled in phase II and III trials, which received more specific treatment regimens [26,28]; and meta-analyses [44,45] confirmed that HPV-positive HNSCC is a separate biologic entity and that these patients have significantly better prognosis than patients with HPV-unrelated tumors. In these studies, the survival benefit was most predominant or restricted in patients with an oropharyngeal primary tumor. The reason why patients with HPV positive HNSCC have better prognosis than those with HPV-unrelated cancer remains to be explained; however their younger age at diagnosis, better performance status, lower tobacco smoking or alcohol drinking habit or distinct biology of the HPV-positive cancers may lead to have better prognosis [2]. There is strong evidence that cigarette smoking may modify the clinical behavior of HPV-positive SCC, adversely affecting the prognosis of these neoplasms [46]. Recently, a recursive partitioning analysis showed that the combination of tumor HPV status, smoking and TN category (T: the size of the original (primary) tumor and N: nearby (regional) lymph nodes that are involved) segregates patients with stage III and IV oropharyngeal SCCs into 3 groups with different prognoses: patients with HPV-induced SCCs were considered to be at low risk, with the exception of smokers with advanced nodal category, who were considered to be at intermediate risk; patients with HPV(-) SCCs were considered to be at high risk, with the exception of non-smokers with tumors of stage T2 or T3, who were considered to be at intermediate risk [47].

Current Management of HPV-Associated Head and Neck Cancer

Treatment for patients with HPV associated oropharyngeal cancer

currently is the same as for those with HPV negative oropharyngeal cancers, except in the context of a clinical trial. Although testing for HPV positivity provides prognostic information, there are insufficient data to alter therapy based upon HPV status [16].

Despite the absence of evidence from randomized, controlled trials to support a de-escalation of treatment intensity, in HPV-positive oropharyngeal carcinomas, some investigators argue that intensive concomitant chemo-radiation regimens may represent overtreatment [13,48]. Since the patients with HPV-positive oropharyngeal carcinoma tend to be younger and have prolonged survival, an aggressive multimodal therapy may result in severe acute and late term toxicities. In this context, most efforts are targeted toward de-escalation of treatment intensity in HPV-positive oropharyngeal squamous cell carcinomas with the intent to reduce toxicity and thereby improve the long-term quality of life, while maintaining efficacy. Recommended treatment de-escalation can be achieved by reducing the total dose of radiotherapy in a concurrent chemo-radiotherapy setting, by using radiotherapy and EGFR inhibitors, including cetuximab, instead of platinum based chemo-radiotherapy or radiotherapy alone instead of chemo-radiotherapy, and primary surgery +/– de-intensified adjuvant treatment instead of up-front chemo-radiotherapy [2].

Ongoing clinical studies are assessing the roles of de-intensification of radiotherapy and/or chemotherapy in this population. Among these (Eastern Cooperative Oncology Group [ECOG] 1308) multicenter study evaluated 80 patients with stage III or IVA HPV associated oropharyngeal cancer received induction chemotherapy with three cycles of cisplatin, paclitaxel, and cetuximab [49]. Lower dose of radiation therapy was given to 62 patients who had a primary site clinical complete response after induction therapy as 54 Gy in 27 fractions, 2 Gy/fraction. The other 15 patients had conventional dose radiotherapy as 69.3 Gy in 33 fractions. The patients who were given 69.3 Gy had clinical partial response or stable disease after induction therapy. In both groups, radiation treatment was given in conjunction with weekly cetuximab. In this study, the patients who had a complete response to the initial induction therapy, the two-year progression free survival was 80% [49]. The same group had similar results in ECOG trial E2399 [50]. In E2399 the two-year progression-free survival for HPV-positive patients was 84% after paclitaxel carboplatin induction followed by radiotherapy with weekly paclitaxel. However in this study conventional dose of radiotherapy as 70 Gy/2 Gy per fraction was used.

Treatment de-intensification may be achieved by the dose reduction or elimination of chemotherapy or replacement of chemotherapy with a targeted agent for HPV-associated cases. For example, the ongoing RTOG 1333 (NRG HN-002) trial compares a radiotherapy-alone regimen versus radiotherapy plus reduced-dose cisplatin in locally advanced HPV-associated disease in non-/light smokers (≤ 10 pack-years) [51]. In the chemotherapy arm of this trial, cisplatin is delivered weekly during 6 weeks of radiotherapy at 40 mg/m2 (total = 240 mg/m2), a decrease from the historical standard of 100 mg/ m2 every 3 weeks for 3 cycles (total = 300 mg/m2).

Another approach is the replacement of cisplatin with cetuximab, an FDA-approved anti-EGFR monoclonal antibody with radio sensitizing properties [52]. In a randomized trial comparing radiotherapy alone to radiotherapy with concurrent cetuximab in stage III/IV head and neck cancer, it was shown that combined therapy improved OS [53]. The survival benefit was greatest among patients with oropharyngeal primary cancers, low tumor stage, high nodal stage, and younger age. These factors are associated with HPV-positive cases. Secondary analyses of this trial suggested that the addition of cetuximab to radiotherapy compared with radiotherapy alone in p16-positive (HPV-associated) oropharyngeal carcinoma improved loco regional control and overall survival [54]. The ability of cetuximab to replace cisplatin in the management of HPV-associated oropharyngeal carcinoma may be decided by RTOG 1016. In this phase III noninferiority trial, cetuximab along with 70 Gy of conformal radiotherapy was compared with a control arm of cisplatin every 3 weeks for 2 doses with 70 Gy of radiation for 987 patients with stage III/IV p16-positive oropharyngeal carcinoma [55]. This trial has completed accrual, and initial results are expected to be announced within the next few years. The results of the trial are critical to our understanding of the role of cetuximab in the treatment of HPV-associated oropharyngeal carcinoma.

Two more phase II ongoing trials; ECOG 3311 (NCT01898494) and NRG HN-002 (NCT02254278) are also evaluate the de-escalation of treatment intensity in HPV-positive oropharyngeal carcinomas. Additional data and longer follow-up will be required from these and other trials before lower-dose radiation treatment, substitution of radiation dose by induction chemotherapy, use of potentially less toxic drugs, use of minimally invasive surgery, or radiotherapy alone can be considered a standard approach for HPV-positive patients. To date, the HPV-positive oropharyngeal carcinoma patients should be treated with standard treatment of other oropharyngeal carcinoma patients.

Conclusions

HPV-associated HNSCC is an entity with unique clinical and molecular characteristics, which mainly arises from the palatine tonsils and base of the tongue. HPV-16 is by far the most common high-risk HPV genotype detected in oropharyngeal SCC. Patients with HPV-positive HNSCC tend to be middle-aged white man, non-smokers, non-drinkers or mild to moderate drinkers, and have a higher socioeconomic status and better performance status than patients with HPV-unrelated HNSCC. Treatment for patients with HPV-associated oropharyngeal cancer currently is the same as for those with HPV negative oropharyngeal cancers, except in the context of a clinical trial. It is likely that the patients with HPV-positive HNSCC will be treated with de-escalated therapies in the future. Based on the randomized trials, over time, traditional cytotoxic chemotherapy may be replaced by targeted agents such as cetuximab, coupled with reduced-dose radiation treatment. The future standard treatment of HPV-associated SCC of the oropharynx is undefined, pending the results of ongoing trials.

Conflict of Interest

The authors declare that they have no conflict of interest.

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